CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209863Orig1s000

OTHER REVIEW(S)

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	September 21, 2018
Requesting Office or Division:	Division of Bone, Reproductive and Urologic Products (DBRUP)
Application Type and Number:	NDA 209863
Product Name and Strength:	Xyosted (testosterone) injection, USP 50 mg, 75 mg, 100 mg
Applicant/Sponsor Name:	Antares Pharma Inc.
FDA Received Date:	April 16, 2018, August 20, 2018, August 29, 2018, September 6, 2018, September 19 2018
OSE RCM #:	2017-432-2
DMEPA Safety Evaluator:	Denise V. Baugh, PharmD, BCPS
DMEPA Team Leader:	Lolita G. White, PharmD

1 PURPOSE OF MEMORANDUM

The Division of Bone, Reproductive and Urologic Products (DBRUP) requested that we review the revisions to the container label, carton labeling, Instructions for Use (IFU), and prescribing information (PI) for Xyosted (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made in previous label and labeling reviews, container label and carton labeling negotiations via email, as well as Instructions for Use (IFU) recommendations based on our previous review of a human factors validation results.[abc]

[a] Fava W. Human Factors Validation Results Review for XYOSTED (NDA 209863). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2017 Oct 18. RCM No.: 2016-2905 and 2017-432.

[b] Baugh, D. Label, Labeling, and Packaging Review for XYOSTED (NDA 209863). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2017 May 12. RCM No.: 2017-432.

[c] Baugh, D. Label, Labeling, and Packaging Review Memo for XYOSTED (NDA 209863). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2018 Aug 14. RCM No.: 2017-432-1.

2 CONCLUSION

The revised container label and carton labeling for Xyosted is acceptable from a medication error perspective. We have no further recommendations at this time.

Additionally, we find the revised Instructions for Use (IFU) is acceptable from a medication error perspective and we have determined that no further human factors validation study of the IFU labeling is required at this time.

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/s/

DENISE V BAUGH
09/21/2018

LOLITA G WHITE
09/22/2018

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	September 21, 2018
To:	Hylton Joffe, MD Director **Division of Bone, Reproductive and Urologic Products (DBRUP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Marcia Williams, PhD Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Kelly Jackson, PharmD Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Lynn Panholzer, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: (Medication Guide (MG) and Instructions for Use (IFU)
Drug Name (established name):	XYOSTED (testosterone enanthate)
Dosage Form and Route:	injection, for subcutaneous use
Application Type/Number:	NDA 209863
Applicant:	Antares Pharma, Inc.

1 INTRODUCTION

On December 20, 2016, Antares Pharma, Inc. submitted for the Agency's review an original New Drug Application (NDA) 209863 for QuickShot Testosterone (testosterone enanthate). The Agency responded with a Complete Response Letter (CRL) filed on March 29, 2018. On April 16, 2018, the Applicant resubmitted the application for the Agency's review in response to the CRL. The proposed indication is testosterone replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Bone, Reproductive and Urologic Products (DBRUP) on April 2, 2018 for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) and Instructions for Use (IFU) for XYOSTED (testosterone enanthate) injection, for subcutaneous use.

2 MATERIAL REVIEWED

- Draft XYOSTED (testosterone enanthate) MG and IFU received on April 16, 2018, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on September 17, 2018 and September 20, 2018, respectively.
- Draft XYOSTED (testosterone enanthate) Prescribing Information (PI) received on April 16, 2018, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on September 17, 2018 and September 14, 2018, respectively.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the MG and IFU the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the MG and IFU document using the Arial font, size 10 where applicable.

In our collaborative review of the MG and IFU we:

- simplified wording and clarified concepts where possible
- ensured that the MG and IFU is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information

- ensured that the MG and IFU is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20.
- ensured that the MG and IFU meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the MG and IFU is consistent with the approved comparator labeling where applicable.

4 CONCLUSIONS

The MG and IFU are acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG and IFU is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG and IFU.

Please let us know if you have any questions.

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/s/

KELLY D JACKSON
09/21/2018

LYNN M PANHOLZER
09/21/2018

MARCIA B WILLIAMS
09/21/2018

LASHAWN M GRIFFITHS
09/21/2018

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: September 19, 2018

To: Jeannie Roule, Regulatory Project Manager
Division of Bone, Reproductive, and Urologic Products (DBRUP)

From: Lynn Panholzer, PharmD, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Matthew Falter, Team Leader, OPDP

Subject: OPDP Labeling Comments for XYOSTED (testosterone enanthate) injection (Xyosted)

NDA: 209863

In response to DBRUP's consult request dated April 2, 2018, OPDP has reviewed the proposed product labeling (PI), Medication Guide, Instructions for Use (IFU), and carton and container labeling for the original NDA submission for Xyosted.

PI and Medication Guide/IFU: OPDP's comments on the proposed PI are based on the draft PI received by electronic mail from DBRUP on September 14, 2018, and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed for the Medication Guide and IFU, and comments on the proposed Medication Guide/IFU will be sent under separate cover.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on September 6, 2018, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Lynn Panholzer at (301) 796-0616 or lynn.panholzer@fda.hhs.gov.

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/s/

LYNN M PANHOLZER
09/19/2018

M E M O R A N D U M

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: Aug 16, 2018

To: Hylton V. Joffe, M.D., Director
Division of Bone, Reproductive, and Urologic Products

Through: Dominic Chiapperino, Ph.D., Director
Martin Rusinowitz, M.D., Senior Medical Officer
Controlled Substance Staff

From: Alicja Lerner, M.D., Ph.D., Medical Officer
Controlled Substance Staff

Subject: **NDA 209863/IND 116022**
Name: XYOSTED, Testosterone Enanthate Injection, QuickShot™ USP, QST
Indication: For the treatment of adult males with hypogonadism.
Dosage: 100 mg/ mL, 150 mg/mL, and 200 mg/mL at injection volume of 0.5 mL administered subcutaneously delivering 50, 75, or 100 mg of testosterone enanthate once weekly
Sponsor: Antares Pharma, Inc.
Filing meeting May 9, 2018
PDUFA September 29, 2018

Materials Reviewed:

- Complete Response, in DARRTS April 2, 2018
- CSS Review by Dr. A. Lerner, in DARRTS Oct 5, 2017 and March 6, 2018
- Meeting Minutes, March 22, 2018
- CSS review, Testosterone TSI # 1351, by Dr. A. Lerner, March 9, 2015
- OSE/DPV reviews by Dr. R. Kapoor, Aug 30, 2017 and June 12, 2018

A. SUMMARY

I. BACKGROUND

This memorandum responds to a consult from the Division of Bone, Reproductive, and Urologic Products (DBRUP) requesting Controlled Substance Staff (CSS) to review the Sponsor's proposed pharmacovigilance plan and labeling changes related to Suicide and Depression, as requested by FDA during the meeting with the Sponsor on Feb 21, 2018.

The Sponsor is developing Testosterone Enanthate Injection for SC administration, QuickShot™ (QST), under NDA (b) (4), indicated for the treatment of adult men with hypogonadism. The QST is designed as a single-use, pressure-assisted autoinjector prefilled with testosterone solution for SC self-administration.

NDA (b) (4) was submitted as a 505(b)(2) NDA using Delatestryl® Injection as the approved listed drug (LD). However, NDA (b) (4) received a CR action on October 20, 2017, due to clinically meaningful increases in blood pressure, and cases of suicidality (2) and depression (2).

During the meeting with the Sponsor on February 21, 2018, FDA requested enhanced pharmacovigilance in the postmarketing period and potential label changes.

The Sponsor submitted the following responses concerning the depression and suicidality issue described in the CR letter:

Enhanced pharmacovigilance in the Postmarketing Period

FDA's Request:
We agree that product labeling and enhanced pharmacovigilance (EPV) in the postmarketing period could address the issue of depression and suicidality.
It is premature to provide agreement on specific labeling for this issue.
In regard to EPV, you should include specific AE terms in your surveillance plan (e.g., for suicidal ideation, suicidal behavior and depression).

The Sponsor agrees to establish enhanced pharmacovigilance for these types of events reported in men receiving XYOSTED during the post-marketing period. EPV is designed to ensure there is targeted and complete follow up for spontaneously reported events that are considered to be of special interest. By handling such events using periodic review and signal detection based on Standardized MedDRA Queries (SMQ) specific for depression and suicide events and increased attempts at getting more information, EPV can provide greater insights into these events when they occur outside of a clinical trial setting. ***When coupled with expedited reporting****, both the manufacturer and the FDA are able to have a more current view of any changes in the reports as they evolve.*

Following the commercial launch of XYOSTED, Antares will conduct the following activities:
1) ***All completed suicide based on MedDRA preferred terms will be handled as expedited reports and submitted to the FDA within 15 days of receipt regardless of expectedness****.*
2) All post-marketing reports of depression and suicidality-type events based on MedDRA preferred terms will be subject to enhanced follow up.
3) Antares' pharmacovigilance staff will provide initial case review via phone at the time of initial case or subsequently by mail or telephone follow up to capture sufficient information to completely categorize reported events.

4) If initial case intake is insufficient to fully describe these events, a minimum of 3 written attempts to contact the reporter will be carried out by Antares in order to have complete follow-up information. If these are unsuccessful, a 4th attempt by phone will be conducted. This is one more attempt than is standard for reported serious adverse events.
5) Antares will provide periodic and cumulative summaries and analysis of all reports of depression and suicidality-type events since approval of XYOSTED as part of the quarterly Periodic Adverse Drug Event Report (PADER) for the first 3 years of marketing of XYOSTED.
6) Antares will discuss the effectiveness of its labeling regarding this safety issue in each PADER and will make recommendations for any changes in labeling, if needed, based on such reports.

Proposed label changes related to suicidality and depression.

Proposed Labeling Changes:

WARNINGS AND PRECAUTIONS

- Suicidal ideation and behavior, including completed suicide, have occurred during clinical trials in patients treated with XYOSTED (5.16).

And…

5.16 (b) (4) Advise patients and caregivers to seek medical attention for manifestations of suicidal ideation or behavior, new onset or worsening depression, anxiety, or other mood changes.

II. CSS has following Recommendations:

1. The Sponsor's proposed **Pharmacovigilance** plan for suicidality and depression is appropriate. In addition to expedited reporting of "completed suicides", CSS recommends expedited reporting also for "attempted suicide" and "suicidal ideation." Providing the suicidality AE data in quarterly PADER submissions is acceptable, too (consistent with the approach proposed by DPV/OSE, review by Dr. R. Kapoor, June 12 2018). However, expedited reporting of suicidality-related cases, as the Sponsor proposed, would be preferred in case there is indeed an unusual effect of this testosterone formulation on suicidality, which could be captured in early stages if expedited reporting would be available.

2. Of note is that the Sponsor already included a warning language on suicidality in section 5.16. CSS proposes consideration of a **Boxed Warning** for suicidality and the addition of suicidality as an AE in **9.3 Dependence** section, as shown below in Discussion section.

III. DISCUSSION

Labeling Considerations

To address suicidality in product labeling for XYOSTED, the Sponsor has included Warnings and Precautions section 5.16, and CSS further recommends consideration of a Boxed Warning and mention of suicidality AEs in section 9.3. These proposed changes are supported by the FAERS cases cited in OSE/DPV review by Dr. R. Kapoor, Aug 30, 2017. In this review, OSE/DPV identified 74 of suicidality cases which included 15 cases of completed suicides, 13 cases of suicidal attempt, and 46 cases of suicidal ideation reported with testosterone use and after exclusion of: duplicates, body builders, women, Nebido cases, overdoses, and cross-sex hormonal therapy. Although the OSE/DPV reviewer states that "*However, a vast majority of the cases did not provide necessary information regarding concomitant medications, past medical history, duration of therapy, time-to-onset of suicidal symptoms, and previous history of suicidal attempts to ascertain a drug-event association,"* in some cases the only drug taken by the patients was testosterone, and in fact some patients describe their suicidality as emerging coincident with their treatment with testosterone therapy (or due to testosterone withdrawal) (CSS review by Dr. A. Lerner, October 5, 2017).

A potential Boxed Warning is further supported by the evidence of suicidality cases during previous testosterone NDAs (Androgel NDA 21015, Testim NDA 21454, Aveed NDA 22219; Nebido-PSUR Nov 2009 – Nov 2010); and literature cases of suicidality related to testosterone and anabolic androgenic steroids abuse (Brower, 1989; Corrigan, 1996; Porcerelli et al., 1998; Thilblin et al., 1999, 2000; Petersson et al., 2006; Darke et al., 2014). It is notable that the supplemental doses of testosterone administered in these hypogonadal men, which are trying to establish normal levels (~1100 ng/dL) from the very low initial levels of testosterone (less than 300 ng/dL) represent an up-to-10-fold increase from their pre-treatment testosterone level. It is plausible that these extreme testosterone level increases for these individuals are producing similar AEs as those observed from overdoses in testosterone abusers.

In addition, while the currently proposed Warning section 5.16 is a valuable addition to labeling, it may not be prominent enough for such a serious adverse event, and might be overlooked. It is important to emphasize that testosterone treatment, especially in older men, is intended mainly to treat uncomfortable effects of aging. Thus, the discrepancy between the risk of the testosterone treatment, such as suicidality, versus benefits of the treatment is significant. Also, suicidality meets the regulatory requirements for the Boxed Warning[1]:

> "*There is an adverse reaction so serious in proportion to the potential benefit from the drug (e.g., a fatal, life-threatening or permanently disabling adverse reaction) that it is essential that it be considered in assessing the risks and benefits of using the dru*g".

Suggested language for the Boxed Warning:

[1] Guidance for Industry - Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drugs and Biological Products, 2011.

Occasional cases of suicidality occurred during clinical trials with XYOSTED, during treatment or following discontinuation of treatment.t.

In **the section 9.3 Dependence**, add "suicidality" as a possible adverse event following TRT discontinuation, as shown below:

After the discontinuation of Testosterone Replacement Therapy in hypogonadal men occasional emergence of suicidality was observed.

*These labeling changes may be appropriate for all testosterone products.

IV. REFERENCES

1. Brower KJ, Blow FC, Eliopulos GA, Beresford P. Anabolic androgenic steroids and suicide. Am J Psychiatry 1989; 146: 1075.

2. Corrigan B Anabolic steroids and the mind. Med J Aust. 1996 Aug 19;165(4):222-6. Review.

3. Darke S, Torok M, Duflou J. Sudden or unnatural deaths involving anabolic-androgenic steroids. J Forensic Sci. 2014 Jul;59(4):1025-8.

4. Petersson A, Garle M, Granath F, Thiblin I. Morbidity and mortality in patients testing positively for the presence of anabolic androgenic steroids in connection with receiving medical care. A controlled retrospective cohort study. Drug Alcohol Depend. 2006 Feb 28;81(3):215-20.

5. Porcerelli JH, Sandler BA. Psychiatr Clin North Am. 1998 Dec;21(4):829-33. Review. Anabolic-androgenic steroid abuse and psychopathology.

6. Thiblin I, Runeson B, Rajs J. Anabolic androgenic steroids and suicide. Ann Clin Psychiatry. 1999 Dec;11(4):223-31.

7. Thiblin I, Lindquist O, Rajs J. Cause and manner of death among users of anabolic androgenic steroids. J Forensic Sci. 2000 Jan;45(1):16-23.

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/s/

ALICJA LERNER
08/16/2018

MARTIN S RUSINOWITZ
08/16/2018

DOMINIC CHIAPPERINO
08/16/2018

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	August 14, 2018
Requesting Office or Division:	Division of Bone, Reproductive, and Urologic Products (DBRUP)
Application Type and Number:	NDA 209863
Product Name and Strength:	Xyosted (testosterone) injection, USP 50 mg, 75 mg, 100 mg
Applicant/Sponsor Name:	Antares Pharma, Inc.
FDA Received Date:	March 29, 2018
OSE RCM #:	2017-432-1
DMEPA Safety Evaluator:	Denise V. Baugh, PharmD, BCPS
DMEPA Team Leader:	Lolita G. White, PharmD

1 PURPOSE OF MEMORANDUM

The Division of Bone, Reproductive, and Urologic Products (DBRUP) requested that we review the revised container label and carton labeling for Xyosted (testosterone injection [Appendix A]) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The revised container label and carton labeling for Xyosted (testosterone injection) is unacceptable from a medication error perspective. The autoinjector label does not include a linear barcode in accordance with 21 CFR 201.25(c)(2) and the NDC number proposed on the carton labeling for the 100 mg product do not align with NDC numbers presented in Section 16.1 (How Supplied) of the full prescribing information.

[a] Baugh D. Label and Labeling Review for Xyosted (NDA 209863). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2017 May 12. RCM No.: 2017-432.

3 RECOMMENDATIONS FOR ANTARES

We recommend the following be implemented prior to approval of this NDA:

A. We note that your trade autoinjector label does not include a linear bar code in accordance with 21 CFR 201.25(c)(2). We recommend that you include a linear bar code to assist with the correct product selection during the dispensing and administration process. The barcode should be horizontally placed and surrounded by enough white space to allow scanners to read the bar code properly. The print density should be consistent to allow for an accurate scan and it should be placed in a conspicuous location where it will not be difficult to read due to distorted text.

B. We note that the package code of the NDC number on the 100 mg Xyosted carton labeling differs from what is presented in the full prescribing information Section 16.1 How Supplied. Revise the NDC number for the '100 mg' carton labeling from "54436-200-(b) (4)" to read "54436-200-04" to minimize the potential for dispensing errors.

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/s/

DENISE V BAUGH
08/14/2018

LOLITA G WHITE
08/14/2018

U.S. FOOD & DRUG ADMINISTRATION

Inter-Center Consult

ICCR Consult Number:	ICCR2018-02873
Document Number:	NDA 209863
Applicant:	Antares Pharma, Inc.
Trade Name:	XYOSTED - Testosterone enanthate injection
Consult Type:	Analytical consult – Cross-reactivity studies
Requestor:	Jeannie Roule
Requestor Home:	CDER/OND/ODEIII/DBRUP
Gatekeeper / Consultant:	Marianela Perez-Torres, Chemistry Branch Chief
Consultants Home:	CDRH/OIR/DCTD/CHTB
Date Requested:	May 9, 2018
Due Date:	August 1, 2018

I. CONSULT SCOPE:

CDER/OND/ODEIII/DBRUP requested CDRH to evaluate information provided on cross-reactivity studies of TE with an immunoassay that measure testosterone levels. Specifically, Clinical Pharmacology reviewers formulated the following questions:

At the Type A meeting on 2/21/2018 for NDA 209863 the applicant claimed that cross-reactivity of testosterone proprionate (TP) ranges from 0 to <7.48%.

1. Do you agree that cross-reactivity of TP to testosterone (T) immunoassays is expected to be <10%?
2. Based on the observed data for TP, what range of cross-reactivity may be expected for T enanthate?

Please reference the applicant's CR submission and the meeting minutes to the Type A meeting.

II. DOCUMENTS REVIEWED:

- CR submitted by Antares on March 2018 - Section 7.2. Immunoassay cross reactivity of testosterone enanthate
- Minutes from the meeting held on February 21, 2018
- Data on Correlation of trough Total Testosterone between ECLIA and LC-MS/MS for the same subjects from studies QST-13-003 and QST-15-005

III. CDRH ASSESSMENT AND COMMENTS TO CDER:

The company provided a comparison of the testosterone results using an LC-MS validated assay (which is not susceptible to interference due to cross-reactivity) and compared to the results of the Roche ECLIA Testosterone assay on the Roche E-170 Modular analyzer.

In study QST-13-003, samples from 139 subjects in the safety population at week 12 were analyzed using both methods. The pretreatment baseline samples from eight of those subjects were also analyzed by both methods. The trough TT correlation between the two methods for samples collected at pretreatment baseline (week 1) and week 12 for each subject from study QST-13-003 was presented.
Data for trough TT analyzed by ECLIA and LC-MS/MS for the same subjects from study QST-15-005 were available at baseline, week 6, and week 12 (Table 2). The trough TT correlation between the two methods for samples collected at pretreatment baseline (week 1), week 6, and week 12 for each subject from safety population in study QST-15-005.

While there is an acceptable correlation between the results obtained by the 2 methods, which would suggest that the antibodies used to capture testosterone in the Roche ECLIA assay may not cross-react with TE, the data is not adequate to characterize if commonly used testosterone immunoassays would significantly cross-react with TE. The limitations of the data are the following:

1. The study was conducted using only one immunoassay. Because each T assay includes different antibodies for the detection of T, one assay is insufficient to represent all other test systems that are currently available in the market. We believe that typical cross-reactivity testing should be conducted using a minimum of 5 different testosterone immunoassays. This number would provide a better representation and coverage of the current testosterone market share (which according to information in the CDRH Registration and Listing Database is approximately ~25 assays). [We note that this information on the minimum number of assays that we would expect was also communicated (b) (4) on a meeting held on July 19, 2018.]

2. It is unclear the concentration of TE in each sample, or if any of the samples is representative of the highest level that is possible in patients injected with TE. Typically, cross-reactivity studies are conducted by spiking the cross-reactant substance at 3 times the highest concentrations that a laboratory would expect to observe among patient specimens submitted for analysis. This should be addressed. Since the TE concentration on each samples was not included, the estimated % cross-reactivity was not provided (and can't be calculated). We note that typically, cross-reactivity is calculated based on the following formula: % Cross-reactivity = 100 x ((measured value – true value)/concentration of cross-reactant).

3. The testosterone concentration of the >150 samples tested ranged from 2 to 900 ng/dL. During the cross-reactivity studies is not necessary to test that many samples, but it is critical to fully characterize the potential interference at levels of analyte that represent medical decision levels. Typically, cross-reactivity studies are conducted both in the absence and in the presence of the analyte (i.e. T) at a concentration near the upper limit of the concentration expected to be found in a patient's specimen.

We recommend requesting Antares Pharma to design a robust study and provide data demonstrating the rate of TE cross-reactivity with commonly-used immunoassays. They may find the Clinical Laboratory Standards Institute's document *EP07-A2 Interference Testing in Clinical Chemistry*, helpful in designing and evaluating TE potential cross-reactivity.

Regarding ClinPharm specific questions we have the following comments:

1. Do you agree that cross-reactivity of TP to testosterone (T) immunoassays is expected to be <10%?
   We have reviewed the data of recently cleared testosterone immunoassays and confirmed that we observed that % of TP cross-reactivity has been below 10%. However, we note that each company have tested different concentrations of TP, thus the data is not necessarily equivalent. The following table summarizes the data:

Assay	510(k) Number	Highest TP conc tested	% Cross-reactivity*
Siemens ADVIA Centaur Testosterone II	k151986	10,000 ng/mL	2.94%
Siemens Dimension Vista LOCI Total Testosterone	k151529	100 ng/mL	0.00%
Abbott ARCHITECT 2nd Generation Testosterone	k120009	100 ng/mL	<10%
Diasorin LIASON Testosterone	k122793	50 ng/mL	7.48%
Roche Elecsys® Testosterone II Immunoassay	k093421	100 ng/mL	2.46%

* % Cross-reactivity = 100 x ((measured value – true value)/concentration of cross-reactant).

2. Based on the observed data for TP, what range of cross-reactivity may be expected for T enanthate?

   It is difficult to anticipate the level of interference or cross-reactivity that a new drug will have, since even the smallest differences in chemical structure could have a different impact on antibody recognition. And as noted in the table above, each assay may present different levels of cross-reactivity when testing the same substance.
   In general, less than 10% cross-reactivity is considered to be non-significant.

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/s/

JEANNIE M ROULE
08/04/2018

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Pharmacovigilance Memo

Date:	June 12, 2018
Reviewer:	Rachna Kapoor, PharmD, MBA, Division of Pharmacovigilance II
Team Leader:	Lynda McCulley, PharmD, BCPS Division of Pharmacovigilance II
Deputy Division Director:	Ida-Lina Diak, PharmD, MS Division of Pharmacovigilance II
Product Name:	Xyosted (testosterone enanthate)
Subject:	Enhanced Pharmacovigilance proposal for depression and suicide
Application Type/Number:	NDA 209863
Applicant/Sponsor:	Antares Pharma, Inc.
OSE RCM #:	2018-969

1 INTRODUCTION

On October 20, 2017, FDA issued a Complete Response (CR) letter to Antares Pharma, Inc., the sponsor for Xyosted (testosterone enanthate), NDA 209863 due to concerns of blood pressure elevations and psychiatric events (i.e., suicide, depression) identified in the development program. On March 29, 2018, the sponsor responded to the CR proposing 1) product labeling modifications to address blood pressure elevations, depression, and suicide and risk mitigation strategies to communicate blood pressure elevations concerns to prescribers and patients (Section 5), and 2) to establish enhanced pharmacovigilance (ePV) in the post marketing period for depression and suicide (Section 6).

On May 8, 2018, the Division of Bone, Reproductive, and Urologic Products (DBRUP) consulted the Division of Pharmacovigilance (DPV) to opine on the utility of an ePV program, including expedited 15-day reporting to FDA, to monitor post market reports of depression and suicide. This DPV memorandum considers whether spontaneous post marketing data would be a useful tool for assessing the risk of depression and suicidality in an ePV program for Xyosted.

Note: The sponsor's full response to CR, dated March 29, 2018, is found in Appendix A.

2 DPV RESPONSE TO THE SPONSOR'S PROPOSAL FOR ENHANCED PHARMACOVIGILANCE (SECTION 6)

DPV has previously reviewed psychiatric events (e.g., depression and suicide-related adverse events) using spontaneous post marketing data from the FDA Adverse Event Reporting System (FAERS) database (See Appendix B for a description of the FAERS database). For example, a July 1, 2016 DPV[1] review of Harvoni (ledipasvir/sofosbuvir) identified 21 cases of depression and suicide-related adverse events; however, all of the FAERS cases were confounded by a history of psychiatric illness and polysubstance abuse, or lacked information on psychiatric history. Most recently, an August 30, 2017 DPV[2] review of testosterone products, including testosterone enanthate, identified 13 cases of suicidal attempt, 15 cases of completed suicide, and 46 cases of suicidal ideation from FAERS. However, a vast majority of the cases did not provide necessary information regarding concomitant medications, past medical history, duration of therapy, time-to-onset of suicidal symptoms, and previous history of suicidal attempts to ascertain a drug-event association. Additionally, no specific trend was noted in this review.

We agree with the sponsor that suicidal ideation and depression has been reported in the Medical Reviews of many testosterone products already approved. Therefore, given what is known of low testosterone and its ability to cause clinical depression in hypogonadal men[3] (and high background rate of depression in U.S. adults over 20 years old [8.1%])[4], it is difficult to attribute these events to testosterone products using spontaneous post marketing data. Furthermore, this data cannot be used to estimate incidence due to uncertainties in the numerator and denominator, as FDA does not receive all adverse events that occur with a given product and we do not know the actual use of a given product.

In conclusion, although we do not believe that expedited reporting of cases describing depression and suicidality related events would help FDA gain a better understanding of this potential safety

issue, we do request that the sponsor provide periodic and cumulative summaries and analyses of all reports of depression and suicidality-type events since approval of Xyosted as part of the quarterly Periodic Adverse Drug Event Report (PADER) for the first three years of marketing of Xyosted. Additionally, we request that the sponsor discuss the effectiveness of its labeling regarding this safety issue in each PADER along with any recommendations for changes in labeling, if needed, based on their findings.

3 REFERENCES

[1] Bersoff-Matcha S, Cao K, and Jones SC. Food and Drug Administration. Office of Surveillance and Epidemiology. Pharmacovigilance review for Harvoni and depression and suicide-related adverse events. Silver Spring, MD, July 1, 2016. (RCM 2016-1421).
[2] Kapoor R and Gada N. Food and Drug Administration. Office of Surveillance and Epidemiology. Pharmacovigilance memo for Androderm, AndroGel, Aveed, Axiron, Delatestryl, Fortesta, Striant, Testim, Testosterone, Vogelxo, and Xyosted and completed suicide, suicidal ideation, and suicide attempt. Silver Spring, MD, August 30, 2017. (RCM 2017-1637).
[3] Shores MM, Sloan KL, Matsumoto AM, Moceri VM, Felker B, and Kivlahan DR. Increased incidence of diagnosed depressive illness in hypogonadal older men. *Arch Gen Psychiatry*. 2004;61:162-167.
[4] Brody DJ, Pratt LA, and Hughes JP. Prevalence of depression among adults aged 20 and over: United States, 2013-2016. NCHS Data Brief. 2018;303. https://www.cdc.gov/nchs/products/databriefs/db303.htm

4 APPENDICES

4.1 APPENDIX A. SPONSOR'S FULL RESPONSE TO COMPLETE RESPONSE

complete-response.pdf

4.2 APPENDIX B. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

FDA Adverse Event Reporting System (FAERS)

FAERS is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary.

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

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/s/

RACHNA KAPOOR
06/12/2018

LYNDA V MCCULLEY
06/12/2018

IDA-LINA DIAK
06/12/2018

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: May 25, 2018

From: Fred Senatore, MD, PhD, FACC, Medical Officer
Division of Cardiovascular and Renal Products / CDER

Through: Martin Rose, MD, JD, Team Leader
Norman Stockbridge, MD, PhD, Division Director
Division of Cardiovascular and Renal Products / CDER

To: Jeannie Roule, RPM
Division of Reproductive and Urological Products / CDER

Subject: NDA 209863: Review of Sponsor's Type A Meeting Package for a post-action CR.

This memo responds to your consult to us dated 08 May 2018 requesting our review of the "Hypertension Discussion" on pages 21-48 of the Type-A Meeting Package as part of the NDA resubmission (NDA 209863 / SN0031 / module 1.6.2: section 7). This follows a complete response (CR) issued to the Applicant on 20 Oct 2017 and the Applicant's itemized response to the CR (SN0028) dated 21 Dec 2017.

DCRP received and reviewed the following: 1) your current consult to us, 2) the Type-A meeting package link in the current consult (\\CDSESUB1\evsprod\NDA209863\209863.enx), 3) your previous consult to us dated 28 December 2017, and 4) our previous review dated 15 Jan 2018 in response to your previous consult request.

The hypertension discussion content of this Type-A meeting package is precisely the same as the hypertension discussion content of the Applicant's response to the CR on which we were consulted on 28 December 2017. Consequently, this review has not changed from the previous review dated 15 Jan 2018 in addressing the same questions.

Summary

We confirm that the baseline characteristics of the patient population in the phase-3 program were representative of the type of patient likely to be encountered in clinical practice for the treatment of hypogonadism with testosterone.

The administration of XYOSTED™ will cause an increase of blood pressure with a mean SBP/DBP effect of ~ 4/1 mmHg within 12 weeks of treatment. This increase will be larger in some individuals. The hypertensive effect of this drug will increase the risk of cardiovascular death, myocardial infarction, stroke, and heart failure, albeit modestly. The risk will increase when given to patients with higher baseline risk (i.e., established cardiovascular disease or multiple cardiac risk factors). We do not feel further clinical studies will provide additional useful information. If DBRUP feels marketing of the product is desirable because the benefit outweighs the cardiovascular and any other risks, then we suggest appropriate language in the PI as suggested in previous consults.

Objective

In this consult, we provide our comments to hypertension issues identified and discussed by Antares Pharma in their Type-A Briefing Package (SN0031) and as was previously identified and discussed in their initial response (SN0028) to DBRUP's CR letter for NDA 209863:

1. Patient population relative to hypertension and concomitant medications.
2. Blood pressure changes in the ABPM study.
3. Effect of XYOSTED™ on hypertension defined by 24-hour mean systolic and diastolic criteria.
4. Effect of XYOSTED™ on patients with co-existing hypertension.
5. Cumulative distribution function curves and ABPM data.
6. Analysis of changes in blood pressure medication.
7. Blood pressure changes in other approved testosterone products.
8. Clinical significance of testosterone-mediated blood pressure changes.
9. Effect of other approved drugs on hypertension and corresponding label.

Background

Antares Pharma developed XYOSTED™ (previously called QuickShot™), administered as a single weekly subcutaneous injection via an autoinjector, for the treatment of adult males with hypogonadism. Two pivotal studies were performed to support NDA 209863: QST-13-003 and QST-15-005.

QST-13-003 was a phase 3, double-blind (to dosage strength), 52 week multiple-dose efficacy and safety study in 150 hypogonadal males (97 completed). The objective was to demonstrate that XYOSTED™, administered subcutaneously once each week at doses of either 50, 75, and 100 mg, produced systemic levels within the age-adjusted normal range (i.e., from 300 to 1100 ng/dL) with minimal excursion outside the normal range. Blood pressure measurements were made by sphygmomanometry during clinic visits. Because of the high variability of blood

pressure readings in this setting, we limited our assessment of blood pressure effects to the ABPM study conducted in QST-13-005.

QST-15-005 was a phase 3, uncontrolled, 26 week multiple-dose safety study in 133 hypogonadal males (113 completed). This study was intended to collect additional safety and exposure data to support labeling based upon the dosing regimen employed in the QST-13-003 study. Safety data collection included blood pressure measurements by ABPM in all 133 subjects. There was no stated primary endpoint. XYOSTED™ was administered subcutaneously once each week. XYOSTED™ was provided in 3 blinded dosing strengths of 50, 75, and 100 mg, each at a volume of 0.5 mL. The study included a 2-7 week screening period, a 12 week titration period, and a 14 week extended treatment period. At the start of the titration period, subjects self-administered XYOSTED™ at the 75 mg dose. Titration from this dose (i.e., increasing or decreasing doses by 25 mg) occurred at week 6, week 12, and week 18. The decision to titrate was dependent on maintaining the trough concentration of total testosterone between 350 and 650 ng/dL.

The ABPM study was designed (b) (4) in collaboration with the Agency. Blood pressure measurements were collected over a 24-hour period at baseline, week-6, and week-12 for all subjects.

DCRP performed an independent analysis of the effect of XYOSTED™ on blood pressure from the ABPM study that included 110 subjects. We concluded that the data was reliable enough for a regulatory decision. Within 12 weeks, the mean SBP increased by + 4mmHg and the mean DBP increased by +1 mmHg with no identified outlier subgroups. The adverse event rate for hypertension (4 of 133 subjects {3%}) was consistent with that from other testosterone products (1—4%). We felt that the modest increase in blood pressure would increase the risk of major adverse cardiovascular events especially when given chronically to patients with high baseline risk (i.e., established cardiovascular disease or multiple cardiac risk factors). Our opinion was to manage this risk through clear warning/precaution in section 5 of the label. Prescribers should be counseled to check blood pressures after 12-weeks of initiation of testosterone and to manage new onset hypertension or exacerbation of pre-existing hypertension as clinically necessary.

DBRUP issued a CR letter because of concerns about hypertension and suicidal ideation. The sections in the CR letter that discussed hypertension are extracted here:

Based on the findings in Studies QST13-003 and QST15-005, we are concerned that your testosterone enanthate product could cause a clinically meaningful increase in blood pressure. For example, your ambulatory blood pressure monitoring (ABPM) assessments, which were conducted in patients without pre-existing hypertension, showed mean increases in systolic and diastolic blood pressure of approximately 4 mmHg and 2 mmHg, respectively. In addition, cumulative distribution function curves generated from these ABPM data demonstrated that approximately 60% of the patients had an increase in systolic blood pressure, with increases of up to 20 mmHg. Approximately 9.5% of patients in the study required initiation or adjustment of antihypertensive medications in order to maintain their blood pressures in the normal range. We are concerned that these unexpected findings based on data from a largely normotensive population may underestimate the effects of your drug on blood pressure in the real world setting, where many patients have co-existing hypertension, with the potential to increase the risk for adverse cardiovascular outcomes.

Information Needed to Resolve the Deficiencies

Further characterize the effects of your product on blood pressure and the impact on cardiovascular risk in the hypogonadal population anticipated to use your product. One approach is to conduct a new ABPM study to assess blood pressure effects in a population more consistent with real-world use of testosterone replacement as opposed to a normotensive study population. This ABPM study would collect key blood pressure data at steady state for your product within the normal range to evaluate the magnitude of effect in the intended population. Collecting data on other parameters that may influence cardiovascular risk (e.g., hematocrit, hemoglobin, cholesterol parameters) in this ABPM study could, together with the blood pressure assessment, facilitate better characterization of the impact of your product on cardiovascular risk with use in a real world setting.

Antares responded to the CR letter by positing that testosterone had a beneficial effect on blood pressure in hypogonadal men. Antares referred to a series of registry studies (i.e., TESTIM in the US: N=848; Hypogonadism in Males: N=2162; RHYME: N=999; TROMSØ: N=1548) that suggested an association between hypogonadism and comorbid conditions portending a risk for an adverse cardiac event: hypertension, obesity, diabetes, and hyperlipidemia. Patients with increased cardiovascular risk factors had a higher incidence of hypogonadism. Antares further stated that in an 8 year study of 77 hypogonadal men with concomitant hypertension that was controlled by antihypertension medication, treatment with testosterone caused a significant and gradual decrease in blood pressure over the years of treatment in response to testosterone (Haider, 2016). The Applicant did not rule out the effect of antihypertension medications on blood pressure control.

Antares Pharma also identified key elements from the hypertension discussion in the CR letter and provided a rebuttal of each element in both their response to the CR letter (SN0028) and in the current Type-A meeting package (SN0033). In lieu of performing a new ABPM study, Antares proposed to add labeling language in section 2 (Dosage and Administration) that patients should have adequately controlled blood pressure prior to initiation of XYOSTED™ therapy, and be periodically monitored while being treated.

Elements from Hypertension issues raised in the CR Letter

1) Patient population relative to hypertension and concomitant medications

Antares Statement of Issue

The Agency suggested that the patient population was not representative of "real world" and were normotensive (not having pre-existing hypertension or hypertension controlled by medication).

Antares Rebuttal

A history of hypertension was present in 49.3% of subjects entering study QST-13-003 and 49.6% of subjects entering QST-15-005. One hundred and forty-one (141) of 283 (49.8%) in the combined QST-13-003 and QST-15-005 studies were on one or more blood pressure medications.

DCRP Comment

We agree with the Applicant.

In study QST-13-003, 49% of the enrolled subjects had hypertension at baseline. The mean blood pressure at baseline was 127/80 mmHg. Our review of other subject characteristics showed that the mean age of the enrolled subjects was 53.4 years, 89% Caucasian. Approximately 50% of the subjects enrolled in this study had at least one cardiac risk factor: obesity, type 2 diabetes, or hyperlipidemia.

In study QST-15-005, sixty-six subjects (50% of those enrolled) had hypertension at baseline and 64 subjects were on at least 1 concomitant medication for hypertension which continued during the study. The mean blood pressure at baseline was 126/78 mmHg. Our review of other subject characteristics showed that the mean age of the enrolled subjects was 54.5 years and 85% were Caucasian. Ninety-nine (99) subjects (75% of the enrolled subjects) had a metabolism / nutritional disorder some of which were cardiac risk factors: obesity (26% enrolled), type 2 diabetes (23% enrolled), or hyperlipidemia (20% enrolled). It was not clear if some of these subjects had more than one risk factor and thus recounted under each disorder.

Based on subject characteristics, we believe that the population enrolled in the phase-3 program is likely representative of the type of patient who would present with hypogonadism and prescribed XYOSTED™.

2) Blood pressure changes in the ABPM study

Antares Statement of Issue

The Agency stated: "your ambulatory blood pressure monitoring (ABPM) assessments, which were conducted in patients without pre-existing hypertension, showed mean increases in systolic and diastolic blood pressure of approximately 4 mmHg and 2 mmHg".

Antares Rebuttal

Demographic data does not support the statement that subjects in the study did not have pre-existing hypertension. The largest changes in BP from the ABPM study was 3.7 mmHg SBP and 1.3 mmHg DBP at week 12. Complimentary in-clinic BP data showed similar results. In conclusion, there is close agreement between the clinic BP and ABPM values; therefore, the clinic BP values can be relied upon to provide data relevant to evaluation of change in BP over time in response to testosterone treatment.

DCRP Comment

We agree with the Applicant's acknowledgement of SBP and DBP elevations but disagree on their assertion that blood pressure values obtained in the clinic setting can be relied upon to provide relevant data.

See our comment in issue # 1 regarding the prevalence of hypertension at baseline. Our own central tendency analysis from ABPM data showed a mean increase in 24-h average SBP of 3.5 mmHg (95% CI: 1.6, 5.3; p-value=0.0003) at week # 6 and 3.7 mmHg (95% CI: 1.5, 5.9; p-value =0.001) at week # 12. The mean increase in 24-h average DBP was 1.2 mmHg (95%CI: 0.4, 2.1; p-value=0.006) at week # 6 and 1.3 mmHg (95%CI: 0.1, 2.5; p-value=0.03) at week # 12. Our analysis is in agreement with the ABPM data reported by Antares.

Integrated blood pressure data from both the 003 and 005 studies, described in the ISS, showed a +4.3 mmHg rise in SBP and a +1.6 mmHg rise in DBP by week 26.

The increase of 4 mmHg SBP and 2 mmHg DBP as stated in the CR letter were reasonable rounded estimates based on the data as presented in the ISS, as well as from the ABPM study.

The expected increase in SBP by approximately 4 mmHg within 12 weeks of treatment may not be detectable in the clinic setting because of high variability using a sphygmomanometer to measure an individual blood pressure.

3) Effect of XYOSTED™ on hypertension defined by 24-hour mean systolic and diastolic criteria

Antares Statement of Issue

The Agency stated: "based on the findings in Studies QST 13-003 and QST 15-005, we are concerned that your testosterone enanthate product could cause a clinically meaningful increase in blood pressure".

Antares Rebuttal

The loss of the usual 10 mmHg drop in nocturnal SBP (i.e., dipper effect) or a rise in night-time SBP and DBP are considered to be a negative prognostic indicator for mortality (observations from the Dublin Outcome Study) and major adverse cardiac events (analyses of IDACO-*International Database on Ambulatory Blood Pressure Monitoring in Relation to Cardiovascular Outcomes*).

Daytime blood pressure did not independently predict mortality and was only weakly associated with major adverse cardiac events (IDACO).

In the QST-15-005 ABPM study, the dipper effect was not attenuated but rather increased from 34% of patients having ≥ 10% BP dips at baseline to 41% of patients at week 6 to 43% at week 12.

Using the diagnostic criteria for hypertension > 130/80 mmHg as a benchmark (O'Brien, 2013), approximately 33% of the subjects had a 24-hour mean SBP > 130 mmHg or 24-hour mean DBP > 80 mmHg at baseline. These numbers did not significantly change over 12 weeks. Also, approximately 25% of the subjects had ≥ 10 mmHg increase in 24-hour mean SBP at week 6 or 12; and 10% had ≥ 10 mmHg increase in 24-hour mean SBP at week 6 and 12.

In summary, the 24-hour ABPM study of the XYOSTED™ population appeared to show limited increased risk, as the impact on nocturnal blood pressure was small and the percentage of subjects with systolic or diastolic hypertension on-treatment changed very little.

DCRP Comment

We disagree with the Applicant.

In the ABPM study, we confirm that compared to daytime increases in SBP, nocturnal SBP showed smaller increases from baseline at week 6 (1 mmHg, SD 17 mmHg) and at week 12 (2 mmHg, SD 22 mmHg).

The IDACO study evaluated the crude and the standardized (i.e., cohort / sex / age) rates of mortality and combined fatal / nonfatal events by subtypes of ambulatory hypertension: isolated nocturnal hypertension (INH), isolated daytime hypertension (IDH) and sustained hypertension (SH). Compared to normotensive individuals, patients with INH, IDH, or SH had a significantly higher incidence of mortality and morbidity (Table 1). The Kaplan-Meier curves for total mortality and CV events (*ischemic death, sudden death, non-fatal MI, coronary revascularization, fatal and non-fatal heart failure*) are shown in Figure 1. Both IDH and INH showed similar incidences of total mortality and CV events over time compared to normotensive individuals.

Table 2 provides unadjusted and adjusted hazard ratios for INH, IDH, and SH relative to the normotensive control group. With cumulative adjustments applied for cohort, sex, age, body mass index, smoking and drinking, serum cholesterol, diabetes, and a history of CV disease, INH was associated with a significantly increased risk for all-cause mortality and all cardiovascular events. With similar adjustments, IDH was associated with a significantly increased risk for all cardiovascular events; SH was associated with a significantly increased risk for all-cause mortality, CV mortality, all cardiovascular events, and stroke.

The key finding of the IDACO study was that irrespective of the type of ambulatory hypertension (i.e., INH, IDH, SH), an elevated blood pressure was a major risk factor for cardiovascular complications.

From our own analysis of the 24-hour average ABPM data, 7.1% of the subjects sustained a SBP > 180 mmHg or a change from baseline 24-h SBP > 20 mmHg at week 12. From our own analysis of hourly average ABPM data, 93% of the subjects had a $\geq$ 20 mmHg SBP change from baseline at week 12, and 96% of the subjects had a $\geq$ 20 mmHg DBP change from baseline at week 12.

As discussed in previous consults, a white paper prepared by members of the Cardiac Safety Research Consortium assessed drug induced increases in blood pressure during drug development for indications not related to the cardiovascular system organ class (Sager et al, 2013). Key messages from this white paper were:

- There is powerful epidemiologic evidence showing that as BP increases in a population, the risk of CV events increases.
- It may be difficult, even impossible, to define the CV risk with a non-CV drug with small mean increases in BP because the CV risk is dependent on multiple factors (i.e., baseline CV risk, baseline BP, and length of treatment). Small central tendency increases in BP are likely to predispose to future CV events. It is therefore prudent that the drug label should assert whether a potential BP effect might be expected and how to deal with it appropriately (i.e., discontinuation, down-titration, initiating or intensifying antihypertensive therapy if the benefit justifies continuation).
- Owing to BP variability, it is not likely that all at-risk patients with significant blood pressure increases would receive medical intervention to restore them to pretreatment BP levels.

In summary, contrary to the rebuttal argument posed by Antares, both INH and IDH carry a substantially increased cardiovascular risk versus normotension. Depending on the manner in which the ABPM data was analyzed, a significant number of subjects had a substantial increase in blood pressure after 12 weeks of treatment. Drug-related small central tendency increases in BP are likely to predispose to future CV events.

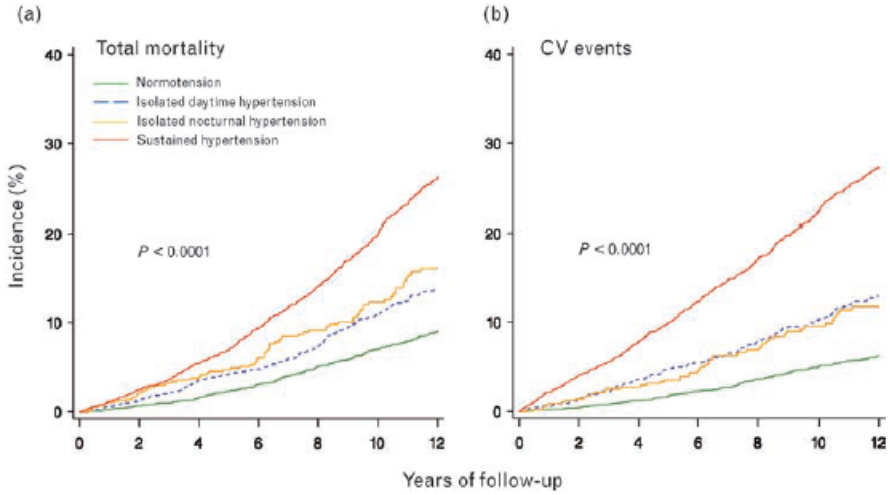
Table 1: Incidence of Events by Ambulatory Blood Pressure Status

	Normotension	Isolated nocturnal hypertension	Isolated daytime hypertension	Sustained hypertension
Number of participants	3837	577	994	3303
All-causes mortality				
Number of deaths	295	81	128	780
Crude rate	7.6 (6.7–8.4)	14.7 (11.5–17.9)‡	12.4 (10.3–14.6)‡	24.1 (22.4–25.8)‡
Standardized rate	10.6 (5.9–15.3)	13.9 (2.2–25.6)	11.2 (3.3–19.1)	18.5 (11.6–25.4)
Cardiovascular mortality				
Number of deaths	76	22	46	357
Crude rate	1.9 (1.5–2.4)	4.0 (2.6–5.7)†	4.5 (3.2–5.8)‡	11.0 (9.9–12.2)‡
Standardized rate	2.8 (0.7–4.9)	3.9 (0–8.7)	4.3 (0–9.0)	8.5 (4.1–12.8)
Noncardiovascular mortality				
Number of deaths	210	55	76	401
Crude rate	5.4 (4.6–6.1)	10.0 (7.3–12.6)†	7.4 (5.7–9.1)*	12.4 (11.2–13.6)‡
Standardized rate	7.5 (3.7–11.3)	9.3 (0.7–17.8)	6.5 (1.4–11.7)	9.2 (5.3–13.1)
All cardiovascular events				
Number of events	188	54	112	755
Crude rate	4.9 (4.2–5.6)	10.1 (7.4–12.8)†	11.2 (9.2–13.3)‡	25.1 (23.3–26.9)‡
Standardized rate	7.0 (3.3–10.7)	9.7 (0.3–19.2)	11.1 (0.9–21.3)	20.1 (12.4–27.8)
Cardiac events				
Number of events	108	31	73	406
Crude rate	2.8 (2.3–3.3)	5.7 (3.7–7.7)†	7.2 (5.6–8.9)‡	13.0 (11.8–14.3)‡
Standardized rate	4.0 (1.3–6.8)	5.6 (0–12.0)	6.5 (0.2–12.9)	10.7 (5.6–15.9)
Stroke				
Number of strokes	78	20	39	344
Crude rate	2.0 (1.6–2.5)	3.7 (2.1–5.3)*	3.8 (2.6–5.0)†	11.0 (9.9–12.2)‡
Standardized rate	2.7 (0.7–4.7)	3.4 (0–8.3)	4.4 (0–9.4)	8.5 (4.0–13.0)

Values are rates (95% confidence interval), expressed as number of events per 1 000 person-years. Rates are crude or standardized for cohort, sex, and age (≤40, 40–60, and ≥60 years) by the direct method. Significance of the difference with the normotensive reference group: *$P<0.05$, †$P<0.01$, and ‡$P<0.001$.

Source: Fan et al on behalf of the IDACO Investigators (2010)

Figure 1: Kaplan-Meier Curves for Total Mortality and CV Events



Cumulative incidence of total mortality (a) and all cardiovascular events (b) by ambulatory blood pressure status. *P* values are for the differences among the four categories by log-rank test.

Source: Fan et al on behalf of the IDACO Investigators (2010). *Note: CV events comprised of ischemic death, sudden death, non-fatal MI, coronary revascularization, fatal and non-fatal heart failure*.

Table 2: Hazard Ratios by Categories of Ambulatory Hypertension

Outcomes	Isolated nocturnal hypertension	Isolated daytime hypertension	Sustained hypertension
All-causes mortality (1284)	81	128	780
Unadjusted	1.99 (1.56–2.55)‡	1.67 (1.35–2.05)‡	3.26 (2.85–3.73)‡
Adjusted	1.29 (1.01–1.65)*	1.07 (0.86–1.32)	1.51 (1.31–1.74)‡
Cardiovascular mortality (501)	22	46	357
Unadjusted	2.10 (1.31–3.38)†	2.32 (1.61–3.35)‡	5.78 (4.51–7.40)‡
Adjusted	1.30 (0.80–2.09)	1.38 (0.95–2.00)	2.19 (1.69–2.85)‡
Noncardiovascular mortality (742)	55	76	401
Unadjusted	1.89 (1.41–2.55)‡	1.38 (1.07–1.80)*	2.35 (1.98–2.77)‡
Adjusted	1.23 (0.91–1.66)	0.90 (0.69–1.18)	1.19 (0.99–1.43)
All cardiovascular events (1109)	54	112	755
Unadjusted	2.08 (1.53–2.81)‡	2.28 (1.81–2.89)‡	5.16 (4.40–6.06)‡
Adjusted	1.38 (1.02–1.87)*	1.46 (1.15–1.85)†	2.48 (2.10–2.94)‡
Cardiac events (618)	31	73	406
Unadjusted	2.05 (1.38–3.06)‡	2.56 (1.91–3.45)‡	4.66 (3.77–5.76)‡
Adjusted	1.41 (0.94–2.10)	1.53 (1.13–2.07)†	2.30 (1.84–2.88)‡
Stroke (481)	20	39	344
Unadjusted	1.85 (1.13–3.02)†	1.90 (1.29–2.78)†	5.52 (4.32–7.06)‡
Adjusted	1.21 (0.74–1.98)	1.35 (0.91–2.00)	2.64 (2.04–3.43)‡

Hazard ratios (95% confidence intervals) express the risk relative to the normotensive group. Numbers of cases are given for each endpoint. The cause of death was unknown in 41 cases. Cox models were adjusted for cohort, sex, age, body mass index, smoking and drinking, serum cholesterol, history of cardiovascular disease and diabetes mellitus. Significance of the hazard ratios: *$P < 0.05$, †$P < 0.01$, and ‡$P < 0.001$.

Source: Fan et al on behalf of the IDACO Investigators (2010)

4) Effect of XYOSTED™ on patients with co-existing hypertension

Antares Statement of Issue

"We are concerned that these unexpected findings based on data from a largely normotensive population may underestimate the effects of your drug on blood pressure in the real world setting, where many patients have co-existing hypertension, with the potential to increase the risk for adverse cardiovascular outcomes."

Antares Rebuttal

Data is presented showing that similar numbers of subjects receiving BP medications and not receiving BP medications were enrolled in QST-15-005. Blood pressure responses to testosterone were similar in each group at week 6 and week 12 for both SBP and DBP in subjects with ≥ 18 hourly ABPM determinations. These findings indicate that blood pressure medication has little impact upon the magnitude of the BP changes.

Data is presented that capture the change in BP for patients without hypertension and with hypertension according to ABPM criteria (i.e., SBP > 130 mmHg or DBP > 80 mmHg). Patients with overtly hypertensive 24-hour blood pressure measurements by ABPM have BP changes of smaller magnitude than those entering the study normotensive. These findings are consistent with regression to the mean and do not demonstrate increased susceptibility to drug-induced hypertension in patients with hypertension at baseline.

DCRP Comment

We agree with the Applicant.

We performed our own analysis showing the change from baseline in average 24-hour ABPM recordings at week 6 and week 12 (Table 3). We also performed a sensitivity analysis removing subjects taking concomitant antihypertensive medications (Table 4). There was no impact on the results when subjects taking concomitant antihypertensive medications were removed.

A scatter plot showing the change from baseline in both SBP and DBP as a function of average 24-hour baseline ABPM is shown in Figure 2. An inverse relationship was observed. Subjects with a higher blood pressure did not experience further increments of blood pressure while on treatment. This finding was consistent with the Applicant's analysis that the elevations in blood pressure were driven by subjects who were normotensive at baseline. The implication for this finding is unclear and could reflect a regression to the mean.

Table 3: Change from Baseline in Average 24-hour ABPM Recordings

Variable	Visit	Total	Mean	Median	SD	Min	Max
ΔSBP	WEEK 6 (DAY36)	106	3.5	3.8	9.7	-16.3	41.2
	WEEK 12 (DAY78)	98	3.7	3.3	11.0	-20.5	31.1
ΔDBP	WEEK 6 (DAY36)	106	1.2	1.0	4.6	-12.9	14.5
	WEEK 12 (DAY78)	98	1.3	1.4	6.0	-26.8	23.2

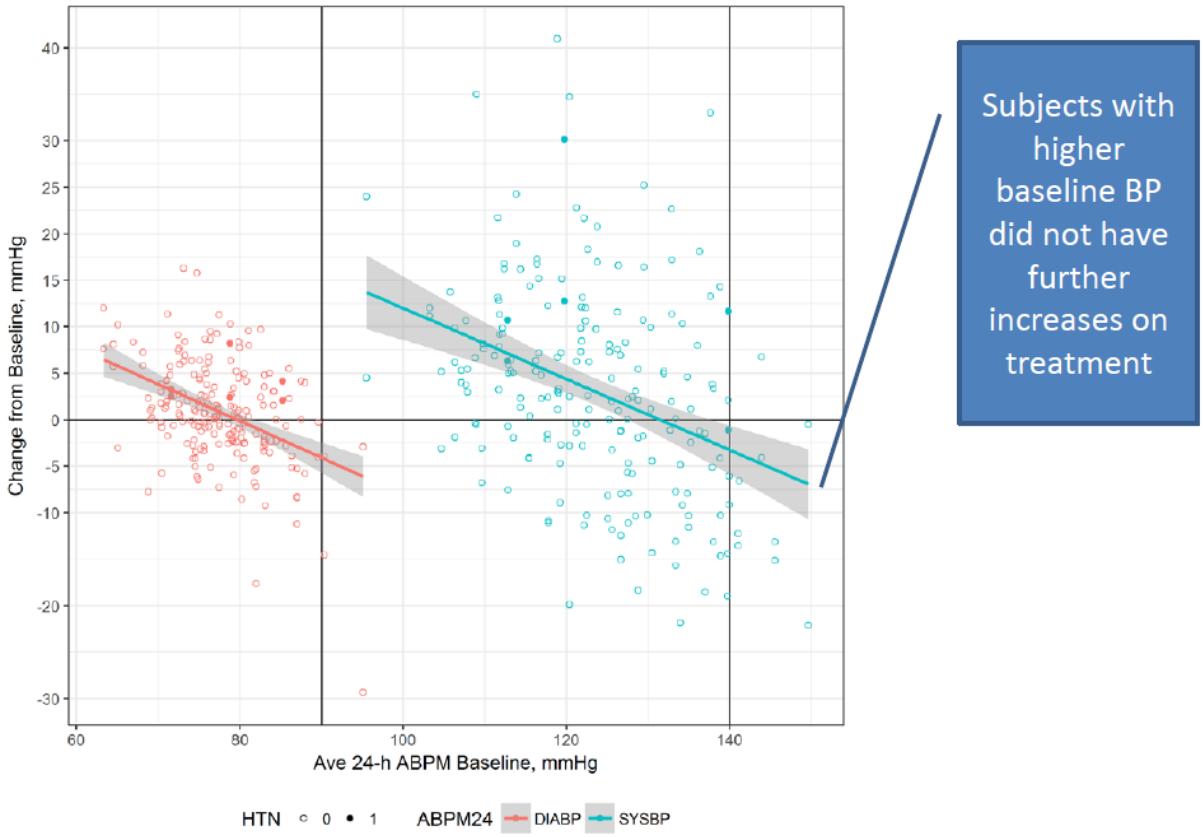
Source: Reviewer Analysis using ADZA2.xpt; cross-reference: (b) (4) report Table 14.2.3.1 (Dr. Christine Garnett, Clinical Analyst)

Table 4: Sensitivity Analysis-Removal of Subjects Taking Concomitant Antihypertensive Medications

Variable	Visit	Total	Mean	Median	SD	Min	Max
ΔSBP	WEEK 6 (DAY36)	58	3.0	2.7	10.7	-18.3	41.0
	WEEK 12 (DAY78)	50	3.8	5.2	12.2	-19.9	35.0
ΔDBP	WEEK 6 (DAY36)	58	0.6	0.3	4.6	-17.6	11.3
	WEEK 12 (DAY78)	50	2.0	1.7	5.5	-8.5	16.3

Source: Reviewer Analysis using ADZA2.xpt and CM.xpt (Dr. Christine Garnett, Clinical Analyst)

Figure 2: Scatter Plot-Change from Baseline vs Baseline SBP and Baseline DBP



Source: Reviewer Analysis (note: solid dot represents hypertension AE) (Dr. Christine Garnett, Clinical Analyst)

5) Cumulative distribution function curves and ABPM data

Antares Statement of Issue

The Agency response letter suggests that cumulative distribution function (CDF) curves demonstrate increases in SBP in up to 60% of patients.

Antares Rebuttal

Sixty percent (60%) of patients have an increase in BP of any degree above zero and 40% have a reduction in BP of any degree below zero. The clinical significance of a treatment, such as testosterone, resulting in both a +20 mmHg and a -20 mmHg change in BP, is unclear and is unlikely attributable to treatment alone. It is mechanistically implausible to believe that XYOSTED™ could be responsible for both extremes in increase and decrease.

DCRP Comment

We disagree with the Applicant's conclusion concerning implausibility.

The CDF curves suggested a normal distribution of subjects around the mean without a group of hyper-responders driving the overall small mean effect.

6) Analysis of changes in blood pressure medication

Antares Statement of Issue

In the CR Letter, the Agency states that approximately 9.5% of patients required initiation or adjustments of antihypertensive medications after initiation of treatment with XYOSTED™.

Antares Rebuttal

Only 4 patients in the 283-patient phase-3 population (1.4%) had changes to medicine for blood pressure for an elevated blood pressure arising after the first dose of study medication.

- In QST-13-003, 21 subjects received a change in dose or a new medication to treat hypertension (20 prior to XYOSTED™ administration and 1 post-administration).
- In QST-15-005, 6 patients had changes to antihypertensive medications post-administration: 3 to manage other conditions (1 for angina, 1 for edema, 1 peri-operatively), and 3 for increasing hypertension.

DCRP Comment

We agree with the Applicant regarding the small number of subjects who had changes in blood pressure medications.

Our analysis of QST-15-005 data showed that 4 subjects (3%) started either a new antihypertensive medication or had a dose change of an antihypertensive medication during the study. These subjects were:

- QST-15-005-(b) (6): started losartan on day 56 based on a hypertensive AE.
- QST-15-005-(b) (6): dose change of amlodipine, HCTZ/lisinopril, metoprolol, verapamil on day 151.
- QST-15-005-(b) (6): dose change of losartan on day 57.
- QST-15-005-(b) (6): started atenolol and HCTZ on days 98 and 147 (on antihypertensive at baseline).

Co-incidentally, there were 4 subjects who reported hypertension as an adverse event but only 1 of these (i.e., subject (b) (6)) started on new antihypertensive treatment.

7) Blood pressure changes in other approved testosterone products

Antares Statement of Issue

In its Complete Response letter, the Agency also suggested that findings related to the increase in blood pressure were “unexpected”.

Antares Rebuttal

The changes in BP observed with a number of other testosterone products are of similar magnitude as changes in BP during the XYOSTED™ program. From the FDA website, there are multiple occasions of hypertension or blood pressure changes related to testosterone supplementation documented in the product labels, NDA reviews, or in an advisory committee conducted by FDA, as well as in peer-reviewed medical literature and FAERS database. Therefore, the Antares contests the FDA's statement that changes in BP or hypertension are "unexpected findings".

- From a review of testosterone NDAs, the treatment-emergent adverse events of Hypertension ranged from 0.2% to 9.4% (mean 4.5%).
- The testosterone product AVEED (NDA 22-219) caused an increase of SBP by 1.5 mmHg -- 2.3 mmHg and DBP by 1-2 mmHg.
- In the clinical trial comparing JATENZO® to Androgel, currently under FDA review, the AC briefing document reported hypertension adverse events of 3.7% JATENZO® and 6.9% Androgel. After 1 year of treatment, the SBP and DBP rose by 3.3 mmHg and 1.6 mmHg respectively for JATENZO® and by 1.8 mmHg and 1.4 mmHg respectively for Androgel.

DCRP Comment

We agree with the Applicant's assertion that other testosterone products raised blood pressure by similar amounts compared with the Applicant's product, but we caveat our agreement by the observation that the data is sparse and there were no reported ABPM studies at the time of this NDA.

Blood pressure data with other testosterone products currently on the market is shown in Table 5. The data in this table were derived from product labels and medical officer reviews obtained from https://www.accessdata.fda.gov/scripts/cder/daf/. There was a paucity of blood pressure data from the other testosterone products and no reported ABPM studies. From the available data, hypertensive adverse events occurred in 1-4% of the safety population evaluated in other testosterone products. This was consistent with what was observed in the XYOSTED™ program. The ΔSBP/ΔDBP data from two products shown in the table are probably unreliable because they likely were measured by sphygmomanometry during office visits.

Most of the other testosterone labels have cardiovascular risk as a precaution.

Table 5: Testosterone Products and Blood Pressure Data

Product	Drug Substance	NDA /ANDA	Mean ΔSBP/ΔDBP	HTN AEs	CV Risk Label
ANDRODERM	testosterone	020489	--	---	Yes
ANDROGEL	testosterone	021015	--	3%	Yes
AVEED	Testosterone Undecanoate	022219	+2/+1	3%	Yes
AXIRON	testosterone	022504	0/0	4%	Yes
DELATESTRYL	Testosterone enanthate	009165	--	--	Yes
DEPO-TESTADIOL	Testosterone cypionate	017968			
DEPO-TESTOSTERONE	Testosterone cypionate	085635	--	--	Yes
FORTESTA	testosterone	021463	“small”	3%	Yes
NATESTO	testosterone	205488	-1-3/-2-5	2%	Yes
STRIANT	testosterone	021543	--	No	Yes
TESTIM	testosterone	021454	--	1%	Yes
TESTOPEL	testosterone	080911	--	--	--
TESTOSTERONE	testosterone	076737	--	--	--
TESTOSTERONE CYPIONATE	Testosterone Cypionate	040530	--	--	--
TESTOSTERONE CYPIONATE/ESTRADIOL CYPIONATE	Testosterone cypionate/estradiol cypionate	085603	--	--	--
TESTOSTERONE ENANTHATE	Testosterone enanthate	040575	--	--	--
TESTOSTERONE UNDECANOATE	Testosterone undecanoate	207583	Undergoing Review		
TESTRED	Methyl testosterone	083976	--	No	yes
VOGELXO	testosterone	204399	--	1%	yes

Source: https://www.accessdata.fda.gov/scripts/cder/daf/

8) Clinical significance of testosterone-mediated blood pressure changes

Antares Statement of Issue

In its CR letter, the Agency has suggested that increases in blood pressure seen with XYOSTED™ could be clinically meaningful, and thusly could have the potential for increased cardiovascular risk and adverse cardiac events.

Antares Rebuttal

The increase in blood pressure by XYOSTED™ is of a magnitude not dissimilar to widely used medications (e.g., glucocorticoids, decongestants, oral contraceptives, tricyclic antidepressants, venlafaxine, acetaminophen, and ibuprofen). The regulatory path to support safe long-term use of an effective product is labeling.

The ACCORD study (ACCORD Study Group, 2010), funded by NHLBI to examine the effect of blood pressure control in hypertensive diabetics, randomized 4733 patients to a standard control group with a targeted SBP $\leq$ 140 mmHg vs an intensive control group with a targeted SBP $\leq$ 120 mmHg. Despite achieving an actual difference of 14 mmHg between the groups, there was no difference in the composite endpoint of death, MI, or stroke at a mean follow-up of 4.7 years.

HOPE-3 (Lonn, 2016) was a double-dummy, double-blinded 2x2 factorial primary prevention trial in a population with intermediate cardiac risk of a first MACE event. Subjects were randomized to rosuvastatin vs placebo, candesartan/HCTZ vs placebo, and the combination of rosuvastatin-candesartan/HCTZ. Of 12,705 subjects, 6356 were randomly assigned to candesartan/HCTZ active (rosuvastatin active + rosuvastatin placebo) and 6349 to candesartan/HCTZ placebo (rosuvastatin active + rosuvastatin placebo). Both groups had a decrease in SBP from baseline, but the decrease was 6 mmHg greater for the candesartan/HCTZ active group compared to its placebo. There were no significant differences between the groups for MACE at a median follow-up of 5.6 years.

The ACCORD and HOPE-3 studies define the limits of the benefit for blood pressure control for primary prevention in patients at intermediate risk of CV events (i.e., typical of hypogonadal patients): 1) MACE outcomes are not improved by SBP control < 140 mmHg; 2) SBP lowering beyond 120 mmHg does not improve cardiac outcomes or survival, and 3) Differences in SBP of 6-14 mmHg do not affect cardiac outcomes. This perspective does not negate the need for blood pressure monitoring and treatment according to the current guideline. Labelling can reflect this need.

DCRP Comment

We disagree with the Applicant's conclusion regarding the limits of blood pressure control (i.e., irrelevance of blood pressure changes) on outcome.

In the ACCORD study of type 2 diabetic subjects, the average age was 62 years, 50% male, > 50% smoking (current or history of), average BMI 32 (i.e., obese), average HbA1c 8.3% (i.e.,

poorly controlled diabetes), average duration of diabetes 10 years (i.e., increased risk of end-organ damage) and average LDL 109 mg/dL. This represented a high risk population with many covariates. One might reasonably ask whether the benefit of lowering blood pressure alone in the setting of uncontrolled other high risk factors would mask the BP-lowering beneficial effect on MACE.

One might also reasonably ask whether the lack of an observed reduction in MACE consequent to lowering blood pressure as seen in the ACCORD and HOPE-3 studies implies that increasing blood pressure would have no effect on the risk of MACE in a population at risk.

As discussed under issue # 3, there is powerful epidemiologic evidence showing that as BP increases in a population, the risk of CV events increases (Sager et al, 2013).

We examined the effect of a +4 mmHg rise in SBP on a sample subject with relatively lower cardiovascular risk and a sample subject with a relatively higher cardiovascular risk. The increase in CV risk based on the blood pressure effect was estimated from the Framingham Risk Model (D'Agostino et al., 2008) shown in Table 6. A relatively lower risk patient defined as a 55 year old male, total cholesterol 185 mg/dL, HDL 43 mg/dL, non-treated SBP 127 mmHg, non-smoker, and non-diabetic had an estimated 10 year risk of 11.2%. A relatively higher risk patient defined as a 65 year old male, total cholesterol 240 mg/dL, HDL 43 mg/dL, non-treated SBP 127 mmHg, smoker, and diabetic has an estimated 10 year risk of 59.5%. An increase in the SBP by +4 mmHg increased the risk in the relatively lower risk patient from 11.2% to 11.8% (0.6 per 1000 patient-years). The same increase in SBP increased the risk in the relatively higher risk patient from 59.5% to 61.7% (2.2 per 1000 patient-years). This suggested that the rise in SBP caused by testosterone enanthate increased the absolute risk of a MACE in subjects with a higher baseline Framingham Model risk score more so than in subjects with a lower baseline score.

The increased risk of 2.2/1000 patient-years is modest. However, when administered chronically, this risk needs to be evaluated in light of the benefit of testosterone treatment.

Table 6: Framingham Risk Model for Male Taking QuickShot™ Testosterone

Risk Factor	Low CV Risk	High CV Risk
Age, y	55	65
Cholesterol, mg/dL	185	240
HDL, mg/dL	43	43
Non-treated SBP, mmHg	127 increased to 131 mmHg	127 increased to 131 mmHg
Smoker, yes (1) or no (0)	0	1
Diabetes, yes (1) or no (0)	0	1
Estimate of 10-y Risk, %	11.2 increased to 11.8	59.5 increased to 61.7
Absolute Risk Difference	0.6 events/1000 pt-yrs	2.2 events/1000 pt-yrs

Source: Reviewer's Analysis (Dr. Christine Garnett, Clinical Analyst)

9) Effect of other approved drugs on hypertension and corresponding label

Antares Statement of Issue

In its Complete Response letter, the Agency suggested the need for further clinical studies in order to better characterize the impact of the effect on blood pressure on the CV risk of XYOSTED™.

Antares Rebuttal

The effects on blood pressure of commonly used medications are and have been adequately handled with proper labeling and without the need for additional clinical studies. One example was the approval of Mirabegron in 2012 for overactive bladder (NDA 202-611) where the Agency sought to mitigate risk for safety events related to hypertension through clear, concise, and prescriptive safety language in the package inert. Another example is the hypertensive effect of NSAIDS where the Agency strengthened the existing warning in prescription drug labels and OTC Drug Acts labels to indicate that NSAIDs can increase the chance of a heart attack or stroke that can occur as early as the first few weeks of therapy. Antares concludes the same can be done for XYOSTED™ and without the need for further studies.

DCRP Comment

We agree with the Applicant.

Assuming that the benefit of XYOSTED™ outweighs the risk, we agree that the modest increase in cardiovascular risk in patients with pre-existing cardiovascular risk can be managed through labeling and possibly through risk mitigation. Specific warnings/precautions in section 5 of the label should state that XYOSTED™ is likely to increase systolic blood pressure in the first

12 weeks of treatment by a mean of 4 mmHg thereby increasing the risk of a major cardiac adverse event especially in patients with established cardiovascular disease or multiple risk factors. Prescribers should be counseled to check blood pressures after 12-weeks of initiation of testosterone and to manage new onset hypertension or exacerbation of pre-existing hypertension as clinically necessary.

References

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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Office of Pharmacovigilance and Epidemiology
Office of Surveillance and Epidemiology Review

Date:	March 8, 2018
Reviewer:	Wei Liu, PhD, MSc Division of Epidemiology II
Team Leader:	Jie (Jenni) Li, PhD Division of Epidemiology II
Division Deputy Director:	Lockwood Taylor, PhD Division of Epidemiology II
Subject:	Review of population-based, longitudinal follow-up studies assessing ambulatory blood pressure elevation and subsequent risk of serious cardiovascular events
Drug Name(s):	XYOSTED™ (Testosterone enanthate autoinjector)
Application Type/Number:	NDA 209863
Sponsor:	Antares Pharma
OSE RCM #:	2018-186

CONTENTS

EXECUTIVE SUMMARY

XYOSTED™ (previously known as QuickShot™) is a drug-device combination product of testosterone enanthate (TE) for use with an autoinjector. In October 2017, the applicant received a Complete Response (CR) regarding their New Drug Application (NDA) for XYOSTED. The agency was concerned about the potential for increased serious cardiovascular (CV) risks due to treatment with XYOSTED. In the phase 3 trial (QST-05-005), compared to baseline blood pressure (BP) measurements, the ambulatory systolic and diastolic BP increased by 3.7 and 1.3 mmHg respectively at Week 12. On December 21, 2017, the sponsor requested to have a Type A Meeting with FDA to discuss the issues raised in the CR and to confirm plans towards resubmission of the NDA. In the Briefing Package, the sponsor argued that because the XYOSTED "has little impact on SBP/DBP and the nighttime BP dipping pattern seems to improve over time, the CV risks from XYOSTED treatment is limited and such risk can be communicated to the medical community and potential users through labeling." The Division of Bone, Reproductive and Urologic Products (DBRUP) consulted the Division of Epidemiology (DEPI) to review and to comment on the observational studies relating the association between BP elevation and subsequent occurrence of adverse CV outcomes.

DEPI identified and reviewed a total of 21 articles published between 1999 and 2017. These are population-based, longitudinal follow-up studies designed to investigate the prognostic value of elevated BP and subsequent risk of CV events, CV and all-cause mortality. BP variation was measured via the 24-hour ambulatory blood pressure monitoring (ABPM). Mean follow-up time reported in these studies ranged from 4 to 16 years.

Overall, the observational studies included in this review suggest an association, albert modest in magnitude, between elevated daytime and nighttime BP and increased risk of CV morbidity and CV mortality. For each 1-standard deviation (SD) increment in BP, there was an approximately 20-50% increased risk of CV outcomes. Nighttime BP measurements seem to be stronger predictors of subsequent CV outcomes than daytime BP measurements. A small number of studies consistently support an association between non-dipping nighttime BP (less than normal decline of BP at night) and a higher risk of CV outcomes. Common limitations of these studies include small sample size (particularly in single-center studies) and heterogeneity in study design (e.g., difference in timing and frequency of ambulatory BP measurements, various lengths of follow-up). Most studies adjusted for patient demographics and baseline CV risk factors in regression models, thus confounding is not a major concern. However, we cannot rule out an effect of residual confounding on the observed associations (e.g., lack of information on change in antihypertensive treatment during follow-up, which may affect the outcome, was not available in most studies).

The sponsor suggests that (in Page 27 of meeting briefing document) "daytime BP did not independently predict mortality outcomes, and was only weakly associated with cardiovascular, coronary, and stroke events" by citing only two observational studies published in the literature (Dolan 2005; Fan 2010). DEPI disagrees to such a claim because our literature review finding is that daytime SBP significantly and independently predicts future risk of CV events (morbidity and mortality).

We also disagree to the claim (in Page 27 of meeting briefing document) that "during the prognostically important nocturnal period of BP measurement, the XYOSTED has little impact on mean systolic or diastolic BP measurements, and seems to increase the overall frequency of dipper." In our view, the proportion of non-dippers (66% at baseline and 57% at Week 12) in the sponsor's clinical trial data suggests a potential CV risk, because our literature review shows that nondipper

patients had worse CV outcomes compared to normal dippers. If approved, XYOSTED may be used by a large population of middle-aged men (with high prevalence of baseline cardiovascular disease) for a relatively long period of time. DEPI recommends the CV risks due to elevated BP be properly labeled for XYOSTED and a risk mitigation program be implemented to reduce potential adverse CV risks.

1 INTRODUCTION

XYOSTED™ (previously known as QuickShot™) is a drug-device combination product of testosterone enanthate (TE) for use with an autoinjector. It is indicated to treat adult men with low level of testosterone associated with symptomatic hypogonadism. In December 2016, the applicant submitted a New Drug Application (NDA) for XYOSTED. The sponsor completed two phase 3 pivotal trials (QST-13-003, QST-15-005) to determine the efficacy and safety of XYOSTED. On October 20, 2017, the sponsor received a Complete Response (CR) from the FDA. Among the issues that were discussed in the CR letter, the agency expressed concerns that the TE product could cause a clinically meaningful rise in blood pressure (BP), and the unexpected findings based on the data from a largely normotensive population may underestimate the effects of the drug on BP in the real-world setting, where many patients have co-existing hypertension, with the potential to increase the risk of serious cardiovascular (CV) outcomes.

Initial concerns for the potential increased CV risks with XYOSTED came from study QST-15-005,[a] where the data suggested a mean increase in 24-hour average ambulatory systolic blood pressure (SBP) of 3.7 mmHg and a mean increase of 24-hour average ambulatory diastolic blood pressure (DBP) of 1.3 mmHg at Week 12, compared to the baseline BP measurements. Among patients with at least 18 hours of BP readings over 24-hours, 15 (26%) had a SBP increase of greater than 10 mmHg or more at Week 12. The Division of Cardiovascular and Renal Products (DCRP) performed an independent analysis of the ABPM data and confirmed the findings reported by the sponsor (Fred Senatore. Review of Sponsor's Type A Meeting Package for a Post-Action CR. January 15, 2018).

On December 21, 2017, the sponsor filed a Post-Action Type A Meeting Request. The sponsor planned to discuss the issues that are raised in the CR with the FDA and to confirm plans to move towards resubmission of the NDA application via 505(b)(2) pathway. In the Type A Meeting Briefing Package, the sponsor identified following key elements from the hypertension discussion in the CR and provided a rebuttal of each element:

- *Patient population relative to hypertension and concomitant medications*
- *Blood pressure changes in the ambulatory blood pressure study clinical studies*
- *Effect of XYOSTED on hypertension defined by 24-hour mean systolic and diastolic criteria*
- *Effect of XYOSTED on patients with co-existing hypertension*
- *Cumulative distribution function curves and ambulatory blood pressure monitoring (ABPM) data*
- *Analysis of changes in blood pressure medication*
- *Blood pressure changes in other approved testosterone replacement therapy (TRT) products*
- *Clinical significance of blood pressure changes in TRT*
- *Effect of other approved drugs on hypertension and corresponding labeling*
- *Overall conclusions related to blood pressure changes on XYOSTED*
- *Proposed labeling change*

The sponsor argued that the ABPM study of XYOSTED-treated population appears to suggest a limited increase in CV risks associated with XYOSTED treatment, because the impact of XYOSTED on nocturnal blood pressure was small (e.g., at Week 12, nocturnal SBP rose on average 1.5 mmHg

[a] Clinic BP measures were analyzed in Study QST-13-003. Thus, only BP data from Study QST-15-005 are used for this discussion because ABPM provides a more reliable measure of a patient's BP variability than isolated clinic measures.

and DBP rose on average 0 mmHg; nocturnal BP decrease of 10% or more [e.g., nighttime BP dipping[1]] was observed in 34% of the subjects at the beginning of the trial and the number increased to 43% at Week 12) and the percent of patients with systolic or diastolic hypertension on-treatment changes very little.[b]

The sponsor included three observational studies in the Briefing Package to support their argument. The Dublin Outcome Study reported that nighttime is superior to daytime ABPM in predicting future CV mortality.[2] The International Database on Ambulatory Blood Pressure Monitoring in Relation to Cardiovascular Outcomes (IDACO) study showed that isolated nocturnal hypertension (e.g., an elevation of BP at night in the presence of a normal daytime BP) was associated with a significantly higher risk of mortality and CV events compared with normotensive individuals.[3] The Ohasama Study found an increased risk of CV mortality associated with diminished nocturnal decline in BP independent of the overall BP load during the 24-hour period.[4] In study QST-05-005, because there was an increasing number of subjects showing the standard nocturnal BP dipping and because of the very small increase in nighttime SBP and DBP observed at Week 12, the sponsor concluded that the data seems to support their argument that there is no major concern for serious CV outcomes for XYOSTED treatment. The sponsor also believes that through meaningful label revisions, the clinical benefit-risk of XYOSTED treatment can be appropriately determined by prescribers.

The Division of Bone, Reproductive and Urologic Products (DBRUP) consulted the Division of Epidemiology (DEPI) to review the published observational studies referenced in the 'Hypertension' section of the Briefing Package. To broaden the 'evidence-base', DEPI also searched literature to identify other observational studies that addressed the review question. Results of the review are reported in this document. Our review is focused on the relationship between daytime or nighttime elevation in SBP or DBP, nighttime dipping pattern and the risks of adverse CV outcomes.

2 REVIEW METHODS AND MATERIALS

DEPI reviewed the 3 observational studies included in the sponsor's Briefing Package (Fan 2010;[3] Dolan 2005,[2] Ohkubo 2002[4]).

Due to a potentially large number of relevant articles, DEPI selected additional studies using the 'Similar Articles Function' in the PubMed website (not by key words).[5] From more than 400 titles/abstracts we screened, DEPI retrieved 40 full-text articles and finally identified 21 eligible articles, defined as articles containing information on measurements of BP variability that was assessed through ambulatory blood pressure monitoring and the ABPM measurements are expressed as continuous variables (e.g., each 10/5 mmHg or 1 standard-deviation [1-SD] increment of SBP/DBP). To standardize reporting across different studies, we classified the CV outcomes into three groups: (1) total CV events which may include fatal or nonfatal stroke, myocardial infarction [MI], heart failure [HF], hospital admission due to cardiac causes, revascularization, deaths from other CV causes, (2) CV mortality including sudden cardiac deaths, deaths from coronary heart disease [CHD], stroke, or other vascular diseases, and (3) all-cause/total mortality.

In addition, we included Glynn et al. (2002)[6] article which used the self-reported BP data recorded in the Physicians' Health Study (PHS) and Women's Health Study (WHS) trials to build statistical

[b] Antares Type A Post-Action Meeting Package. NDA209863 QuickShot™ Testosterone Enanthate Injection, USP (QST) Type A, Post-Action Meeting, submitted on Dec. 21, 2017. EDR Location: //CDSESUB1/EVSPROD/NDA209863/209863.enx

models to predict the future risk of cardiovascular events. We also included two studies on additional safety outcomes: Ingelsson et al. (2006) examined the association between nocturnal BP pattern and the risk of congestive heart failure (CHF)[7], and Perkiomaki et al. (2017) studied various ABPM measurements and the long-term risk of atrial fibrillation (AF).[8]

We excluded studies that are conducted in special diseased populations (e.g., diabetic mellitus,[9-11] patients on hemodialysis[12]). When studies had several adjustment models, the relative risk estimates from fully adjusted models were extracted. We did not perform a manual search of the reference list from included full-text articles.

We decided not to combine the individual HR estimates using meta-analysis technique, due to the heterogeneity in design of reviewed studies.

3 REVIEW RESULTS

3.1 CHARACTERISTICS OF ENROLLED OBSERVATIONAL STUDIES

The 21 articles included in this review are published between 1999 and 2017. These are longitudinal follow-up studies conducted in Europe (e.g., Belgium, Finland, Sweden, UK), North America (US, Canada), and Asia (Japan, China). Study cohorts included community-based samples, elderly populations, and individuals with hypertension. Four studies reported data from multiple cohorts (Fan 2010[3]; Glynn 2002[6]; Palatini 2014[13]; Salles 2016[14]). The mean/median patient follow-up time reported in these studies ranged from 4 to 16 years. In most studies, baseline patient demographic variables and CV risk factors are included as covariates in the multivariate regression/prediction models. **Table 1** in the appendix summarizes the characteristics of the enrolled studies.

3.2 BP VARIABILITY MEASURED BY 24-HOUR ABPM AND RISK OF TOTAL CARDIOVASCULAR EVENTS

3.2.1 Systolic BP Changes

The relationship between daytime ambulatory SBP elevation and the risk of total CV events was evaluated in 8 articles (Bjorklund 2004[15], Dolan 2009[16]; Fagard 2005[17]; Fagard 2008[18]; Mesquita 2010[19]; Palatini 2014[13]; Staessen 1999[20], and Clement 2003[21]). These articles plus the article by de la Sierra et al. (2011)[22] examined the relationship between nighttime ambulatory SBP increase and risk of total CV events. Eight studies reported the relationship between change in average 24-hour ambulatory SBP and the risk of total CV events (Dolan 2009[16]; Fagard 2008[18]; Mesquita 2010[19]; Palatini 2014[13]; Salles 2016[14]; Staessen 1999[20]). Clement et al.'s article (2003)[21] was conducted in patients with treated hypertension. de la Sierra et al. (2011)[22] conducted subgroup analyses in subjects with or without a prior history of CV disease.

In five of the 8 studies, daytime SBP elevation significantly and independently predicted the risk of CV events. Of these 5 studies, the multivariate-adjusted (MV-adjusted) hazard ratio (HR) ranged from 1.18 to 1.47 for each 1 standard deviation (e.g., 1-SD) higher daytime SBP (**Table 1**). In the remaining 3 studies, there was a non-significantly increased risk associated with a 1-SD increment of daytime SBP (MV-adjusted HR ranged from 1.03 to 1.11).

Increase in nighttime SBP was a statistically significant predictor of the risk of CV events in all 9 studies reviewed (MV-adjusted HR ranged from 1.21 to 1.57 for a 1-SD or 10 mmHg increment in nighttime SBP). In patients with treated hypertension, Clement et al. (2003) reported a HR for total CV events of 1.40 (95% CI: 1.20-1.65) for each 1-SD increment in nighttime SBP after adjusting for other

CV risk factors. However, the MV-adjusted HR dropped to 1.27 (95% CI: 1.07-1.51) after additional adjustment for office BP measures at baseline.[21] In the de la Sierra (2012) study, nighttime SBP was significantly associated with future occurrence of CV events (MV-adjusted HR=1.45, 95% CI: 1.29-1.59 for each 1-SD increment). In sensitivity analysis, the MV-adjusted HR for a 1-SD increase in nighttime SBP was 1.21 (95% CI: 1.02-1.38) in subjects with a previous history of CV disease; the corresponding HR for those without a history of CV disease was 1.53 (95% CI: 1.36-1.71).[22]

Five of the 8 articles showed a statistically significant increased risk for CV events associated with the 24-hour average SBP increase. For each 1-SD increment of 24-hour SBP, the MV-adjusted HR ranged from 1.23 to 1.50. In three studies, there was a non-significantly increased risk (MV-adjusted HR ranged from 1.18 to 1.22 for a 1-SD increment).

Table 1 Increase in ambulatory systolic blood pressure and risk of total cardiovascular events

	Hazard ratio (HR), 95% confidence interval (CI)		
	Daytime average	Nighttime average	24-hour average
Bjorklund, 2004†	1.23 (1.07-1.42)	1.18 (1.03-1.34)	1.23 (1.07-1.42)
Clement, 2003†	1.47 (1.24-1.74)	1.40 (1.20-1.65)	1.50 (1.27-1.78)
de la Sierra, 2011†	N.A.	1.45 (1.29-1.59)	N.A.
Dolan, 2009†	1.18 (1.00-1.37)	1.25 (1.08-1.46)	1.29 (1.10-1.51)
Fagard, 2005†	1.33 (1.07-1.64)	1.42 (1.16-1.74)	N.A.
Fagard, 2008†	1.03 (0.77-1.36)	1.34 (1.06-1.69)	1.20 (0.91-1.58)
Mesquito, 2010†	1.33 (1.10-1.60)	1.57 (1.32-1.86)	1.41 (1.20-1.65)
Palatini, 2014‡	1.05 (0.84-1.33)	1.48 (1.20-1.84)	1.22 (0.93-1.60)
Salles, 2016†	N.A.	N.A.	1.39 (1.27-1.51)
Staessen, 1999‡	1.11 (0.98-1.25)	1.21 (1.09-1.35)	1.18 (0.96-1.34)

† for a 1-SD (standard deviation) increment; ‡ for each 10 mmHg increment
N.A.=not available

3.2.2 Diastolic BP Changes

Six studies reported daytime or nighttime ambulatory DBP increase and the risk of total CV events (Lind 2004[15], Clement 2003[21]; Fagard 2005**[17]**; Fagard 2008[18]; Mestiquita 2010[19]; Palatini 2014[13]). Five of the 6 studies also reported the association between increase in 24-hour average DBP and risk of total CV events (Lind 2004[15], Fagard 2008[18]; Mesquita 2010[19]; Palatini 2014[13]).

Nighttime DBP elevation was significantly and independently associated with increased risk of CV events in 5 studies (**Table 2**). For each 1-SD increment in nighttime DBP, the MV-adjusted HR ranged from 1.26 to 1.82. Daytime and 24-hour average DBP were weaker predictors of CV events compared to nighttime DBP. For the association between daytime DBP and risk of CV events, a statistically significant association was observed in 2 studies with the MV-adjusted HR ranging from 1.26 to 1.35 for a 1-SD increment in daytime DBP. Three of the 5 studies reported that 24-hour average DBP was

significantly associated with an increased risk of CV events (MV-adjusted HR ranged from 1.30 to 1.48 for a 1-SD increment in 24-hour average DBP).

Table 2 Increase in ambulatory diastolic blood pressure and risk of total cardiovascular events

	Hazard ratio (HR), 95% confidence interval (CI)		
	Daytime average	Nighttime average	24-hour average
Bjorklund, 2004†	1.01 (0.87-1.17)	1.05 (0.91-1.22)	1.03 (0.89-1.20)
Clement, 2003†	1.35 (1.13-1.61)	1.26 (1.06-1.50)	1.32 (1.11-1.57)
Fagard, 2005†	1.26 (1.00-1.59)	1.40 (1.16-1.74)	N.A.
Fagard, 2008†	1.08 (0.83-1.40)	1.38 (1.12-1.75)	1.21 (0.92-1.61)
Mesquito, 2010†	0.99 (0.98-1.02)	1.37 (1.13-1.66)	1.30 (1.06-1.59)
Palatini, 2014‡	1.14 (0.83-1.56)	1.82 (1.36-2.44)	1.48 (1.03-2.12)

† for a 1-SD (standard deviation) increment; ‡ for each 10 mmHg increment
N.A.=not available

3.3 BP VARIABILITY MEASURED BY 24-HOUR ABPM AND RISK OF CARDIOVASCULAR MORTALITY

3.3.1 Systolic BP Changes

Four articles reported the predictive value of daytime and nighttime ambulatory SBP variation on the risk of CV mortality (Fagard 2008[18]; Kikuya 2005[23]; Palatini 2014[13]; Staessen 1999[20]). Seven articles assessed the predictive value of 24-hour average SBP variability and risk of CV mortality (Fagard 2008[18]; Dolan 2005[2]; Huang 2011[24]; Kikuya 2005[23]; Palatini 2014[13]; Salles 2016[14]; Staessen 1999[20]).

As shown in **Table 3** below, nighttime SBP elevation was a statistically significant predictor of CV mortality in all 4 studies reviewed (MV-adjusted HR ranged from 1.23 to 1.83 for a 1-SD or 10 mmHg increment). Results were mixed for the daytime or 24-hour average SBP. For each 1-SD or 10 mmHg increment in daytime SBP, a significantly increased CV mortality risk was observed in one study (MV-adjusted HR=1.23, 95% CI: 1.10-1.58). A non-significantly increased risk was seen in the other 3 studies (MV-adjusted HR ranged from 1.06 to 1.49 for each 1-SD or 10 mmHg daytime SBP increment). In five of the 7 studies, there was a statistically significant increased association between CV mortality and a higher 24-hour ambulatory SBP (MV-adjusted HR ranged from 1.19 to 1.84 for each 1-SD or 10 mmHg increment).

Table 3 Increase in ambulatory systolic blood pressure and cardiovascular mortality

	Hazard ratio (HR), 95% confidence interval (CI)		
	Daytime average	Nighttime average	24-hour average
Fagard, 2008†	1.06 (0.75-1.49)	1.41 (1.06-1.87)	1.23 (0.88-1.71)
Doland, 2005‡	N.A.	N.A.	1.19 (1.13-1.27)

Huang, 2011†	N.A.	N.A.	1.71 (1.16-2.52)
Kikuya, 2005‡	1.23 (1.10-1.58)	1.34 (1.14-1.59)	1.32 (1.10-1.58)
Palatini, 2014‡	1.49 (0.93-2.38)	1.83 (1.17-2.86)	1.84 (1.08-3.13)
Salles, 2016	N.A.	N.A.	1.51 (1.37-1.68)
Staessen, 1999‡	1.17 (0.96-1.44)	1.23 (1.03-1.46)	1.20 (0.98-1.49)

† for a 1-SD (standard deviation) increment; ‡ for each 10 mmHg increment
N.A.=not available

3.3.2 Diastolic BP Changes

Predictive significance of daytime or nighttime DBP and risk of CV mortality was reported in three studies (Fagard 2008[18], Kikyua 2005[23], Palatini 2004[13]). A statistically significant association between daytime SBP and CV mortality was observed in one study (MV-adjusted HR=1.94, 95% CI: 1.01-3.74 for 10 mmHg increment). In two of the 3 studies reviewed, there was a significant association between nighttime SBP and CV mortality (MV-adjusted HR was 1.19 and 3.34 for each 5 and 10 mmHg increase, respectively). Two studies showed a statistically significant association between 5/10 mmHg increase in 24-hour average DBP and CV mortality (MV-adjusted HR ranged from 1.09 to 3.35, although the remaining two studies showed a statistically non-significant increased risk (**Table 4**).

Table 4 Increase in ambulatory diastolic blood pressure and cardiovascular mortality

	Hazard ratio (HR), 95% confidence interval (CI)		
	Daytime average	Nighttime average	24-hour average
Fagard, 2008†	0.97 (0.70-1.34)	1.33 (0.97-1.83)	1.06 (0.75-1.52)
Doland, 2005‡	N.A.	N.A.	1.09 (1.02-1.11)
Kikuya, 2005‡	1.10 (0.95-1.26)	1.19 (1.02-1.38)	1.13 (0.97-1.33)
Palatini, 2014§	1.94 (1.01-3.74)	3.34 (1.83-6.11)	3.35 (1.61-6.96)

† for a 1-SD (standard deviation) increment; ‡ for each 5 mmHg increment; § for each 10 mmHg increment
N.A.=not available

3.4 BP VARIABILITY MEASURED BY 24-HOUR ABPM AND ALL-CAUSE MORTALITY

3.4.1 Systolic BP changes

Five studies reported the association between day- or night-time SBP increase and all-cause mortality (Ben-Dov 2007[25]; Clement 2003[21]; Fagard 2008[18]; Palatini 2014[13]; Staessen 1999[20]). Seven studies reported the risk of all-cause mortality associated with rising 24-hour SBP recording (Clement 2003[21]; Dolan 2005[2]; Fagard 2008[18]; Huang 2011[24]; Palatini 2014[13]; Salles 2016[14]; Staessen 1999[20]).

As shown in **Table 5**, only one article (Ben-Dov et al. 2007) reported a statistically significant association between a 1-SD increase in daytime SBP and the risk of all-cause mortality (MV-adjusted HR=1.32, 95% CI: 1.19-1.47). Three of the five articles reported a significantly increased risk of all-cause mortality associated with a 1-SD increase in nighttime SBP (MV-adjusted HR ranged from 1.17 to 1.83). Increasing mean value of 24-hour SBP was a significant predictor of all-cause mortality in

three of the 7 articles reviewed (MV-adjusted HR ranged from 1.09 to 1.71 for each 1-SD or 10 mmHg BP increment).

Table 5 Increase in ambulatory systolic blood pressure and all-cause mortality

	Hazard ratio (HR), 95% confidence interval (CI)		
	Daytime average	Nighttime average	24-hour average
Ben-Dov, 2007†	1.32 (1.19-1.47)	1.35 (1.22-1.49)	N.A.
Clement, 2003†	1.18 (0.94-1.50)	1.18 (0.94-1.49)	1.18 (0.94-1.48)
Dolan, 2005‡	N.A.	N.A.	1.13 (1.08-1.19)
Fagard, 2008†	0.97 (0.74-1.28)	1.24 (0.99-1.56)	1.09 (0.84-1.43)
Palatini, 2014‡	1.35 (0.93-1.95)	1.83 (1.32-2.54)	1.71 (1.13-2.58)
Salles, 2016†	N.A.	N.A.	1.26 (1.15-1.39)
Staessen, 1999‡	1.17 (0.96-1.44)	1.23 (1.03-1.46)	1.20 (0.98-1.49)

† for a 1-SD (standard deviation) increment; ‡ for each 10 mmHg incremen
N.A.=not available

3.4.2 Diastolic BP changes

None of the 4 studies reported a statistically significant association between daytime DBP variability and all-cause mortality (Ben-Dov 2007[25]; Clement 2003[21]; Fagard 2008[18]; Palatini 2014[13]). Two of the 4 studies reported a statistically significant association between a 1-SD or 5 mmHg nighttime DBP increase and enhanced risk of all-cause mortality, with MV-adjusted HR ranged from 1.21 to 2.76. Two studies showed a significant association between increasing 24-hour average DBP recording and the risk of all-cause mortality with MV-adjusted HR ranged from 1.05 (for 5 mm Hg increment) to 2.32 (for 10 mmHg increment).[2,13]

Table 6 Increase in ambulatory diastolic blood pressure and all-cause mortality

	Hazard ratio (HR), 95% confidence interval (CI)		
	Daytime average	Nighttime average	24-hour average
Ben-Dov, 2007†	1.12 (0.98-1.27)	1.21 (1.09-1.36)	N.A.
Clement, 2003†	1.22 (0.95-1.56)	1.22 (0.96-1.56)	1.22 (0.96-1.55)
Dolan, 2005‡	N.A.	N.A.	1.05 (1.02-1.09)
Fagard, 2008†	0.97 (0.74-1.26)	1.23 (0.94-1.60)	1.07 (0.80-1.42)
Palatini, 2014§	1.57 (0.96-2.55)	2.76 (1.76-4.32)	2.32 (1.34-4.01)

† for a 1-SD (standard deviation) increment; ‡ for each 5 mmHg increment; § for each 10 mmHg increment
N.A.=not available

3.5 NOCTURNAL DIPPING AND CARDIOVASCULAR OUTCOMES

Salles et al. (2016) examined the prognostic value of nocturnal SBP fall and risk of adverse CV outcomes in hypertensive patients enrolled in the Ambulatory Blood Pressure Collaboration in Patients with Hypertension (ABC-H) study. Non-dipping was defined as the absence of nocturnal SBP decline by 10%. Compared to normal dippers, nondippers had worse CV outcomes compared to normal dippers. The HR for total CV events increased by 39% (MV-adjusted HR=1.39, 95% CI: 1.27-1.51). The HR for CV mortality and all-cause mortality increased by 51% (MV-adjusted HR=1.51, 95% CI: 1.37-1.68) and 26% (MV-adjusted HR=1.26, 95% CI: 1.15-1.39), respectively.[14]

Using the Spanish ABPM data, Hermida et al. found that, among normotensive individuals, nondippers (e.g., nighttime relative SBP decline < 10%) had a higher risk of total CV events compared with normal dippers (MV-adjusted HR=1.61, 95% CI: 1.09-2.37). Similar result was observed in hypertensive individuals, the MV-adjusted HR was 1.54 (95% CI: 1.01-2.36) comparing nondippers to normal dippers.[26]

In Ohasama Study, each 5% decrease in the decline of nocturnal SBP was associated with a 18% increase in the risk of CV mortality (95% CI: 7-28%); each 5% decrease in the decline of nocturnal DBP was associated with about 20% increase in the risk of CV mortality (95% CI: 8-30%). This increased risk due to diminished nocturnal BP decline was present regardless of the average 24-hour ABPM values[4]

Using the ABPM Service Database in Israel, Ben-Dov et al. found that the MV-adjusted HR for all-cause mortality was 1.30 (95% CI: 1.00-1.69) comparing non-dippers with normal dippers. Among hypertensive individuals, the MV-adjusted HR was 1.33 (95% CI: 1.04-1.71) comparing nondippers to dippers.[25]

3.6 OTHER STUDIES REVIEWED BY DEPI

The International Database on Ambulatory Blood Pressure in Relation to Cardiovascular Outcomes (IDACO) was a multi-center study designed to test the prognostic significance of nocturnal BP in individuals with normal daytime BP on office or on ambulatory measurement. Isolated daytime hypertension (IDH) based on ABPM was defined as daytime ambulatory BP ≥ 135/85 mmHg and nighttime ambulatory BP < 120/70 mm Hg; isolated nighttime hypertension (INH) was defined as daytime BP < 135/85 mmHg and nighttime BP ≥ 120/70 mmHg. In MV-adjusted analyses, INH was associated with a significantly increased risk of all-cause mortality (HR=1.29, 95% CI: 1.01-1.65) and total CV events (HR=1.38, 95% CI: 1.02-1.87). The IDH was associated with significant increases in all CV events (HR=1.46, 95% CI: 1.15-1.85) but not all-cause mortality (MV-adjusted HR=1.07, 95% CI: 0.86-1.32).[3]

In a prospective, population-based cohort study, 903 Finnish with or without hypertension aged 40 to 59 years were followed for a mean period of 16 years. Among the components of baseline ABPM measures, nighttime average SBP had the strongest univariate association with risk of new onset of atrial fibrillation (AF). After adjusting for other baseline covariates, higher nighttime SBP retained as a significant predictor of the outcome. For every 5 mmHg increase in nighttime SBP, the risk of AF increased by 7% (MV-adjusted HR=1.07, 95% CI: 1.004-1.15).[8]

Using the self-reported BP measures in PHS and WHS trials, Glynn et al. (2002) reported that both SBP and DBP were significant contributors in the subsequent development of CV events. For each 10 mmHg increase in self-reported SBP, the MV-adjusted HR was 1.20 (95% CI: 1.16-1.24) in males and

1.30 (95% CI 1.22-1.38) in females. For each 10 mmHg increase in self-reported DBP, the MV-adjusted HR was 1.32 (95% CI: 1.24-1.40) in males and 1.25 (95% CI: 1.12-1.39) in females.[6]

Using the Uppsala Longitudinal Study of Adult Men Cohort data, Ingelsson et al. developed multivariate prediction models to quantify the risk of incident congestive heart failure (CHF) associated with the 24-hour ABPM variables in a community-based sample of 951 Swedish elderly men followed prospectively for more than 9 years. After adjusting for antihypertensive treatment and other established CHF risk factors (smoking, BMI, MI, diabetes, serum cholesterol level), each 1-SD (~ 9 mmHg) increase in nighttime ambulatory DBP increased the risk of CHF by 26% (MV-adjusted HR=1.26, 95% CI: 1.02-1.55). A 'nondipping' BP pattern increased the risk of CHF by more than 2-fold (MV-adjusted HR=2.29, 95% CI: 1.16-4.52) even after adjusting for conventional office BP measurement.[7]

4 DISCUSSION

Epidemiology studies included in this review generally suggest an association, albert modest in magnitude, between elevated BP and risk of CV outcomes. Elevation of daytime and nighttime BP are both associated with increased risk of total CV events, CV disease mortality in primarily older men and women (mean age 55-71 years), and in patients with or without a prior history of CV disease. For each 1-SD increment in BP (daytime, nighttime, or 24-hour average), there is an approximately 20-50% fold increase in risk of CV outcomes (morbidity and mortality) during the course of an average 4-16 years of follow-up. Across all studies, nighttime BP measurements seem to be stronger predictors of subsequent CV outcomes than daytime BP measurements. Finally, a small number of studies consistently supports an association between non-dipping nighttime BP and a higher risk of CV outcomes.

Epidemiological studies covered by this review generally used population-based, longitudinal follow-up design to examine the prognostic importance of BP variability measured by 24-hour ABPM in predicting subsequent development of CV morbidity and/or CV mortality. Most studies applied repeated ABPM evaluations allowing assessment of BP variation during the years of follow-up. Limitations of these studies include small sample size (particularly in single-center studies) and heterogeneity in study design (e.g., differences in patient demographics as well as in ABPM methods such as timing and frequency of ambulatory BP measurement, varying length of follow-up). Most studies adjusted for patient demographics and baseline CV risk factors in regression models, thus confounding is not a major concern. However, we cannot rule out an effect of residual confounding on the observed associations (e.g., lack of information on change in antihypertensive treatment during follow-up, which may affect the outcome, was not available in most studies).

Our literature search may be incomplete due to the time constrain and the large number of relevant, published studies. However, the relative consistent evidence observed in the identified studies suggests that the impact of the potential incomplete search is likely minimal. Second, with regard to the measurement of BP variation, we took the continuous scale directly from each study. However, because BP distribution is influenced by several factors including age, gender, racial/ethnic group, and underlying health condition, a 1-SD elevation of each respective measurement in different studies may represent different level of BP elevation. For example, in the Dublin Outcome Study, 1-SD of 24-hour ambulatory SBP was 20.3 mmHg,[27] whereas in Japanese population, 1-SD of 24-hour ambulatory SBP was about 13 mmHg.[4,23]

5 CONCLUSIONS AND RECOMMENDATIONS TO DBRUP

The sponsor seems to suggest that (in page 27 of the meeting briefing document) 'daytime BP elevation did not independently predict mortality outcomes, and was only weakly associated with cardiovascular, coronary, and stroke events' by citing only two of the studies published in the literature (Dolan 2005[2]; Fan 2010[3]). DEPI disagrees to such claim because a large number of observational studies indicate that, not only nighttime BP, but also daytime BP changes, predicts a higher CV risk. Furthermore, the reviewed observational studies suggest that even a small increase in BP (e.g., 5/10 mmHg increment) could lead to significantly increased risk of long-term CV outcomes.

We also disagree with the sponsor's claims (in page 27 of the meeting briefing document) that 'during the prognostically important nocturnal period of BP measurement, the XYOSTED has little impact on mean systolic or diastolic BP measurements, and seems to increase the overall frequency of dipper.' In our view, more than half of the subjects showed abnormal dipping pattern (e.g., less than 10% nocturnal BP decline relative to daytime BP), the number of non-dippers in the clinical trial data suggests a potential CV risk, given that non-dipping is associated with a higher risk for CV outcomes.

If approved, XYOSTED may be used by a large population of middle-aged men (with high prevalence of baseline cardiovascular disease) for a relatively long period of time, which raise concerns for increased risk of long-term CV disease. DEPI recommends the CV risks due to elevated BP be properly labeled for XYOSTED and a risk mitigation program be implemented to reduce potential adverse CV risks.

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Appendix Table 1 Observational studies of ambulatory blood pressure measurements and subsequent risk of cardiovascular outcomes

Author, year	Place(s)	Time	Mean age, yrs.	Men, %	Follow-up time	Cohort description	Confounders
Ben-Dov, 2007	Israel	1991-2005	55 (16)	47	Median: 6.5 y	Patients in the ABPM Service Database, except those <16 years and pregnant women, and subjects with poor ABPM (<50 valid measurements)	Age, sex, hypertension, diabetes
Bjorklund, 2004	Sweden	1991-2000	71 (NA)	100	Mean: 6.6 (2)	70-year old men living in Uppsala, Sweden with valid 24-hour ABPM data at baseline	Antihypertensive treatment, smoking, diabetes, hyperlipidemia, BMI
Clement, 2003	Belgium	N.A.	56 (13)	48	Median: 5 y	Adults with documented hypertension, excluding those with recent stroke, AMI, hospitalization for chronic heart failure, revascularization, planned cardiovascular interventions, pregnancy	Age, sex, smoking, diabetes, serum cholesterol, BMI, use of lipid-lowering drugs, history of cardiovascular disease, clinic BP measures
de la Sierra, 2011	Spain	2005-2010	66 (11)	55	Median: 4 y	Spanish ABPM Registry including hypertensive patients with high or very high added cardiovascular risk	Age, sex, BMI, smoking, diabetes, glucose, creatinine, lipid profile, CHD, CHF, duration of hypertension
Dolan, 2005	Ireland	1980-2002	Alive: 51.5 (14.2); dead due to CVD: 67.5 (11.9)	Alive: 45%; dead due to CVD: 56%		Untreated hypertensive patients referred to a single blood pressure clinic with baseline clinic and ABPM measurements were followed prospectively for a mean follow-up time of 7.9 years (interquartile range, 5.6-10.6)	Age, gender, BMI, diabetes mellitus, history of cardiovascular events, current smoking status, clinic blood pressure measurements (CBPM)
Dolan, 2009	UK, Ireland, Scotland	N.A.	63 (9)		Median: 5.5 y	Adults 40-79 years old with hypertension and at least three other cardiovascular risk factors (ASCOT-BPLA Study)	Age, sex, BMI, smoking, diabetes, total cholesterol, clinic blood pressure, antihypertensive treatment group
Fagard, 2005	Belgium	1990-2003	71 (9)	40	Median: 10.9 y	Elderly patients registered in a primary care database in Flanders, Belgium	Age, gender, BMI, use of BP lowering drugs, smoking, serum cholesterol, diabetes, clinic BP measures
Fagard, 2008	Belgium	N.A.	69 (9)	50	Median: 6.76 y	Belgium ABPM database which contains hypertensive patients with history of cardiovascular disease	Age, sex, smoking, total cholesterol, diabetes, antihypertensive treatment and history of coronary heart disease, cerebrovascular disease and congestive

							heart failure and office BP measures.
Fan, 2010	10 centers in EU, Asia, America	N.A.	55 (15)	53%	Median: 10.7 y	Random sample of adults (≥18 years) with baseline data on ABPM, cardiovascular risk factors and biochemical measurements were followed prospectively for a median time of 10.7 years (5^{th} and 95^{th} interval 2.5-15.4). Classified into four groups: normotensive (e.g., reference group), untreated individuals with isolated daytime hypertension (IDH) based on ABPM, untreated individuals with isolated nocturnal hypertension (INH) based on ABPM, and patients with hypertension sustained in day- and night-time (IDACO Study)	Age, sex, BMI, smoking, drinking, serum cholesterol, history of cardiovascular disease, diabetes mellitus
Glynn, 2002	United States	N.A.	PHS: 53 (10); WHI: 54 (7)	100 (PHS) 0 (WHS)	PHS: 13 y WHS: 6.2 y	The Physician's Health Study (PHS): randomized trial of US male physicians, aged 40 to 84 years at baseline, without prior cardiovascular events. The Women's Health Study (WHS): randomized trial of US female health professionals aged ≥ 45 years without prior cardiovascular events	Age, BMI, current hypertension treatment, diabetes, parental history of MI before 60 y, smoking status (never, former, current), exercise (none, < 2times/week, ≥2 times/week), and alcohol intake (<1drink/week, 1-6 drinks/week, ≥1 drink/day)
Hansen, 2006	Denmark	N.A.	Range: 42-72	45	Mean: 9.5 y	A random sample of Danish men and women, aged 41 to 72 years, without major cardiovascular diseases	Age, current smoking, fasting blood glucose, ratio of total to HDL cholesterol
Hermida, 2013	Spain	2000-2007	54 (15)	47	Median: 5.6 y	MAPES study – Spanish subjects ≥ 18 years, either normotensive or untreated hypertensive, with baseline ABPM data	Age, sex, diabetes, sleep apnea, obesity, smoking chronic kidney disease, anemia, duration of nighttime sleep, glucose, creatinine, uric acid, cholesterol, triglycerides
Huang, 2011	Taiwan	N.A.	52 (13)	54	Median: 15 y	Community-based study in Taiwan which contains a cohort of normotensive or untreated hypertensive subjects	Age, sex, BMI, smoking, fasting plasma glucose, and total cholesterol/HDL cholesterol ratio
Ingelsson, 2006	Sweden	1990-2002	N.A.	100%	Median: 9.1 y	Community-based sample of elderly men free of congestive heart failure (CHF), valvar disease, and left ventricular hypertension at baseline; median follow-up time: 9.1 years (range: 0.1-11.4 years)	MI, diabetes, smoking, BMI, serum cholesterol, antihypertensive treatment

Kikuya, 2005	Japan	1987-2002	62 (10)	35	Median: 10.8 y	Individual residents aged 40 years or older from a general population of a rural Japanese community (Ohasama Study)	Age, sex, smoking, use of anti-hypertensive medication, history of cardiovascular complications, diabetes mellitus, hypercholesterolemia
Mesquita, 2010	Portugal	1991-2007	51 (12)	54	Mean: 8.2 y	Hypertensive population ≥ 18 years old, without history of congestive heart failure, cerebrovascular disease, MI, coronary bypass or angioplasty, cardiac valve disease, renal insufficiency, peripheral artery disease, atrial fibrillation or other major arrhythmias or hepatic disease	Age, sex, smoking, BMI, diabetes, antihypertensive treatment, office BP
Ohkubo, 2002	Japan	1987-2000	51 (15)	56	Median: 5.5	Individual residents aged 40 years or older from a general population of a rural Japanese community (Ohasama Study)	Age, sex, total cholesterol, serum creatinine, average ambulatory blood pressure, smoking, diabetes mellitus
Palatini, 2014	ABP Int'l Study	N.A.	61 (11)	40%	9 y	Multi-national prospective cohort studies including a random sample or untreated hypertensive, with baseline information on ABPM and CV risk factors	Age, sex, smoking, use of anti-hypertensive medication, history of cardiovascular complications, diabetes mellitus, hypercholesterolemia
Perkiomaki, 2017	Finland	N.A.	52 (6)	50	Mean: 16 y	Population-based prospective cohort study including subjects initially aged 40-59 years without significant heart disease	Age, BMI
Salles, 2016	10 cohorts in EU, Asia, America	N.A.	Range: 51-70	Range: 29-78	Median: 8 y	Hypertensive patients enrolled in the Ambulatory Blood Pressure Collaboration in Patients with Hypertension (ABC-H) study	Age, sex, diabetes, smoking, antihypertensive treatment, pre-existing CVD
Staessen, 1999	Europe	1988-1999	70 (6)	N.A.	Median: 4.4 y	Elderly patients (≥60 years) attending family practices and outpatient clinics at primary and secondary referral hospitals (Syst-Eur Trial).	Age, sex, cardiovascular complication at entry, current smoking status, residence in western Europe

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M E M O R A N D U M

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: March 6, 2018

To: Hylton V. Joffe, M.D., Director
Division of Bone, Reproductive, and Urologic Products

Through: Dominic Chiapperino, Ph.D., Acting Director
Martin Rusinowitz, M.D., Senior Medical Officer
Controlled Substance Staff

From: Alicja Lerner, M.D., Ph.D., Medical Officer
Controlled Substance Staff

Subject: **NDA 209863/IND 116022**
Name: XYOSTED, Testosterone Enanthate Injection, QuickShot™ USP, QST
Indication: Treatment of adult males with hypogonadism.
Dosage: 100 mg/ mL, 150 mg/mL, and 200 mg/mL with injection volume of 0.5 mL, administered subcutaneously, delivering 50, 75, or 100 mg of testosterone enanthate once weekly
Sponsor: Antares Pharma, Inc.
Internal meeting February 14, 2018
Type A, Post-Action Meeting with the Sponsor: Feb 21, 2018

Materials Reviewed:

- Updated briefing package in DARRTS Jan 19, 2018
- CSS Review by Dr. A. Lerner in DARRTS Oct 5 2017
- CSS review Testosterone TSI # 1351, by Dr. A. Lerner, March 9, 2015
- OSE/DPV review by R. Kapoor, PharmD, in DARRTS Aug 30 2017

A. SUMMARY

I. BACKGROUND

This memorandum responds to a consult from the Division of Bone, Reproductive, and Urologic Products (DBRUP) requesting the Controlled Substance Staff (CSS) to review and provide preliminary comments on the "Depression/Suicide" section of the meeting package, including the Sponsor's depression/suicide-related proposals.

The Sponsor has developed Testosterone Enanthate Injection for subcutaneous (SC) administration, under NDA (b) (4) with proposed trade name QuickShot™ (QST), for the treatment of adult men with hypogonadism. The QST is designed as a single-use, pressure-assisted autoinjector, prefilled with testosterone solution for SC self- administration.

QuickShot™ (QST) NDA (b) (4) was submitted as a 505(b)(2) NDA using Delatestryl® Injection as the approved listed drug (LD), however it received a Complete Response (CR) on October 20, 2017, due to clinically meaningful increases in blood pressure, as well as cases of suicidality (2) and depression (2).

The Sponsor requests a Type A – Post-Action Meeting to:

• Confirm that the FDA agrees with the proposals in the briefing book as a means of addressing the concerns raised in the CR letter.

• Better understand the FDA's remaining issues, and reach agreement on their resolution.

The Sponsor has submitted the following explanations regarding the occurrence of suicidality and depression during the NDA 209863 clinical studies:

1. It is known that depression is more common in men with hypogonadism than in eugonadal men, and that the increased frequency of depression is a known risk factor for suicidality.
    - In a study cited by the Sponsor (Westley, 2015), in a population that was referred for evaluation of borderline low testosterone levels, 56% of patients had depression or depressive symptoms.
    - In a study cited by the Sponsor (Zarrouf et al., 2009), it was noted that testosterone replacement therapy (TRT) may have an antidepressant effect in depressed patients, especially those with hypogonadism.
      (CSS note: The authors also observed, in their meta-analysis, that the subgroup treated with testosterone gel separated significantly from the group that received placebo, whereas the results with an intramuscular (IM) route of administration were not significantly different from those achieved with placebo.)
    - The Sponsor cites FAERS data from 2006-2016 that shows depression aggregated reporting among testosterone treated patients at a rate of 2.37%.
    - The Sponsor cites FAERS data from 2006-2016 showing aggregated reporting for suicidality among testosterone treated patients at a rate of 0.51%.

2. Sponsor states that although TRT may improve depression symptoms in older men with low testosterone level, FAERS data reviewed by the Sponsor, and the individual TEAEs from clinical development studies, suggest that mood worsening might occur despite TRT use.

3. The Sponsor provides data in the NDA on depression and suicide extracted from FDA reviews for multiple testosterone products which shows that, during TRT, the incidence of depression was up to 12.8% for Testim (NDA 21-454) and 10% for Androgel (NDA 21-015). There were cases of suicidality, either suicidal ideation (1 subject withTestim) or suicide attempt (1 subject with Androgel) and there were also 2 completed suicides (Aveed, NDA 22-219).

To mitigate the risk of depression and suicidality the Sponsor has proposed the following labeling changes (verbatim):

Section 5.16 (b) (4)
Suicidal ideation and behavior, including completed suicide, have occurred during clinical trials in patients treated with XYOSTED. Advise patients and caregivers to seek medical attention for manifestations of suicidal ideation or behavior, new onset or worsening depression, anxiety, or other mood changes.

The Sponsor has also posed the following questions regarding suicidality:

2. Does FDA agree that the sponsor's explanations, data interpretations and discussions of the issues pertaining to suicide ideation contained in the briefing book, along with the proposed labeling changes, are responsive to the suicide ideation issues raised in the October 20, 2017 CRL and may be adequate to support a re-submission, in response to that CRL?

a. If not, what specific issues remain unaddressed relative to suicide ideation, and can those issues be addressed via enhanced pharmacovigilance of adverse event reports of suicidal ideation and behaviors?

b. If they cannot be addressed via enhances pharmacovigilance in the Post Marketing setting, how does the FDA propose the sponsor address them, and why does the FDA feel such studies or data are scientifically required for approval?

3. After reviewing the enclosed Briefing Book, what issue does FDA feel still needs to be brought in front of an Advisory Committee meeting specific to XYOSTED?

CSS response to question 2:
For the Sponsor
We agree that the labeling changes in Warning and Precautions, section 5.16, are adequate to address the risk of suicidality. We also agree with your overall explanations, and the need for monitoring patients on testosterone replacement therapy (TRT) for depression and suicidality during the post-marketing period.

CSS RECOMMENDATIONS FOR THE DIVISION
Considering the seriousness and potential fatal outcome of the adverse event (AE) of suicidality, CSS agrees with the Sponsor that the discussion in Warnings and Precautions, section 5.16, of the label will resolve the issue and provide adequate warning for patients and physicians for this particular product. However, as the Sponsor indicates, there remain other cases of suicidality during other testosterone NDAs and, as described below, suicidality has been observed during post-marketing for a number of other testosterone products (OSE/DPV review by R. Kapoor, PharmD, 08/30/2017). Therefore, the language for section 5.16 should be added to all testosterone products. These are the reasons for this recommendation:

- OSE/DPV examined suicidality related to testosterone use in post-marketing data and identified 74 cases, including 15 cases of completed suicides, 13 cases of suicide attempt, and 46 cases of suicidal ideation reported with testosterone use. However, OSE/DPV provided a "high level summary of the FAERS cases review" of suicidality without analysis of individual cases or a literature search. CSS reviewed the individual cases (Dr. Lerner Oct 5 2017) and found that there were 3 types of AEs where there may be a causal relationship between testosterone treatment (or withdrawal of testosterone) and suicidality, where additional data would be helpful:
  -There were a number of cases where the onset of suicidality appears directly related to the initiation or treatment with TRT.
  -There were a number of cases where suicidality resolved upon testosterone discontinuation.
  -There were a number of cases where the onset of suicidality is directly related to the withdrawal of testosterone therapy.

- Depression and suicidality are known AEs in people abusing testosterone and anabolic steroids and may occur during the drug use or after drug discontinuation (CSS review Testosterone TSI # 1351, Dr. A. Lerner, March 9, 2015). The population of older hypogonadal men are at higher risk of depression (Barrett-Connor et al. 1999, Shores et al., 2004; Amore et al., 2008; Makhlouf et al., 2008). Additionally, depressed men with lower levels of testosterone were shown to be at higher risk of suicide (Sher, 2013). In the QST, NDA 209863, 15-30% of hypogonadal men had a history of depression, and some subjects were discontinued due to AEs of depression. Treatment with testosterone may cause depression as an AE (see labeling).

- The data from other testosterone NDAs, provided by the Sponsor, confirms the occurrence during TRT of depression , up to 12.8% for Testim, and 10% for Androgel (NDA 21-015) and there were cases of suicidality, either suicidal ideation (Testim) or suicide attempt (Androgel), (one subject in each) and there were also 2 completed suicides for Aveed (NDA 22-219).

- CSS agrees with the Sponsor that "*patients (particularly older patients) featuring depressed mood as part of their presentation may need to be monitored for response after testosterone is instituted and may require treatment with other more specific*"(page 50). We think that all patients receiving TRT should be monitored for depression and suicidality.

We agree with DPP that this formulation has misuse potential. We also think that this formulation is the most likely to be abused testosterone formulation on the market and will have higher potential for abuse and misuse by both men with hypogonadism and healthy men body builders and athletes. It should therefore be dispensed in small amounts and with periodic checks of testosterone levels.

CSS response to question 2 a, b:
For the Sponsor
If the above mentioned labeling changes are implemented, enhanced pharmacovigilance would help to address the issue of increased suicidality with QST treatment.

For the Division
We agree with DPP that monitoring for suicidality and depression should be incorporated in future studies. CSS believes that suicidality signal may be applicable for all testosterone products.

CSS response to question 3 for the Sponsor:

If the above mentioned label changes are implemented, we agree there is no need for an Advisory Committee.

CSS RECOMMENDATIONS FOR THE DIVISION

For all testosterone products consider adding in section 9.3, Dependence, "suicidality" as a possible adverse event following TRT discontinuation:

> *After the discontinuation of treatment with testosterone at therapeutic dose in hypogonadal men emergence of suicidality was observed.*

If there is a new TRT study with QST, consider the following:

1. During TRT, the tendency to develop depression and suicidality should be monitored with appropriate questionnaires.

2. CSS also recommends evaluation of dependence and withdrawal at the end of the trial(s) for potential development of depression and suicidality after discontinuation of therapeutic doses of testosterone. All AEs should be collected for at least 4 weeks from drug discontinuation, at weekly intervals. Additionally, we recommend that appropriate depression, suicidality, and insomnia scales be administered.

3. Abuse potential and misuse should also be monitored.. Refer to the *Guidance for Industry: Assessment of Abuse Potential of Drugs* (January 2017) for additional information.

IV. REFERENCES

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/s/

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03/06/2018

MARTIN S RUSINOWITZ
03/06/2018

DOMINIC CHIAPPERINO
03/06/2018

CONSULTATIVE REVIEW AND EVALUATION OF CLINICAL DATA

Consultant Reviewer:	Daniel Lee, MD, Medical Officer, ODE I-DPP
Consultation Requestor:	Jeannie Roule, RPM, ODE III-DBRUP
Subject of Request:	Concerns Related to Depression and Suicide Following Issuance of a Complete Response for NDA 209863
Date of Request:	01/02/2018
Date Received:	01/02/2018
Desired Completion Date:	02/01/2018

I. Consult Background

Antares Pharma, Inc. (henceforth referred to as the Sponsor) submitted a New Drug Application (NDA) on December 20, 2016, for a proposed auto-injectable testosterone replacement therapy developed for the treatment of men with hypogonadism. The NDA underwent review by the DBRUP for ten months and, on October 20, 2017, FDA issued a Complete Response Letter (CRL) to the Sponsor. The CRL expressed concerns regarding potential drug-induced elevation of ambulatory blood pressure, potential drug-induced depression, and potential drug-induced suicidal behavior.

The Sponsor re-analyzed data pertaining to these issues and requested a Type A Post-Action Meeting to reach agreement with DBRUP regarding issues involving a potential Advisory Committee meeting and product re-submission via the 505(b)(2) pathway. DBRUP requested the assistance of DPP in answering the Sponsor questions below.

II. Pre-Meeting Sponsor Question #2

2. Does FDA agree that the sponsor's explanations, data interpretations and discussions of the issues pertaining to suicide ideation contained in the briefing book, along with the proposed labeling changes, are responsive to the suicide ideation issues raised in the October 20, 2017 CRL and may be adequate to support a re-submission, in response to that CRL?

DPP Response: Yes, the Sponsor's assessment appears reasonable. While we do not feel labeling changes regarding depression and suicide are necessary based on the current safety signal, we cannot rule out the possibility that exposure to the testosterone auto-injector contributed to the observed depression and suicide events. Causality determination is confounded by the presence of multiple other potential causal factors in each case.

In-depth analysis revealed several significant commonalities shared between cases:

- ***both suicide cases occurred in white men significantly older than the median age of the cohort***
- ***all cases involved men with two or more chronic medical conditions***
- ***both depression cases involved men with chronic pain requiring multiple daily administrations of one or more opiates***
- ***both suicide cases involved interpersonal problems. The completed suicide appeared to involve interpersonal isolation and the attempt appeared to involve marital conflict.***

The four individuals in question were at an elevated risk of suicide prior to enrollment due to these commonalities. We acknowledge the fact that these cases occurred solely in the treatment arm; however, the timing of each event relative to product exposure and lack of resolution following de-challenge argue against direct attribution of depression and suicidal behavior to the product. The completed suicide occurred long after the product had been presumably cleared from the participant's system and all four events occurred after months of well-tolerated exposure to a presumably stable dose of testosterone. Please see our in-depth discussion of each case in Section IV for further details.

Our biggest concern with the testosterone auto-injector is the potential for misuse due to the Sponsor's plan to dispense the product in three-month increments. Testosterone is a potent psychotropic substance and, if overdose or misuse occurs, it is expected to precipitate extreme changes in behavior. This risk could be mitigated by dispensing the product in smaller quantites.

a. If not, what specific issues remain unaddressed relative to suicide ideation, and can those issues be addressed via enhanced pharmacovigilance of adverse event reports of suicidal ideation and behaviors?

DPP Response: If DBRUP plans to require no further pre-approval trials related to the hypertension concern, we believe enhanced pharmacovigilance for suicidal ideation, suicidal behaviors, and depression is sufficient for approval.

However, if DBRUP plans to require further pre-approval or postmarketing trials related to the hypertension concern, we recommend that direct monitoring and evaluation of depression, suicidal ideation, and suicide behavior be incorporated into these trials.

b. If they cannot be addressed via enhances pharmacovigilance in the Post Marketing setting, how does the FDA propose the sponsor address them, and why does the FDA feel such studies or data are scientifically required for approval?

Please see our answer to Question 2a above.

III. Pre-Meeting Sponsor Question #3

After reviewing the enclosed Briefing Book, what issue does FDA feel still needs to be brought in front of an Advisory Committee meeting specific to XYOSTED?

DPP Response: We do not believe the identified depression or suicide concerns necessitate Advisory Committee assemblage. However, if an Advisory Committee is convened for the hypertension concern, we would be happy to assist DBRUP in any manner needed.

IV. Supporting Information

A. QST-13-003 Case Report (b) (6) (Completed Suicide)

Event Narrative

A 72-year-old single white man living alone with a past medical history notable for hypogonadism, Type 2 diabetes, erectile dysfunction, and left eye retinal detachment committed suicide via an unknown method (b) (6) roughly one week after withdrawing from the testosterone trial. He received his final 75mg testosterone injection (b) (6), (Study Day (b) (6)). The man reported no psychiatric adverse events during his trial participation prior to the suicide and no adjustments had been made to his testosterone dosing during the trial.

The lead up to the suicide began (b) (6) when he left a voicemail for investigative staff in which he stated his intension to drop out of the trial for "personal reasons". Staff called the man (b) (6) and he scheduled an early termination visit (b) (6) The investigative staff attempted to contact him repeatedly after he failed to appear for this appointment and, (b) (6), they sent a certified letter to his last known address. On (b) (6) (b) (6) the man's stepson contacted the investigative site, reported having received the certified letter, and reported to staff that his stepfather committed suicide (b) (6)

Concomitant Medications and Herbal Supplements Taken During the Trial

1. Metformin 500 mg by mouth twice per day
2. Aspirin 325 mg by mouth daily
3. Glyburide 5 mg by mouth twice per day
4. Sildenafil 100 mg PO daily as needed for sex
5. Tadalafil 5 mg PO daily as needed for sex (appears to have been prescribed for cases in which sildenafil did not provide the desired effect, based on available information)
6. Omeprazole 40 mg by mouth daily
7. Testosterone cream 1 dab applied topically daily (it is unclear if use continued during the trial or if use resumed after dropping out of the trial)
8. Saw Palmetto 1 tablet by mouth daily
9. GABA supplement 1 tablet by mouth daily
10. Kelp 1 tablet by mouth daily
11. L-arginine 1 tablet by mouth daily
12. Vitamin B complex 1 tablet by mouth daily
13. Vitamin B_6 1 tablet by mouth daily
14. Vitamin B_{12} 1 tablet by mouth daily
15. Chromium picolinate 1 tablet by mouth daily
16. St. John's Wort 1 tablet by mouth daily
17. 5-Hydroxytryptophan 1 tablet by mouth daily
18. Valerian 1 tablet by mouth daily
19. Melatonin 1 tablet by mouth at night

Epidemiologic Risk Factors Pertaining to This Case

From a suicide risk assessment standpoint, this individual was at high risk of suicide prior to enrollment in the trial due to his age, race, sex, medical issues, social isolation, probable physical disability (detached retina), and probable untreated major depressive disorder (1, 2).

In the 2016 update by the National Center for Health Statistics, suicide rates for geriatric white men were estimated at 38.8 per 100,000 (1, 2). Suicide rates increase further when chronic pain, chronic medical issues, untreated major depressive disorder, physical disability, and social isolation are present (3); however, exact rates when these risk factors are present have not been established (1-3). For context, 38.88 per 100,000 is triple the rate found in the general population, but less than a quarter of the rate found in major depressive disorder drug trials (1, 2).

Likely Contribution of Untreated Major Depressive Disorder and Herbal Supplement Drug-Drug Interactions to the Suicide

Analysis of this individual's herbal supplements strongly indicatives the presence of untreated major depressive disorder. The supplements in question are typically used to self-treat for low mood, fatigue, difficulty sleeping, low energy, difficulty concentrating, and weight gain. Assuming suicidal ideation was present prior to the suicide, he appears to have met full Diagnostic and Statistical Manual criteria for major depressive disorder based on the symptoms his regimen of herbal supplements was intended to treat.

We note several potential problems with the man's drug regimen that may have contributed to the suicide:

- Chronic concomitant use of B vitamin complex and a B_6 supplement in an individual with reduced clearance due to age and polypharmacy may have resulted in B_6 toxicity. B_6 toxicity is associated with ataxia, painful skin lesions, photosensitivity, gastrointestinal symptoms, numbness, and reduced ability to sense pain or extreme temperatures. Risk of suicide is negatively correlated with perceived health and function (1-3).
- St. John's Wort and 5-Hydroxytryptophan both increase serotonin levels and are sometimes used as an alternative to antidepressants (4). However, combining the two may result in anxiety, restlessness, mood swings, suicidal ideation, anger, or irritability while simultaneously failing to treat the depression (4); the amount of active drug present in many nutritional supplements often varies widely from tablet to tablet and from manufacturer to manufacturer.
- St. John's Wort has negative pharmacological interactions with many drugs, including the sildenafil, tardenafil, 5-hydroxytryptophan, and omeprazole this individual was taking (4).
- It is possible for individuals to experience fatigue, dissociation, agitation, anger, irritability, and restlessness concurrently; this experience is extremely unpleasant and often prompts a suicide attempt when it occurs, per our clinical experience. Concurrent ingestion of St. John's Wort, 5-hydroxytryptophan, valerian, and melatonin along with one or more testosterone formulations could theoretically cause this combination of symptoms (4).
- Concurrent use of two testosterone formulations may have been occurring. This individual had access to multiple formulations of testosterone. Testosterone overdose is

associated with agitation, anger, restlessness, and suicide attempts in certain populations of men (5-7).

- Labeling for prescription antidepressants contain a box warning for increased suicidal ideation (3, 8, 9). No evidence exists demonstrating that individuals taking herbal serotonin reuptake inhibitors incur different risks than those taking prescription selective serotonin reuptake inhibitors (4).

The Individual's Behavior Prior to the Suicide

This individual used a topical version of testosterone for an unknown period before the trial and tolerated the switch to the 75 mg auto-injector well for roughly half of a year before the suicide. Nothing in the sequence of events suggests the suicide was precipitated by testosterone exposure or withdrawal. One would expect a drug-induced psychiatric adverse event to manifest relatively early in treatment or soon after abrupt cessation of drug exposure. The sequence of events argues against attribution of suicide to the product.

The fact that this individual called the research site to withdrawal from the trial six days before the suicide suggests that he had decided to commit suicide on or before (b) (6) His scheduling of an early termination visit for the day after he committed suicide also appears to have been purposeful. Interviews with individuals who chronically contemplate suicide often contain statements from the suicidal individual describing a feeling of relief and having a new-found sense of purpose upon making the decision to suicide (3). Misery is overshadowed by new-found resolve as they proceed to give away possessions, end on-going commitments, and cut ties with friends and family (3). These individuals often appear to be improving to outside observers prior to suicide because of the new goal-directed behavior (3). This individual's behavior is suggestive of a planned, methodical approach to committing suicide.

B. QST-13-003 Case Report (b) (6) (Attempted Suicide)

Event Narrative

A 62-year-old married white man cohabitating with his wife and having a past medical history notable for major depressive disorder, hypogonadism, hypercholesterolemia, chronic back pain, erectile dysfunction, and chronic constipation, attempted suicide using an unknown quantity of tramadol that he was not prescribed. Following the overdose, he was medically cleared in less than 24 hours and psychiatrically hospitalized from (b) (6) to (b) (6) Diagnoses listed on his psychiatric discharge summary included "Major Depressive Disorder, Borderline trust (sic), Overdose with tramadol, Urinary restriction, and Conflict with Wife." He was discharged to an outpatient partial hospitalization program following hospitalization for an unknown duration of time. His last exposure to testosterone was six days prior to the attempt (b) (6)

Concomitant Medications Taken During the Trial

1. Aspirin 81 mg by mouth daily

2. Venlafaxine XR 37.5 mg by mouth daily
3. Tamulosin 0.4 mg by mouth daily
4. Pantoprazole 40 mg by mouth daily
5. Simvastatin 40 mg by mouth daily
6. Fenofibrate 145 mg by mouth daily
7. Milk of Magnesia 30 mg by mouth every eight hours as needed for constipation
8. Paroxetine 10 mg by mouth daily
9. Testosterone [dosage unknown]

Epidemiologic Risk Factors Pertaining to This Case

Similar risk factors are present to the individual that committed suicide. This man would be considered slightly lower risk of suicide because he was younger and healthier than the previous individual (1-3). He was also married and cohabitating with his partner (1-3). These factors are considered protective for men; however, marital discord appears to have negated some or all protective aspects of marriage and cohabitation (1-3).

Likely Contribution of Inadequate Pharmacological Treatment of Major Depressive Disorder to the Suicide Attempt

Minimum dosages required for effective treatment of major depressive disorder in the majority of cases are venlafaxine XR 75 mg by mouth daily and paroxetine 20 mg by mouth daily (8, 9). These minimum effective dosages are supported by clinical trials, FDA-approved instructions for use, expert consensus, and our experience in clinical practice (8, 9). Drug-drug interaction at CYP2D6 likely raised blood levels of paroxetine, but not to the extent required to achieve blood levels comparable to those found with paroxetine 20 mg (8, 9). Labeling for paroxetine and venlafaxine XR contain a box warning for increased suicidal ideation which is not dose dependent (3, 8, 9).

Additionally, concurrent use of two different formulations of testosterone may have been occurring during the trial.

The Individual's Behavior Prior to and During the Suicide Attempt

Given the barriers one must typically overcome to access someone else's medication and the mention of conflict with wife and borderline trust on his discharge summary, the tramadol he ingested was likely prescribed to his wife. It is quite telling that he overdosed on a medication he was not prescribed, despite having access to many of his own medications. His bypassing of more lethal methods, the relatively short period required for medical clearance prior to psychiatric hospitalization, and the fact that the medication likely belonged to his wife suggests that this individual overdosed on a relatively small number of tramadol tablets and that he did not intend to die.

Ingestion of a small amount of someone else's medication is a common tactic employed by individuals with personality disorders to emotionally hurt their romantic partner or trap them in a dysfunctional relationship (3). In these cases, the personality-disordered individual makes a

suicidal gesture without intent to die whenever attempts are made to end the relationship (3). The evidence suggests that the suicide attempt in this case was a form of acting out against his wife in the context of inadequately treated depression.

C. QST-15-005 Case Report 015-010 (Worsening Depression)

Event Narrative

A 59-year-old Hispanic man with a past medical history notable for hypertension, hypercholerestemia, hypothyroidism, osteoarthritis in both knees, degenerative disc disease, erectile dysfunction, hypogonadism, vitamin D deficiency, fusion of most of his cervical and lumbar spine, multiple tendon repairs, repair of cartilage in both knees, a previous major depressive episode, and surviving an abdominal aortic aneurysm reported worsening of pre-existing depression at Week (b) (6) ((b) (6)). He was scheduled for an early termination visit then proceeded to no-show and no-call for multiple scheduled early termination appointments.

Concomitant Medications and Herbal Supplements Taken During the Trial

1. Esomeprazole 40 mg by mouth daily
2. Levothyroxine 125 mcg by mouth daily
3. Rosuvastatin 40 mg by mouth daily
4. Fenofibric Acid 135 mg by mouth daily
5. Metoprolol 50 mg by mouth daily
6. Tadalafil 20 mg by mouth daily as needed for sex
7. Methadone 5 mg by mouth three times per day
8. Hydrocodone/Acetaminophen 7.5 mg/325 mg by mouth five times per day
9. Oxycodone 5 mg by mouth four times per day
10. Amoxicillin 500 mg by mouth daily
11. Hyaluronan [Dosage Unknown]
12. Testosterone gel 1.25 g/actuation apply topically daily
13. Sertraline 50 mg by mouth daily [Initiated when depression worsened]

Too Little Information to Determine Cause

Based on the past medical history and medication regimen, this individual likely lived in constant pain. He may have also been continually obtunded due to his opiate regimen. Metoprolol and opiate exposure are associated with an increased risk of developing depression.

D. QST 15-005 Case Report 020-012 (Worsening Depression)

Event Narrative

A 54-year-old white man with a past medical history notable for hypogonadism, cervical radiculopathy, hiatal hernia, prostatitis, and erectile dysfunction reported development of a major depressive episode following three months of exposure to the product (b) (6) The individual continued to report depression six weeks after the product was discontinued.

His "early withdrawal" testosterone level was measured as being 7.06 ug/L at 12:08 pm on February 12, 2016. This is double his previous testosterone level which was 3.42 ug/L at 7:52 am on January 20, 2016.

Concomitant Medications Taken During the Trial

1. Tramadol 50 mg by mouth daily
2. Oxycodone 10 mg by mouth four times per day
3. Depomedrol injection 40 mg [frequency of administration unknown]
4. Testosterone 5 g applied topically daily
5. Ranitidine 150 mg by mouth twice per day
6. Bupropion 150 mg by mouth daily [Initiated when depression began]
7. Ciprofloxacin 500 mg by mouth twice per day
8. Tamulosin 0.4 mg by mouth twice per day

Too Little Information to Determine Cause

The timing of depressive symptoms is closer to what one would expect for product-induced depression. However, the lack of resolution following de-challenge argues against attribution of depression to the product. Chronic pain is another potential etiology.

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/s/

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02/14/2018

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02/14/2018

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: January 15, 2018

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To: Jeannie Roule, RPM
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Subject: NDA 209863: Review of Sponsor's Type A Meeting Package for a post-action CR.

This memo responds to your consult to us requesting our review and our comments on the "Hypertension" section of the post-CR Type-A Meeting Package. DCRP received and reviewed your consult request dated 28 December 2017, and the EDR provided in the consult request (\\CDSESUB1\evsprod\NDA209863\209863.enx). The meeting package (i.e. briefing book) is located in SN0028/module 1.6.2. Section 7 of the briefing book details discussion of the hypertension issues raised by DBRUP in its CR letter.

Summary

We confirm that the baseline characteristics of the patient population in the phase-3 program were representative of the type of patient likely to be encountered in clinical practice for the treatment of hypogonadism with testosterone.

The administration of XYOSTED™ will cause an increase of blood pressure with a mean effect of ~ 4/1 mmHg within 12 weeks of treatment. This increase will be larger in some individuals. The hypertensive effect of this drug will increase the risk of cardiovascular death, myocardial infarction, stroke, and heart failure, albeit modestly. The risk will increase when given to patients

with higher baseline risk (i.e., established cardiovascular disease or multiple cardiac risk factors). We do not feel further clinical studies will provide additional useful information. If DBRUP feels marketing of the product is desirable because the benefit outweighs the cardiovascular and any other risks, then we suggest appropriate language in the PI as suggested in this and in the previous consult.

Objective

In this consult, we provide our comments to key elements identified and discussed by Antares Pharma concerning hypertension issues raised in DBRUP's CR letter for NDA 209863:

1. Patient population relative to hypertension and concomitant medications.
2. Blood pressure changes in the ABPM study.
3. Effect of XYOSTED™ on hypertension defined by 24-hour mean systolic and diastolic criteria.
4. Effect of XYOSTED™ on patients with co-existing hypertension.
5. Cumulative distribution function curves and ABPM data.
6. Analysis of changes in blood pressure medication.
7. Blood pressure changes in other approved testosterone products.
8. Clinical significance of testosterone-mediated blood pressure changes.
9. Effect of other approved drugs on hypertension and corresponding label.

Background

Antares Pharma developed XYOSTED™ (previously called QuickShot™), administered as a single weekly subcutaneous injection via an autoinjector, for the treatment of adult males with hypogonadism. Two pivotal studies were performed to support NDA 209863: QST-13-003 and QST-15-005.

QST-13-003 was a phase 3, double-blind (to dosage strength), 52 week multiple-dose efficacy and safety study in 150 hypogonadal males (97 completed). The objective was to demonstrate that XYOSTED™, administered subcutaneously once each week at doses of either 50, 75, and 100 mg, produced systemic levels within the age-adjusted normal range (i.e., from 300 to 1100 ng/dL) with minimal excursion outside the normal range. Blood pressure measurements were made by sphygmomanometry during clinic visits. Because of the high variability of blood pressure readings in this setting, we limited our assessment of blood pressure effects to the ABPM study conducted in QST-13-005.

QST-15-005 was a phase 3, uncontrolled, 26 week multiple-dose safety study in 133 hypogonadal males (113 completed). This study was intended to collect additional safety and exposure data to support labeling based upon the dosing regimen employed in the QST-13-003 study. Safety data collection included blood pressure measurements by ABPM in all 133 subjects. There was no stated primary endpoint. XYOSTED™ was administered subcutaneously once each week. XYOSTED™ was provided in 3 blinded dosing strengths of 50, 75, and 100 mg, each at a volume of 0.5 mL. The study included a 2-7 week screening period, a 12 week titration period, and a 14 week extended treatment period. At the start of the

titration period, subjects self-administered XYOSTED™ at the 75 mg dose. Titration from this dose (i.e., increasing or decreasing doses by 25 mg) occurred at week 6, week 12, and week 18. The decision to titrate was dependent on maintaining the trough concentration of total testosterone between 350 and 650 ng/dL.

The ABPM study was designed (b) (4) in collaboration with the Agency. Blood pressure measurements were collected over a 24-hour period at baseline, week-6, and week-12 for all subjects.

DCRP performed an independent analysis of the effect of XYOSTED™ on blood pressure from the ABPM study that included 110 subjects. We concluded that the data was reliable enough for a regulatory decision. Within 12 weeks, the mean SBP increased by + 4mmHg and the mean DBP increased by +1 mmHg with no identified outlier subgroups. The adverse event rate for hypertension (4 of 133 subjects {3%}) was consistent with that from other testosterone products (1—4%). We felt that the modest increase in blood pressure would increase the risk of major adverse cardiovascular events especially when given chronically to patients with high baseline risk (i.e., established cardiovascular disease or multiple cardiac risk factors). Our opinion was to manage this risk through clear warning/precaution in section 5 of the label. Prescribers should be counseled to check blood pressures after 12-weeks of initiation of testosterone and to manage new onset hypertension or exacerbation of pre-existing hypertension as clinically necessary.

DBRUP issued a CR letter because of concerns about hypertension and suicidal ideation. The sections in the CR letter that discussed hypertension are extracted here:

> Based on the findings in Studies QST13-003 and QST15-005, we are concerned that your testosterone enanthate product could cause a clinically meaningful increase in blood pressure. For example, your ambulatory blood pressure monitoring (ABPM) assessments, which were conducted in patients without pre-existing hypertension, showed mean increases in systolic and diastolic blood pressure of approximately 4 mmHg and 2 mmHg, respectively. In addition, cumulative distribution function curves generated from these ABPM data demonstrated that approximately 60% of the patients had an increase in systolic blood pressure, with increases of up to 20 mmHg. Approximately 9.5% of patients in the study required initiation or adjustment of antihypertensive medications in order to maintain their blood pressures in the normal range. We are concerned that these unexpected findings based on data from a largely normotensive population may underestimate the effects of your drug on blood pressure in the real world setting, where many patients have co-existing hypertension, with the potential to increase the risk for adverse cardiovascular outcomes.

Information Needed to Resolve the Deficiencies

Further characterize the effects of your product on blood pressure and the impact on cardiovascular risk in the hypogonadal population anticipated to use your product. One approach is to conduct a new ABPM study to assess blood pressure effects in a population more consistent with real-world use of testosterone replacement as opposed to a normotensive study population. This ABPM study would collect key blood pressure data at steady state for your product within the normal range to evaluate the magnitude of effect in the intended population. Collecting data on other parameters that may influence cardiovascular risk (e.g., hematocrit, hemoglobin, cholesterol parameters) in this ABPM study could, together with the blood pressure assessment, facilitate better characterization of the impact of your product on cardiovascular risk with use in a real world setting.

Antares Pharma identified key elements from the hypertension discussion in the CR letter and provided a rebuttal of each element. In lieu of performing a new ABPM study, Antares proposes to add labeling language in section 2 (Dosage and Administration) that patients should have adequately controlled blood pressure prior to initiation of XYOSTED™ therapy, and be periodically monitored while being treated.

Elements from Hypertension issues raised in the CR Letter

1) Patient population relative to hypertension and concomitant medications

Antares Statement of Issue

The Agency suggested that the patient population was not representative of “real world” and were normotensive (not having pre-existing hypertension or hypertension controlled by medication).

Antares Rebuttal

A history of hypertension was present in 49.3% of subjects entering study QST-13-003 and 49.6% of subjects entering QST-15-005. One hundred and forty-one (141) of 283 (49.8%) in the combined QST-13-003 and QST-15-005 studies were on one or more blood pressure medications.

DCRP Comment

In study QST-13-003, 49% of the enrolled subjects had hypertension at baseline. The mean blood pressure at baseline was 127/80 mmHg. Our review of other subject characteristics showed that the mean age of the enrolled subjects was 53.4 years, 89% Caucasian. Approximately 50% of the subjects enrolled in this study had at least one cardiac risk factor: obesity, type 2 diabetes, or hyperlipidemia.

In study QST-15-005, sixty-six subjects (50% of those enrolled) had hypertension at baseline and 64 subjects were on at least 1 concomitant medication for hypertension which continued during the study. The mean blood pressure at baseline was 126/78 mmHg. Our review of other subject characteristics showed that the mean age of the enrolled subjects was 54.5 years and

85% were Caucasian. Ninety-nine (99) subjects (75% of the enrolled subjects) had a metabolism / nutritional disorder some of which were cardiac risk factors: obesity (26% enrolled), type 2 diabetes (23% enrolled), or hyperlipidemia (20% enrolled). It was not clear if some of these subjects had more than one risk factor and thus recounted under each disorder.

Based on subject characteristics, we believe that the population enrolled in the phase-3 program is likely representative of the type of patient who would present with hypogonadism and prescribed XYOSTED™.

2) Blood pressure changes in the ABPM study

Antares Statement of Issue

The Agency stated: “your ambulatory blood pressure monitoring (ABPM) assessments, which were conducted in patients without pre-existing hypertension, showed mean increases in systolic and diastolic blood pressure of approximately 4 mmHg and 2 mmHg”.

Antares Rebuttal

Demographic data does not support the statement that subjects in the study did not have pre-existing hypertension. The largest changes in BP from the ABPM study was 3.7 mmHg SBP and 1.3 mmHg DBP at week 12. Complimentary in-clinic BP data showed similar results. In conclusion, there is close agreement between the clinic BP and ABPM values; therefore, the clinic BP values can be relied upon to provide data relevant to evaluation of change in BP over time in response to testosterone treatment.

DCRP Comment

See our comment in issue # 1 regarding the prevalence of hypertension at baseline. Our own central tendency analysis from ABPM data showed a mean increase in 24-h average SBP of 3.5 mmHg (95% CI: 1.6, 5.3; p-value=0.0003) at week # 6 and 3.7 mmHg (95% CI: 1.5, 5.9; p-value =0.001) at week # 12. The mean increase in 24-h average DBP was 1.2 mmHg (95%CI: 0.4, 2.1; p-value=0.006) at week # 6 and 1.3 mmHg (95%CI: 0.1, 2.5; p-value=0.03) at week # 12. Our analysis is in agreement with the ABPM data reported by Antares.

Integrated blood pressure data from both the 003 and 005 studies, described in the ISS, showed a +4.3 mmHg rise in SBP and a +1.6 mmHg rise in DBP by week 26.

The increase of 4 mmHg SBP and 2 mmHg DBP as stated in the CR letter were reasonable rounded estimates based on the data as presented in the ISS, as well as from the ABPM study.

The expected increase in SBP by approximately 4 mmHg within 12 weeks of treatment may not be detectable because of high variability in the clinic setting using a sphygmomanometer to measure an individual blood pressure.

3) Effect of XYOSTED™ on hypertension defined by 24-hour mean systolic and diastolic criteria

Antares Statement of Issue

The Agency stated: “based on the findings in Studies QST 13-003 and QST 15-005, we are concerned that your testosterone enanthate product could cause a clinically meaningful increase in blood pressure”.

Antares Rebuttal

The loss of the usual 10 mmHg drop in nocturnal SBP (i.e., dipper effect) or a rise in night-time SBP and DBP are considered to be a negative prognostic indicator for mortality (observations from the Dublin Outcome Study) and major adverse cardiac events (analyses of IDACO-*International Database on Ambulatory Blood Pressure Monitoring in Relation to Cardiovascular Outcomes*).

Daytime blood pressure did not independently predict mortality and was only weakly associated with major adverse cardiac events (IDACO).

In the QST-15-005 ABPM study, the dipper effect was not attenuated but rather increased from 34% of patients having ≥ 10% BP dips at baseline to 41% of patients at week 6 to 43% at week 12.

Using the diagnostic criteria for hypertension > 130/80 mmHg as a benchmark (O’Brien, 2013), approximately 33% of the subjects had a 24-hour mean SBP > 130 mmHg or 24-hour mean DBP > 80 mmHg at baseline. These numbers did not significantly change over 12 weeks. Also, approximately 25% of the subjects had ≥ 10 mmHg increase in 24-hour mean SBP at week 6 or 12; and 10% had ≥ 10 mmHg increase in 24-hour mean SBP at week 6 and 12.

In summary, the 24-hour ABPM study of the XYOSTED™ population appeared to show limited increased risk, as the impact on nocturnal blood pressure was small and the percentage of subjects with systolic or diastolic hypertension on-treatment changed very little.

DCRP Comment

In the ABPM study, we confirm that compared to daytime increases in SBP, nocturnal SBP showed smaller increases from baseline at week 6 (1 mmHg, SD 17 mmHg) and at week 12 (2 mmHg, SD 22 mmHg).

The IDACO study evaluated the crude and the standardized (i.e., cohort / sex / age) rates of mortality and combined fatal / nonfatal events by subtypes of ambulatory hypertension: isolated nocturnal hypertension (INH), isolated daytime hypertension (IDH) and sustained hypertension (SH). Compared to normotensive individuals, patients with INH, IDH, or SH had a significantly higher incidence of mortality and morbidity (Table 1). The Kaplan-Meier curves for total mortality and CV events (*ischemic death, sudden death, non-fatal MI, coronary revascularization, fatal*

and non-fatal heart failure) are shown in Figure 1. Both IDH and INH showed similar incidences of total mortality and CV events over time compared to normotensive individuals.

Table 2 provides unadjusted and adjusted hazard ratios for INH, IDH, and SH relative to the normotensive control group. With cumulative adjustments applied for cohort, sex, age, body mass index, smoking and drinking, serum cholesterol, diabetes, and a history of CV disease, INH was associated with a significantly increased risk for all-cause mortality and all cardiovascular events. With similar adjustments, IDH was associated with a significantly increased risk for all cardiovascular events; SH was associated with a significantly increased risk for all-cause mortality, CV mortality, all cardiovascular events, and stroke.

The key finding of the IDACO study was that irrespective of the type of ambulatory hypertension (i.e., INH, IDH, SH), an elevated blood pressure was a major risk factor for cardiovascular complications.

From our own analysis of the 24-hour average ABPM data, 7.1% of the subjects sustained a SBP > 180 mmHg or a change from baseline 24-h SBP > 20 mmHg at week 12. From our own analysis of hourly average ABPM data, 93% of the subjects had a $\geq$ 20 mmHg SBP change from baseline at week 12, and 96% of the subjects had a $\geq$ 20 mmHg DBP change from baseline at week 12.

As discussed in previous consults, a white paper prepared by members of the Cardiac Safety Research Consortium assessed drug induced increases in blood pressure during drug development for indications not related to the cardiovascular system organ class (Sager et al, 2013). Key messages from this white paper were:

- There is powerful epidemiologic evidence showing that as BP increases in a population, the risk of CV events increases.
- It may be difficult, even impossible, to define the CV risk with a non-CV drug with small mean increases in BP because the CV risk is dependent on multiple factors (i.e., baseline CV risk, baseline BP, and length of treatment). Small central tendency increases in BP are likely to predispose to future CV events. It is therefore prudent that the drug label should assert whether a potential BP effect might be expected and how to deal with it appropriately (i.e., discontinuation, down-titration, initiating or intensifying antihypertensive therapy if the benefit justifies continuation).

- Owing to BP variability, it is not likely that all at-risk patients with significant blood pressure increases would receive medical intervention to restore them to pretreatment BP levels.

In summary, contrary to the rebuttal argument posed by Antares, both INH and IDH carry a substantially increased cardiovascular risk versus normotension. Depending on the manner in which the ABPM data was analyzed, a significant number of subjects had a substantial increase in blood pressure after 12 weeks of treatment. Drug-related small central tendency increases in BP are likely to predispose to future CV events.

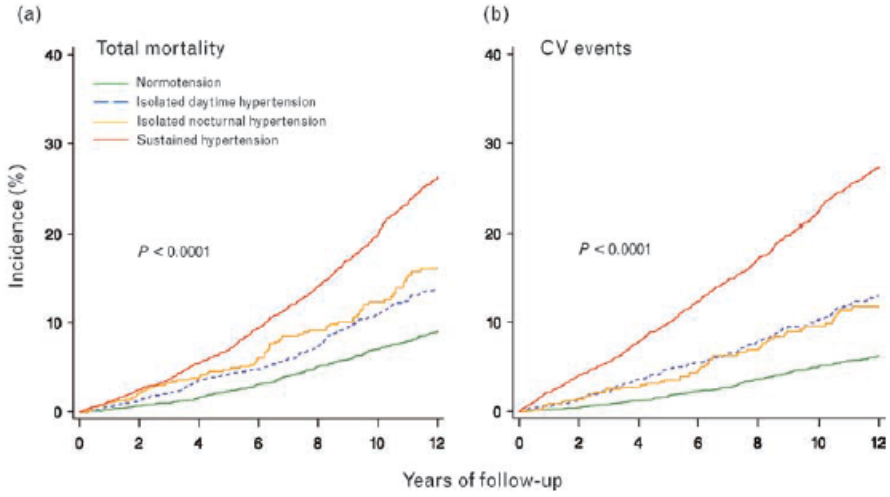
Table 1: Incidence of Events by Ambulatory Blood Pressure Status

	Normotension	Isolated nocturnal hypertension	Isolated daytime hypertension	Sustained hypertension
Number of participants	3837	577	994	3303
All-causes mortality				
Number of deaths	295	81	128	780
Crude rate	7.6 (6.7–8.4)	14.7 (11.5–17.9)‡	12.4 (10.3–14.6)‡	24.1 (22.4–25.8)‡
Standardized rate	10.6 (5.9–15.3)	13.9 (2.2–25.6)	11.2 (3.3–19.1)	18.5 (11.6–25.4)
Cardiovascular mortality				
Number of deaths	76	22	46	357
Crude rate	1.9 (1.5–2.4)	4.0 (2.6–5.7)†	4.5 (3.2–5.8)‡	11.0 (9.9–12.2)‡
Standardized rate	2.8 (0.7–4.9)	3.9 (0–8.7)	4.3 (0–9.0)	8.5 (4.1–12.8)
Noncardiovascular mortality				
Number of deaths	210	55	76	401
Crude rate	5.4 (4.6–6.1)	10.0 (7.3–12.6)‡	7.4 (5.7–9.1)*	12.4 (11.2–13.6)‡
Standardized rate	7.5 (3.7–11.3)	9.3 (0.7–17.8)	6.5 (1.4–11.7)	9.2 (5.3–13.1)
All cardiovascular events				
Number of events	188	54	112	755
Crude rate	4.9 (4.2–5.6)	10.1 (7.4–12.8)‡	11.2 (9.2–13.3)‡	25.1 (23.3–26.9)‡
Standardized rate	7.0 (3.3–10.7)	9.7 (0.3–19.2)	11.1 (0.9–21.3)	20.1 (12.4–27.8)
Cardiac events				
Number of events	108	31	73	406
Crude rate	2.8 (2.3–3.3)	5.7 (3.7–7.7)†	7.2 (5.6–8.9)‡	13.0 (11.8–14.3)‡
Standardized rate	4.0 (1.3–6.8)	5.6 (0–12.0)	6.5 (0.2–12.9)	10.7 (5.6–15.9)
Stroke				
Number of strokes	78	20	39	344
Crude rate	2.0 (1.6–2.5)	3.7 (2.1–5.3)*	3.8 (2.6–5.0)†	11.0 (9.9–12.2)‡
Standardized rate	2.7 (0.7–4.7)	3.4 (0–8.3)	4.4 (0–9.4)	8.5 (4.0–13.0)

Values are rates (95% confidence interval), expressed as number of events per 1 000 person-years. Rates are crude or standardized for cohort, sex, and age (≤40, 40–60, and ≥60 years) by the direct method. Significance of the difference with the normotensive reference group: *$P < 0.05$, †$P < 0.01$, and ‡$P < 0.001$.

Source: Fan et al on behalf of the IDACO Investigators (2010)

Figure 1: Kaplan-Meier Curves for Total Mortality and CV Events



Cumulative incidence of total mortality (a) and all cardiovascular events (b) by ambulatory blood pressure status. *P* values are for the differences among the four categories by log-rank test.

Source: Fan et al on behalf of the IDACO Investigators (2010). *Note: CV events comprised of ischemic death, sudden death, non-fatal MI, coronary revascularization, fatal and non-fatal heart failure*.

Table 2: Hazard Ratios by Categories of Ambulatory Hypertension

Outcomes	Isolated nocturnal hypertension	Isolated daytime hypertension	Sustained hypertension
All-causes mortality (1284)	81	128	780
Unadjusted	1.99 (1.56–2.55)‡	1.67 (1.35–2.05)‡	3.26 (2.85–3.73)‡
Adjusted	1.29 (1.01–1.65)*	1.07 (0.86–1.32)	1.51 (1.31–1.74)‡
Cardiovascular mortality (501)	22	46	357
Unadjusted	2.10 (1.31–3.38)†	2.32 (1.61–3.35)‡	5.78 (4.51–7.40)‡
Adjusted	1.30 (0.80–2.09)	1.38 (0.95–2.00)	2.19 (1.69–2.85)‡
Noncardiovascular mortality (742)	55	76	401
Unadjusted	1.89 (1.41–2.55)‡	1.38 (1.07–1.80)*	2.35 (1.98–2.77)‡
Adjusted	1.23 (0.91–1.66)	0.90 (0.69–1.18)	1.19 (0.99–1.43)
All cardiovascular events (1109)	54	112	755
Unadjusted	2.08 (1.53–2.81)‡	2.28 (1.81–2.89)‡	5.16 (4.40–6.06)‡
Adjusted	1.38 (1.02–1.87)*	1.46 (1.15–1.85)†	2.48 (2.10–2.94)‡
Cardiac events (618)	31	73	406
Unadjusted	2.05 (1.38–3.06)‡	2.56 (1.91–3.45)‡	4.66 (3.77–5.76)‡
Adjusted	1.41 (0.94–2.10)	1.53 (1.13–2.07)†	2.30 (1.84–2.88)‡
Stroke (481)	20	39	344
Unadjusted	1.85 (1.13–3.02)†	1.90 (1.29–2.78)†	5.52 (4.32–7.06)‡
Adjusted	1.21 (0.74–1.98)	1.35 (0.91–2.00)	2.64 (2.04–3.43)‡

Hazard ratios (95% confidence intervals) express the risk relative to the normotensive group. Numbers of cases are given for each endpoint. The cause of death was unknown in 41 cases. Cox models were adjusted for cohort, sex, age, body mass index, smoking and drinking, serum cholesterol, history of cardiovascular disease and diabetes mellitus. Significance of the hazard ratios: *$P < 0.05$, †$P < 0.01$, and ‡$P < 0.001$.

Source: Fan et al on behalf of the IDACO Investigators (2010)

4) Effect of XYOSTED™ on patients with co-existing hypertension

Antares Statement of Issue

"We are concerned that these unexpected findings based on data from a largely normotensive population may underestimate the effects of your drug on blood pressure in the real world setting, where many patients have co-existing hypertension, with the potential to increase the risk for adverse cardiovascular outcomes."

Antares Rebuttal

Data is presented showing that similar numbers of subjects receiving BP medications and not receiving BP medications were enrolled in QST-15-005. Blood pressure responses to testosterone were similar in each group at week 6 and week 12 for both SBP and DBP in subjects with $\geq$ 18 hourly ABPM determinations. These findings indicate that blood pressure medication has little impact upon the magnitude of the BP changes.

Data is presented that capture the change in BP for patients without hypertension and with hypertension according to ABPM criteria (i.e., SBP > 130 mmHg or DBP > 80 mmHg). Patients with overtly hypertensive 24-hour blood pressure measurements by ABPM have BP changes of smaller magnitude than those entering the study normotensive. These findings are consistent with regression to the mean and do not demonstrate increased susceptibility to drug-induced hypertension in patients with hypertension at baseline.

DCRP Comment

We performed our own analysis showing the change from baseline in average 24-hour ABPM recordings at week 6 and week 12 (Table 3). We also performed a sensitivity analysis removing subjects taking concomitant antihypertensive medications (Table 4). There was no impact on the results when subjects taking concomitant antihypertensive medications were removed.

A scatter plot showing the change from baseline in both SBP and DBP as a function of average 24-hour baseline ABPM is shown in Figure 2. An inverse relationship was observed. Subjects with a higher blood pressure did not experience further increments of blood pressure while on treatment. This finding was consistent with the Applicant's analysis that the elevations in blood pressure were driven by subjects who were normotensive at baseline. The implication for this finding is unclear and could reflect a regression to the mean.

Table 3: Change from Baseline in Average 24-hour ABPM Recordings

Variable	Visit	Total	Mean	Median	SD	Min	Max
ΔSBP	WEEK 6 (DAY36)	106	3.5	3.8	9.7	-16.3	41.2
	WEEK 12 (DAY78)	98	3.7	3.3	11.0	-20.5	31.1
ΔDBP	WEEK 6 (DAY36)	106	1.2	1.0	4.6	-12.9	14.5
	WEEK 12 (DAY78)	98	1.3	1.4	6.0	-26.8	23.2

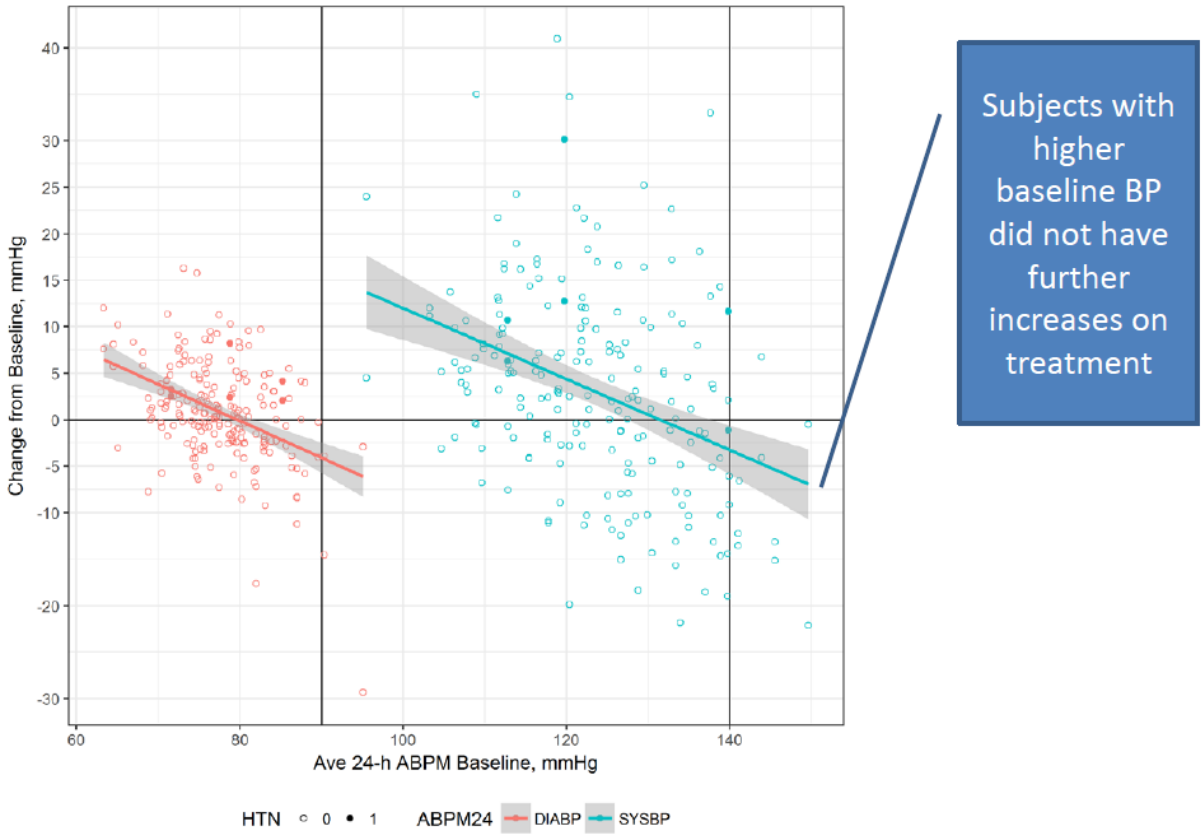
Source: Reviewer Analysis using ADZA2.xpt; cross-reference: (b) (4) report Table 14.2.3.1

Table 4: Sensitivity Analysis-Removal of Subjects Taking Concomitant Antihypertensive Medications

Variable	Visit	Total	Mean	Median	SD	Min	Max
ΔSBP	WEEK 6 (DAY36)	58	3.0	2.7	10.7	-18.3	41.0
	WEEK 12 (DAY78)	50	3.8	5.2	12.2	-19.9	35.0
ΔDBP	WEEK 6 (DAY36)	58	0.6	0.3	4.6	-17.6	11.3
	WEEK 12 (DAY78)	50	2.0	1.7	5.5	-8.5	16.3

Source: Reviewer Analysis using ADZA2.xpt and CM.xpt

Figure 2: Scatter Plot-Change from Baseline vs Baseline SBP and Baseline DBP



Source: Reviewer Analysis (note: solid dot represents hypertension AE)

5) Cumulative distribution function curves and ABPM data

Antares Statement of Issue

The Agency response letter suggests that cumulative distribution function (CDF) curves demonstrate increases in SBP in up to 60% of patients.

Antares Rebuttal

Sixty percent (60%) of patients have an increase in BP of any degree above zero and 40% have a reduction in BP of any degree below zero. The clinical significance of a treatment, such as testosterone, resulting in both a +20 mmHg and a -20 mmHg change in BP, is unclear and is unlikely attributable to treatment alone. It is mechanistically implausible to believe that XYOSTED™ could be responsible for both extremes in increase and decrease.

DCRP Comment

The CDF curves suggested a normal distribution of subjects around the mean without a group of hyper-responders driving the overall small mean effect.

6) Analysis of changes in blood pressure medication

Antares Statement of Issue

In the CR Letter, the Agency states that approximately 9.5% of patients required initiation or adjustments of antihypertensive medications after initiation of treatment with XYOSTED™.

Antares Rebuttal

Only 4 patients in the 283-patient phase-3 population (1.4%) had changes to medicine for blood pressure for an elevated blood pressure arising after the first dose of study medication.

- In QST-13-003, 21 subjects received a change in dose or a new medication to treat hypertension (20 prior to XYOSTED™ administration and 1 post-administration).
- In QST-15-005, 6 patients had changes to antihypertensive medications post-administration: 3 to manage other conditions (1 for angina, 1 for edema, 1 peri-operatively), and 3 for increasing hypertension.

DCRP Comment

Our analysis of QST-15-005 data showed that 4 subjects (3%) started either a new antihypertensive medication or had a dose change of an antihypertensive medication during the study. These subjects were:

- QST-15-005-(b) (6): started losartan on day 56 based on a hypertensive AE.
- QST-15-005-(b) (4): dose change of amlodipine, HCTZ/lisinopril, metoprolol, verapamil on day 151.
- QST-15-005-(b) (4): dose change of losartan on day 57.
- QST-15-005-(b) (6): started atenolol and HCTZ on days 98 and 147 (on antihypertensive at baseline).

Co-incidentally, there were 4 subjects who reported hypertension as an adverse event but only 1 of these (i.e., subject (b) (6)) started on new antihypertensive treatment.

7) Blood pressure changes in other approved testosterone products

Antares Statement of Issue

In its Complete Response letter, the Agency also suggested that findings related to the increase in blood pressure were “unexpected”.

Antares Rebuttal

The changes in BP observed with a number of other testosterone products are of similar magnitude as changes in BP during the XYOSTED™ program. From the FDA website, there are multiple occasions of hypertension or blood pressure changes related to testosterone supplementation documented in the product labels, NDA reviews, or in an advisory committee conducted by FDA, as well as in peer-reviewed medical literature and FAERS database.

Therefore, the Antares contends the FDA's statement that changes in BP or hypertension are "unexpected findings".

- From a review of testosterone NDAs, the treatment-emergent adverse events of Hypertension ranged from 0.2% to 9.4% (mean 4.5%).
- The testosterone product AVEED (NDA 22-219) caused an increase of SBP by 1.5 mmHg -- 2.3 mmHg and DBP by 1-2 mmHg.
- In the clinical trial comparing JATENZO® to Androgel, currently under FDA review, the AC briefing document reported hypertension adverse events of 3.7% JATENZO® and 6.9% Androgel. After 1 year of treatment, the SBP and DBP rose by 3.3 mmHg and 1.6 mmHg respectively for JATENZO® and by 1.8 mmHg and 1.4 mmHg respectively for Androgel.

DCRP Comment

Blood pressure data with other testosterone products currently on the market is shown in Table 5. The data in this table were derived from product labels and medical officer reviews obtained from https://www.accessdata.fda.gov/scripts/cder/daf/. There was a paucity of blood pressure data from the other testosterone products and no reported ABPM studies. From the available data, hypertensive adverse events occurred in 1-4% of the safety population evaluated in other testosterone products. This was consistent with what was observed in the XYOSTED™ program. The ΔSBP/ΔDBP data from two products shown in the table are probably unreliable because they likely were measured by sphygmomanometry during office visits.

Most of the other testosterone labels have cardiovascular risk as a precaution.

Table 5: Testosterone Products and Blood Pressure Data

Product	Drug Substance	NDA /ANDA	Mean ΔSBP/ΔDBP	HTN AEs	CV Risk Label
ANDRODERM	testosterone	020489	--	---	Yes
ANDROGEL	testosterone	021015	--	3%	Yes
AVEED	Testosterone Undecanoate	022219	+2/+1	3%	Yes
AXIRON	testosterone	022504	0/0	4%	Yes
DELATESTRYL	Testosterone enanthate	009165	--	--	Yes
DEPO-TESTADIOL	Testosterone cypionate	017968			
DEPO-TESTOSTERONE	Testosterone cypionate	085635	--	--	Yes
FORTESTA	testosterone	021463	“small”	3%	Yes
NATESTO	testosterone	205488	-1-3/-2-5	2%	Yes
STRIANT	testosterone	021543	--	No	Yes
TESTIM	testosterone	021454	--	1%	Yes
TESTOPEL	testosterone	080911	--	--	--
TESTOSTERONE	testosterone	076737	--	--	--
TESTOSTERONE CYPIONATE	Testosterone Cypionate	040530	--	--	--
TESTOSTERONE CYPIONATE/ESTRADIOL CYPIONATE	Testosterone cypionate/estradiol cypionate	085603	--	--	--
TESTOSTERONE ENANTHATE	Testosterone enanthate	040575	--	--	--
TESTOSTERONE UNDECANOATE	Testosterone undecanoate	207583	Undergoing Review		
TESTRED	Methyl testosterone	083976	--	No	yes
VOGELXO	testosterone	204399	--	1%	yes

Source: https://www.accessdata.fda.gov/scripts/cder/daf/

8) Clinical significance of testosterone-mediated blood pressure changes

Antares Statement of Issue

In its CR letter, the Agency has suggested that increases in blood pressure seen with XYOSTED™ could be clinically meaningful, and thusly could have the potential for increased cardiovascular risk and adverse cardiac events.

Antares Rebuttal

The increase in blood pressure by XYOSTED™ is of a magnitude not dissimilar to widely used medications (e.g., glucocorticoids, decongestants, oral contraceptives, tricyclic antidepressants, venlafaxine, acetaminophen, and ibuprofen). The regulatory path to support safe long-term use of an effective product is labeling.

The ACCORD study (ACCORD Study Group, 2010), funded by NHLBI to examine the effect of blood pressure control in hypertensive diabetics, randomized 4733 patients to a standard control group with a targeted SBP $\leq$ 140 mmHg vs an intensive control group with a targeted SBP $\leq$ 120 mmHg. Despite achieving an actual difference of 14 mmHg between the groups, there was no difference in the composite endpoint of death, MI, or stroke at a mean follow-up of 4.7 years.

HOPE-3 (Lonn, 2016) was a double-dummy, double-blinded 2x2 factorial primary prevention trial in a population with intermediate cardiac risk of a first MACE event. Subjects were randomized to rosuvastatin vs placebo, candesartan/HCTZ vs placebo, and the combination of rosuvastatin-candesartan/HCTZ. Of 12,705 subjects, 6356 were randomly assigned to candesartan/HCTZ active (rosuvastatin active + rosuvastatin placebo) and 6349 to candesartan/HCTZ placebo (rosuvastatin active + rosuvastatin placebo). Both groups had a decrease in SBP from baseline, but the decrease was 6 mmHg greater for the candesartan/HCTZ active group compared to its placebo. There were no significant differences between the groups for MACE at a median follow-up of 5.6 years.

The ACCORD and HOPE-3 studies define the limits of the benefit for blood pressure control for primary prevention in patients at intermediate risk of CV events (i.e., typical of hypogonadal patients): 1) MACE outcomes are not improved by SBP control < 140 mmHg; 2) SBP lowering beyond 120 mmHg does not improve cardiac outcomes or survival, and 3) Differences in SBP of 6-14 mmHg do not affect cardiac outcomes. This perspective does not negate the need for blood pressure monitoring and treatment according to the current guideline. Labelling can reflect this need.

DCRP Comment

In the ACCORD study of type 2 diabetic subjects, the average age was 62 years, 50% male, > 50% smoking (current or history of), average BMI 32 (i.e., obese), average HbA1c 8.3% (i.e., poorly controlled diabetes), average duration of diabetes 10 years (i.e., increased risk of end-organ damage) and average LDL 109 mg/dL. This represented a high risk and potentially non-

modifiable population. One might reasonably ask whether the benefit of lowering blood pressure alone in the setting of uncontrolled other high risk factors would mask the effect on MACE.

One might also reasonably ask whether the lack of an observed reduction in MACE consequent to lowering blood pressure as seen in the ACCORD and HOPE-3 studies implies that increasing blood pressure would have no effect on the risk of MACE in a population at risk.

As discussed under issue # 3, there is powerful epidemiologic evidence showing that as BP increases in a population, the risk of CV events increases (Sager et al, 2013).

We examined the effect of a +4 mmHg rise in SBP on a sample subject with relatively lower cardiovascular risk and a sample subject with a relatively higher cardiovascular risk. The increase in CV risk based on the blood pressure effect was estimated from the Framingham Risk Model (D'Agostino et al., 2008) shown in Table 6. A relatively lower risk patient defined as a 55 year old male, total cholesterol 185 mg/dL, HDL 43 mg/dL, non-treated SBP 127 mmHg, non-smoker, and non-diabetic had an estimated 10 year risk of 11.2%. A relatively higher risk patient defined as a 65 year old male, total cholesterol 240 mg/dL, HDL 43 mg/dL, non-treated SBP 127 mmHg, smoker, and diabetic has an estimated 10 year risk of 59.5%. An increase in the SBP by +4 mmHg increased the risk in the relatively lower risk patient from 11.2% to 11.8% (0.6 per 1000 patient-years). The same increase in SBP increased the risk in the relatively higher risk patient from 59.5% to 61.7% (2.2 per 1000 patient-years). This suggested that the rise in SBP caused by testosterone enanthate increased the absolute risk of a MACE in subjects with a higher baseline Framingham Model risk score more so than in subjects with a lower baseline score.

The increased risk of 2.2/1000 patient-years is modest. However, when administered chronically, this risk needs to be evaluated in light of the benefit of testosterone treatment.

Table 6: Framingham Risk Model for Male Taking QuickShot™ Testosterone

Risk Factor	Low CV Risk	High CV Risk
Age, y	55	65
Cholesterol, mg/dL	185	240
HDL, mg/dL	43	43
Non-treated SBP, mmHg	127 increased to 131 mmHg	127 increased to 131 mmHg
Smoker, yes (1) or no (0)	0	1
Diabetes, yes (1) or no (0)	0	1
Estimate of 10-y Risk, %	11.2 increased to 11.8	59.5 increased to 61.7
Absolute Risk Difference	0.6 events/1000 pt-yrs	2.2 events/1000 pt-yrs

Source: Reviewer's Analysis

9) Effect of other approved drugs on hypertension and corresponding label

Antares Statement of Issue

In its Complete Response letter, the Agency suggested the need for further clinical studies in order to better characterize the impact of the effect on blood pressure on the CV risk of XYOSTED™.

Antares Rebuttal

The effects on blood pressure of commonly used medications are and have been adequately handled with proper labeling and without the need for additional clinical studies. One example was the approval of Mirabegron in 2012 for overactive bladder (NDA 202-611) where the Agency sought to mitigate risk for safety events related to hypertension through clear, concise, and prescriptive safety language in the package inert. Another example is the hypertensive effect of NSAIDS where the Agency strengthened the existing warning in prescription drug labels and OTC Drug Acts labels to indicate that NSAIDs can increase the chance of a heart attack or stroke that can occur as early as the first few weeks of therapy. Antares concludes the same can be done for XYOSTED™ and without the need for further studies.

DCRP Comment

Assuming that the benefit of XYOSTED™ outweighs the risk, we agree that the modest increase in cardiovascular risk in patients with pre-existing cardiovascular risk can be managed through labeling and possibly through risk mitigation. Specific warnings/precautions in section 5 of the label should state that XYOSTED™ is likely to increase systolic blood pressure in the first 12 weeks of treatment with a mean increase of 4 mmHg thereby increasing the risk of a major cardiac adverse event especially in patients with established cardiovascular disease or multiple risk factors. Prescribers should be counseled to check blood pressures after 12-weeks of initiation of testosterone and to manage new onset hypertension or exacerbation of pre-existing hypertension as clinically necessary.

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/s/

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01/16/2018

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: December 20, 2017

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To: Jeannie Roule, RPM
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Subject: NDA 209863: Addendum to consult requested 19 Jul 2017 and entered into DARRTS on 03 Aug 2017.

Summary

We performed an independent analysis of the effect of QuickShot™ Testosterone (QST) on blood pressure from an ABPM study of 110 subjects to support the review of NDA 209863.

There was a mean elevation of SBP by +4 mmHg and a mean elevation of DBP by +1 mmHg occurring mostly over 6 weeks and with a small increment to the observed elevation at 12 weeks from treatment initiation. No outlier subgroup was identified. These results broadly agreed with the sponsor's analysis.

The modest increase in blood pressure caused by QST is expected to increase the relative risk for serious cardiovascular adverse events (i.e., myocardial infarction, stroke, heart failure, death). The absolute increase in cardiovascular events will be higher in patients with higher baseline risk (i.e., established cardiovascular disease or multiple cardiac risk factors).

Objective

In 3 previous consults, we provided advice on the design features of an ABPM study and interpretation of the ABPM results to support NDA 209863. In this consult, we provide our final opinion on blood pressure elevations during testosterone administration by answering the following questions:

1. Are the data submitted by the applicant reliable enough for regulatory decision making?
2. If so, what is the effect on BP? What is the central tendency and what is the spread of the effect around the central tendency? How many subjects required change in BP meds and what is the interpretation of this rate?
3. Were there any subgroups at increased risk for increases in BP?
4. Is the effect on BP of this product consistent with the effects of other testosterone products?
5. What is the increase in CV risk expected based on the BP effect?
6. If the drug is approved, what suggestions do we have for information about BP to be conveyed in the label? In particular, when is the maximal effect on BP observed and are any specific warnings required?

Background

Antares Pharma developed QuickShot™ (QST), administered as a single weekly subcutaneous injection via an autoinjector, for the treatment of adult males with hypogonadism. Two pivotal studies were performed to support NDA 209863: QST-13-003 and QST-15-005.

QST-13-003 was a phase 3, double-blind (to dosage strength), 52 week multiple-dose efficacy and safety study in 150 hypogonadal males (97 completed). The objective was to demonstrate that QST, administered subcutaneously once each week at doses of either 50, 75, and 100 mg, produced systemic levels within the age-adjusted normal range (i.e., from 300 to 1100 ng/dL) with minimal excursion outside the normal range. Blood pressure measurements were made by sphygmomanometry during clinic visits. Because of the high variability of blood pressure readings in this setting, we limited our assessment of blood pressure effects on the ABPM study conducted in QST-13-005.

QST-15-005 was a phase 3, uncontrolled, 26 week multiple-dose safety study in 133 hypogonadal males (113 completed). This study was intended to collect additional safety and exposure data to support labeling based upon the dosing regimen employed in the QST-13-003 study. Safety data collection included blood pressure measurements by ABPM in all 133 subjects. There was no stated primary endpoint. QST was administered subcutaneously once each week. QST was provided in 3 blinded dosing strengths of 50, 75, and 100 mg, each at a volume of 0.5 mL. The study included a 2-7 week screening period, a 12 week titration period, and a 14 week extended treatment period. At the start of the titration period, subjects self-administered QST at the 75 mg dose. Titration from this dose (i.e., increasing or decreasing doses by 25 mg) occurred at week 6, week 12, and week 18. The decision to titrate was dependent on maintaining the trough concentration of total testosterone between 350 and 650 ng/dL.

Safety stopping criteria included an increase in PSA ≥ 1.4 ng/mL above baseline, hematocrit > 55%, major adverse cardiac events (MI, new onset angina, cardiac revascularization, TIA, and stroke), anaphylaxis, depression, and suicide ideation.

The ABPM study was designed (b) (4) in collaboration with the Agency. Blood pressure measurements were collected over a 24-hour period at baseline, week-6, and week-12 for all subjects.

Subject disposition is shown Table 1.

Table 1: Subject Disposition

Description	**Number of Subjects (%)**
Enrolled	133
Completed the study	113 (85%)
Discontinued	20 (15%)
• Adverse Event	4 (3%)
• Withdrew consent	4 (3%)
• Lost to Follow-up	1 (1%)
• Fulfilled stopping criteria	1 (1%)
• Protocol Violation	2 (2%)
• Terminated by Sponsor	1 (1%)
• Other	2 (2%)
• Multiple reasons	5 (4%)

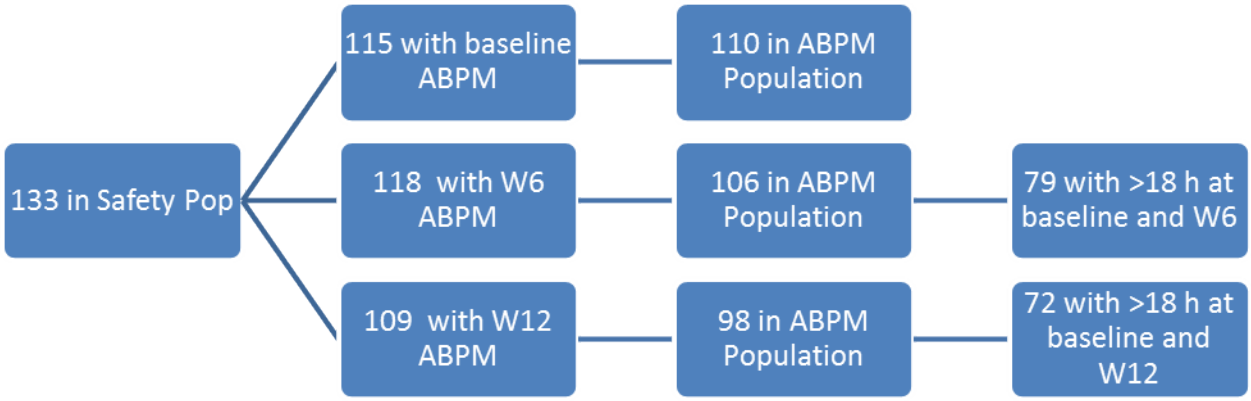
Source: Table 14.1.1.1, 005-CSR

The mean age of the enrolled subjects was 54.5 years and 85% were Caucasian. Ninety-nine (99) subjects (75% of the enrolled subjects) had a metabolism / nutritional disorder some of which were cardiac risk factors: obesity (26% enrolled), type 2 diabetes (23% enrolled), or hyperlipidemia (20% enrolled). It was not clear if some of these subjects had more than one risk factor and thus recounted under each disorder. Sixty-six subjects (50% of those enrolled) had hypertension at baseline and 64 subjects were on at least 1 concomitant medication for hypertension which continued during the study. Four (4) subjects started either a new antihypertensive medication or had a dose change of an antihypertensive medication during the study.

There were 4 subjects who reported hypertension as an AE. Of those 4 subjects, 1 subject started new antihypertensive treatment.

Our analysis of subject disposition that led to the ABPM dataset is shown in Figure 1. Of 133 subjects in the safety population, 115 had baseline ABPM data, 118 had week # 6 ABPM data, and 109 had week # 12 ABPM data. However, the ABPM dataset comprised 110 subjects at baseline, 106 subjects at week # 6 and 98 subjects at week # 12. Of this, there were 79 subjects with > 18 hours of data at baseline and week # 6, and 72 subjects with > 18 hours of data at baseline and week # 12. Therefore, approximately 25% of the data in the ABPM population was missing at week # 6, and 26% of the data was missing at week # 12.

Figure 1: ABPM population: enrolled subjects with at least 1 pre-dose and 1-post dose ABPM recording



Source: Reviewer analysis using ADZA3.xpt.

Responses to Specific Review Questions

1) Are the data submitted by the applicant reliable enough for regulatory decision making?

Yes, we believe the data were reliable enough for a regulatory decision.

We conducted an independent sensitivity analysis to evaluate the effect of subjects with missing data on the overall ABPM dataset (described in our response to review question # 2). The results showed no impact on the overall dataset.

2) What is the central tendency and what is the spread of the effect around the central tendency? How many subjects required change in BP meds and what is the interpretation of this rate?

Central Tendency Analysis: The 24-h average ABPM recordings are shown in Table 2. The change from baseline in the 24-h average ABPM recordings is shown in Table 3. The mean increase in 24-h average SBP was 3.5 mmHg (95% CI: 1.6, 5.3; p-value=0.0003) at week # 6 and 3.7 mmHg (95% CI: 1.5, 5.9; p-value =0.001) at week # 12. The mean increase in 24-h average DBP was 1.2 mmHg (95%CI: 0.4, 2.1; p-value=0.006) at week # 6 and 1.3 mmHg (95%CI: 0.1, 2.5; p-value=0.03) at week # 12.

Table 2: Descriptive Summary of Average 24-hour ABPM Recordings

Variable	Visit	N	N with <18 h	Mean	Median	SD	Min	Max
SBP	Baseline	110	14	123.3	122.5	10.9	95.5	149.6
	WEEK 6 (DAY36)	106	14	125.9	124.9	11.4	103.0	157.5
	WEEK 12 (DAY78)	98	16	127.0	125.3	12.2	102.6	170.6
DBP	Baseline	110	14	77.4	77.0	5.7	63.3	95.1
	WEEK 6 (DAY36)	106	14	78.2	78.1	5.5	65.8	92.5
	WEEK 12 (DAY78)	98	16	78.8	78.0	5.9	65.8	98.3

Source: Reviewer Analysis using ADZA3.xpt; cross-reference: (b) (4) Report Table 14.2.3.1

Table 3: Change from Baseline in Average 24-hour ABPM Recordings

Variable	Visit	Total	Mean	Median	SD	Min	Max
ΔSBP	WEEK 6 (DAY36)	106	3.5	3.8	9.7	-16.3	41.2
	WEEK 12 (DAY78)	98	3.7	3.3	11.0	-20.5	31.1
ΔDBP	WEEK 6 (DAY36)	106	1.2	1.0	4.6	-12.9	14.5
	WEEK 12 (DAY78)	98	1.3	1.4	6.0	-26.8	23.2

Source: Reviewer Analysis using ADZA2.xpt; cross-reference: (b) (4) *Report Table 14.2.3.1*

In addition to evaluating the 24-h average ABPM recordings, we performed an analysis evaluating the average time-matched hourly difference between baseline and on-treatment (Week 6 and Week 12) ABPM recordings. The results are shown in Table 4. These results were similar to that from the average 24-hour analysis. We performed this additional analysis because the statistical analysis plan from the ABPM report did not specify how their analysis was conducted.

Table 4: Change from Time-Matched Baseline in Average 24-hour ABPM Recordings

Variable	Visit	Total	Mean	Median	SD	Min	Max
ΔSBP	WEEK 6 (DAY36)	106	2.5	2.7	10.4	-22.1	41.0
	WEEK 12 (DAY78)	98	3.7	3.2	11.9	-21.8	35.0
ΔDBP	WEEK 6 (DAY36)	106	0.7	0.4	4.8	-17.6	11.3
	WEEK 12 (DAY78)	98	1.0	1.0	6.1	-29.3	16.3

Source: Reviewer Analysis using ADZA3.xpt; time-matched change from baseline = mean of the hourly difference between on-treatment and baseline ABPM recordings

Two sensitivity analyses were performed to evaluate the influence of missing data and concomitant antihypertensive medications on the increase in 24-h average SBP/DBP. There was no impact on the results when subjects with less than 18 hours of ABPM recordings were removed (Table 5), or when subjects taking concomitant antihypertensive medications were removed (Table 6).

Table 5: Sensitivity Analysis-Removal of Subjects with less than 18-hours of recordings

Variable	Visit	Total	Mean	Median	SD	Min	Max
ΔSBP	WEEK 6 (DAY36)	79	3.3	3.9	8.3	-16.3	21.6
	WEEK 12 (DAY78)	72	3.8	3.2	9.9	-14.2	31.1
ΔDBP	WEEK 6 (DAY36)	79	1.4	0.8	3.7	-8.3	13.1
	WEEK 12 (DAY78)	72	1.4	0.6	4.5	-9.1	12.4

Source: Reviewer Analysis using ADZA3.xpt; cross-reference: Table 14.2.3.1-Sensitivity Analysis (18 Hour Rule)

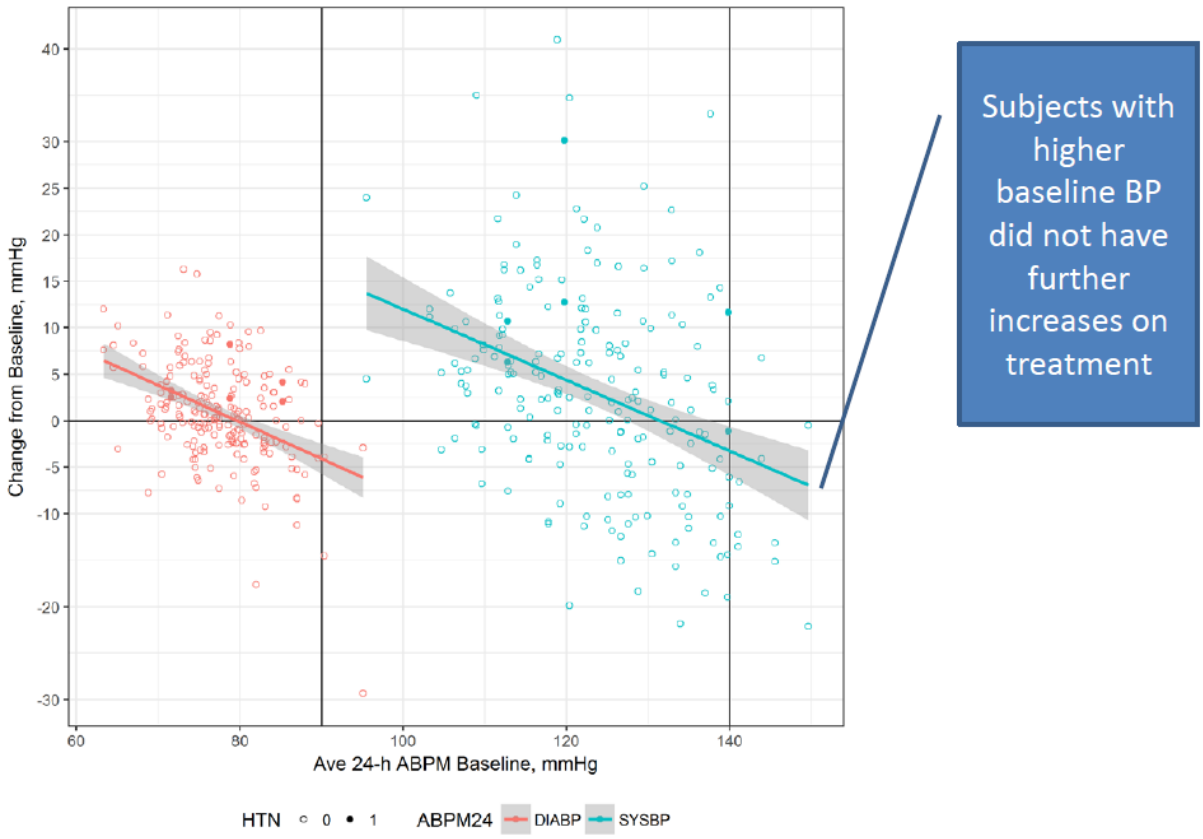
Table 6: Sensitivity Analysis-Removal of Subjects Taking Concomitant Antihypertensive Medications

Variable	Visit	Total	Mean	Median	SD	Min	Max
ΔSBP	WEEK 6 (DAY36)	58	3.0	2.7	10.7	-18.3	41.0
	WEEK 12 (DAY78)	50	3.8	5.2	12.2	-19.9	35.0
ΔDBP	WEEK 6 (DAY36)	58	0.6	0.3	4.6	-17.6	11.3
	WEEK 12 (DAY78)	50	2.0	1.7	5.5	-8.5	16.3

Source: Reviewer Analysis using ADZA2.xpt and CM.xpt

A scatter plot showing the change from baseline in both SBP and DBP as a function of average 24-hour baseline ABPM is shown in Figure 2. An inverse relationship was observed Subjects with a higher blood pressure did not experience further increments of blood pressure while on treatment. This finding was consistent with the Applicant's analysis that the elevations in blood pressure were driven by subjects who were normotensive at baseline. The implication for this finding is unclear and could reflect a regression to the mean.

Figure 2 : Scatter Plot-Change from Baseline vs Baseline SBP and DBP



Source: Reviewer Analysis (note: solid dot represents hypertension AE)

Outlier Analysis: Our outlier analyses were based on a modification of the outlier definition provided by the Applicant: 1) SBP exceeding 180 mmHg and a change in SBP ≥ 20 mm Hg or 2) DBP exceeding 105 mmHg and a change in DBP ≥ 15 mmHg. The ABPM statistical analysis plan stated that these criteria were based on mean daily systolic and diastolic blood pressures.

We performed two analyses as shown in Table 7. We evaluated outliers based on 1) 24-hour average ABPM and 2) hourly average ABPM.

Instead of using "SBP exceeding 180 mmHg and a change in SBP ≥ 20 mm Hg", we used SBP exceeding 180 mmHg or a change in SBP ≥ 20 mm Hg. Similarly, instead of using "DBP exceeding 105 mmHg and a change in DBP ≥ 15 mmHg", we used DBP exceeding 105 mmHg or a change in DBP ≥ 15 mmHg. We felt that SBP > 180 mmHg or a change in SBP ≥ 20 mmHg independently could be classified as an outlier. We felt similarly about the DBP changes.

With the 24-hour average ABPM analysis, 2.8% and 7.1% of the subjects had a SBP > 180 mmHg or change from baseline 24-h SBP >20 mmHg at Weeks 6 and 12, respectively. None of the subjects met both criteria. Also, 0 and 1.0% subjects had a DBP > 105 mmHg or change

from baseline 24-h DBP >15 mmHg at Weeks 6 and 12, respectively. None of the subjects met both criteria.

With the hourly average ABPM analysis, 85% and 93% of the subjects had a ≥ 20 mmHg SBP change from baseline at Weeks 6 and 12, respectively. Also, 93% and 96% of the subjects had a ≥ 20 mmHg DBP change from baseline at Weeks 6 and 12, respectively.

The 24-hour average ABPM outlier analysis we conducted approximated the Applicant's outlier analysis. We believe that the 24-hour average outlier analysis avoids spurious results due to intrinsic variability in blood pressure measurements that might be more reflected in hourly average readings.

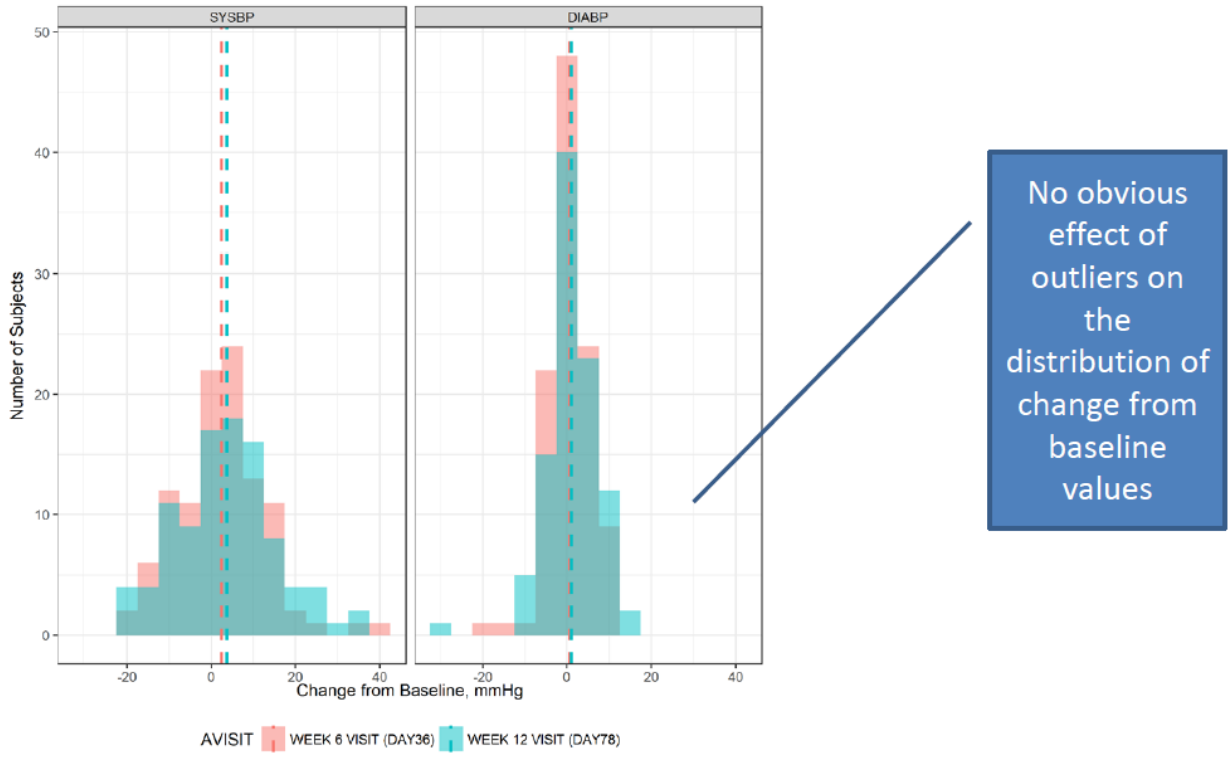
There was no obvious effect of outliers on the distribution of change from baseline values, as shown in Figure 3.

Table 7: Outliers using 24-hour average ABPM and Hourly average ABPM

	SBP > 180 mmHg or >= 20 change from baseline SBP	DBP > 105 mmHg or >= 15 change from baseline DBP
24-h average ABPM		
Week 6	3/106 (2.8%)	0/106
Week 12	7/98 (7.1%)	1/98 (1.0%)
	>= 20 change from baseline SBP	>= 15 change from baseline DBP
Hourly average ABPM		
Week 6	90/106 (84.9%)	99/106 (93.4%)
Week 12	91/98 (92.9%)	94/98 (95.9%)

Source: Reviewer Analysis

Figure 3: Distribution of Change from Baseline-Average 24-hour ABPM

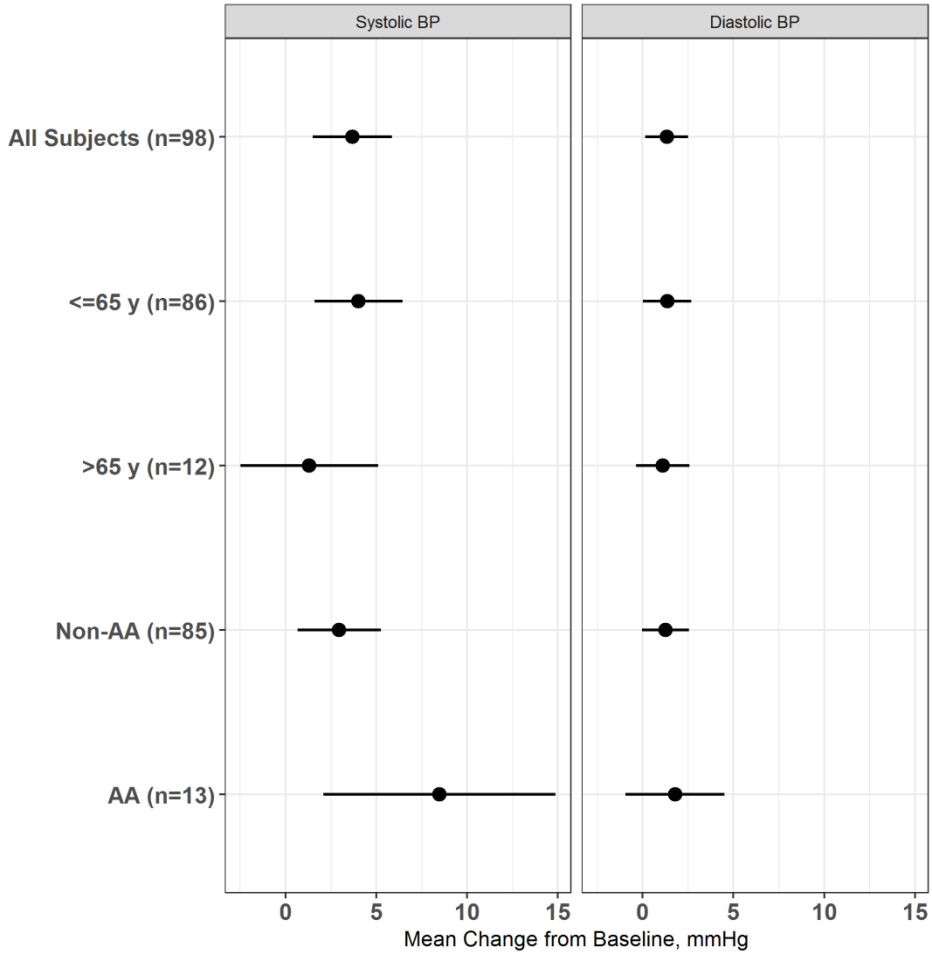


Source: Reviewer Analysis

3) Were there any subgroups at increased risk for increases in BP?

Data were available on 2 subgroups in the ABPM study: subjects ≥ 65 years old (n=12) and black/African American subjects (n=13). The sample sizes were too small to draw meaningful conclusions as to whether these subgroups had an increased risk for elevated blood pressure. We noted a higher point estimate of the systolic blood pressure increase from baseline in the African American population (8.5 mmHg, 95% CI: 2—15 mmHg) compared to the "non-African American" population (3.0 mmHg, 95% CI: 0.7—5.2) (Figure 4). However, because the data are sparse, the confidence interval was wide and a reliable interpretation is not possible.

Figure 4: Forest Plot of Mean (95% CI) Change from Baseline 24-h Average BP by Subgroup at Week 12



Source: Reviewer's analysis using sponsor's data adza2.xpt and dm.xpt

4) Is the effect on BP of this product consistent with the effects of other testosterone products?

Blood pressure data with other testosterone products currently on the market is shown in Table 8. The data in this table were derived from product labels and medical officer reviews obtained from drugs@fda.gov. There was paucity of blood pressure data from the other testosterone products and no reported ABPM studies. From the available data, hypertensive adverse events occurred in 1-4% of the safety population evaluated in other testosterone products. This was consistent with what was observed in the QST program. The ΔSBP/ΔDBP data from two products shown in the table are probably unreliable because they likely were measured by sphygmomanometry during office visits.

Table 8 : Testosterone Products and Blood Pressure Data

Product	Drug Substance	NDA /ANDA	Mean ΔSBP/ΔDBP	HTN AEs	CV Risk Label
ANDRODERM	testosterone	020489	--	---	Yes
ANDROGEL	testosterone	021015	--	3%	Yes
AVEED	Testosterone Undecanoate	022219	+2/+1	3%	Yes
AXIRON	testosterone	022504	0/0	4%	Yes
DELATESTRYL	Testosterone enanthate	009165	--	--	Yes
DEPO-TESTADIOL	Testosterone cypionate	017968			
DEPO-TESTOSTERONE	Testosterone cypionate	085635	--	--	Yes
FORTESTA	testosterone	021463	"small"	3%	Yes
NATESTO	testosterone	205488	-1-3/-2-5	2%	Yes
STRIANT	testosterone	021543	--	No	Yes
TESTIM	testosterone	021454	--	1%	Yes
TESTOPEL	testosterone	080911	--	--	--
TESTOSTERONE	testosterone	076737	--	--	--
TESTOSTERONE CYPIONATE	Testosterone Cypionate	040530	--	--	--
TESTOSTERONE CYPIONATE/ESTRADIOL CYPIONATE	Testosterone cypionate/estradiol cypionate	085603	--	--	--
TESTOSTERONE ENANTHATE	Testosterone enanthate	040575	--	--	--
TESTOSTERONE UNDECANOATE	Testosterone undecanoate	207583	Undergoing Review		
TESTRED	Methyl testosterone	083976	--	No	yes
VOGELXO	testosterone	204399	--	1%	yes

Source: Drugs@FDA.gov

5) What is the increase in CV risk expected based on the BP effect?

The results of this ABPM CST-005 study portend a modest increase in cardiovascular risk, with a greater absolute increase in risk in patients with higher baseline cardiovascular risk.

The increase in CV risk based on the blood pressure effect was estimated from the Framingham Risk Model (D'Agostino et al., 2008) shown in Table 9. A relatively lower risk patient defined as a 55 year old male, total cholesterol 185 mg/dL, HDL 43 mg/dL, non-treated SBP 127 mmHg, non-smoker, and non-diabetic had an estimated 10 year risk of 11.2%. A relatively higher risk patient defined as a 65 year old male, total cholesterol 240 mg/dL, HDL 43 mg/dL, non-treated SBP 127 mmHg, smoker, and diabetic has an estimated 10 year risk of 59.5%. An increase in the SBP by +4 mmHg increased the risk in the relatively lower risk patient from 11.2% to 11.8% (0.6 per 1000 patient-years). The same increase in SBP increased the risk in the relatively higher risk patient from 59.5% to 61.7% (2.2 per 1000 patient-years). This suggested that the rise in SBP caused by testosterone enanthate increased the absolute risk of a major cardiac adverse event in subjects with a higher baseline Framingham Model risk score more so than in subjects with a lower baseline score.

The increased risk of 2.2/1000 patient-years is modest. However, when administered chronically over many years, this risk needs to be evaluated in light of the benefit of testosterone treatment.

Table 9 : Framingham Risk Model for Male Taking QuickShot™ Testosterone

Risk Factor	Low CV Risk	High CV Risk
Age, y	55	65
Cholesterol, mg/dL	185	240
HDL, mg/dL	43	43
Nontreated SBP, mmHg	127 increased to 131 mmHg	127 increased to 131 mmHg
Smoker, yes (1) or no (0)	0	1
Diabetes, yes (1) or no (0)	0	1
Estimate of 10-y Risk, %	11.2 increased to 11.8	59.5 increased to 61.7
Absolute Risk Difference	0.6 events/1000 pt-yrs	2.2 events/1000 pt-yrs

Source: Reviewer's Analysis

As discussed in the original consult, a white paper prepared by members of the Cardiac Safety Research Consortium assessed drug induced increases in blood pressure during drug development for indications not related to the cardiovascular system organ class (Sager et al, 2013). Key messages from this white paper were:

- There is powerful epidemiologic evidence showing that as BP increases in a population, the risk of CV events increases.
- It may be difficult, even impossible, to precisely define the CV risk with a non-CV drug with small mean increases in BP because the CV risk is dependent on multiple factors (i.e., baseline CV risk, baseline BP, and length of treatment). Small central tendency increases in BP are likely to predispose to future CV events. It is therefore prudent that the drug label should assert whether a potential BP effect might be expected and how to deal with it appropriately (i.e., discontinuation, down-titration, initiating or intensifying antihypertensive therapy if the benefit justifies continuation).
- Owing to BP variability, it is not likely that all at-risk patients with significant blood pressure increases would receive medical intervention to restore them to pretreatment BP levels.

6) If the drug is approved, what suggestions do we have for information about BP to be conveyed in the label? In particular, when is the maximal effect on BP observed and are any specific warnings required?

Specific warnings/precautions in section 5 of the label should state that QST is likely to increase systolic blood pressure in the first 12 weeks of treatment with a mean increase of 4 mmHg. Increased blood pressure increases the risk of cardiovascular events made greater in patients with established cardiovascular disease or multiple risk factors. Prescribers should be counseled to check blood pressures after 12-weeks of initiation of testosterone and to manage new onset hypertension or exacerbation of pre-existing hypertension as clinically necessary.

References

D'Agostino RB, et al., General Cardiovascular Risk Profile for Use in Primary Care: The Framingham Heart Study. Circulation. 2008;117:743-753.

Sager, P, et al., Assessment of drug-induced increases in blood pressure during drug development: report from the Cardiac Safety Research Consortium, American Heart Journal. 2013; 165: 477-488

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Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Brief Drug Utilization Review

Date:	12/01/2017
Drug Utilization Analysts:	Corinne Woods, RPh, MPH Division of Epidemiology II Shekhar Mehta, PharmD Division of Epidemiology II
Team Leader:	LCDR Travis Ready, PharmD Division of Epidemiology II
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Product Name:	Testosterone
Application Type/Number:	Multiple
Applicant/Sponsor:	Multiple
OSE RCM #:	2017-2072

TABLE OF CONTENTS

EXECUTIVE SUMMARY

No testosterone products are currently FDA approved for long-term therapy in adolescent male patients. The Division of Bone and Reproductive Urology Products (DBRUP) requested data on patterns of long-term testosterone use among adolescent males, and possible conditions related to testosterone therapy. Outpatient retail pharmacy data revealed low numbers of young male patients received dispensed prescriptions for testosterone. An algorithm was used to determine long-term testosterone use based upon patterns of prescription claims captured in an administrative database of pharmacy and outpatient medical claims from a robust sample of commercial health care insurance plans. The analyses revealed a small fraction of young male patients with testosterone claims met our definition of long-term testosterone therapy. Based on claims data, the most prevalent conditions captured in patients with long-term testosterone use were for relatively nonspecific diagnoses: testicular hypofunction, delayed puberty, and lack of expected physiological development. Small percentages of patients with long-term testosterone use had claims for more specific conditions, such as Klinefelter syndrome, panhypopituitarism, or pituitary dwarfism.

1 INTRODUCTION

1.1 BACKGROUND

The DBRUP requested that the Division of Epidemiology II (DEPI II) provide information on adolescent boys who have conditions for which chronic use of testosterone would be indicated. This request is to help inform issues related to products subject to the Pediatric Research Equity Act. Using the currently available proprietary databases, this review provides outpatient utilization patterns using healthcare claims as well as outpatient retail pharmacy prescription data over the last 8-11 years.

1.2 PRODUCT INFORMATION

Testosterone is available in a variety of dosage formulations: transdermal cream, gel, ointment, patch, and solution; injectable nasal gel; pellet implant; mucoadhesive buccal system; and injectable solution. Two testosterone products and two testosterone-related products are approved to stimulate puberty in carefully selected males with delayed puberty.[a] Other forms of testosterone are approved for primary hypogonadism or hypogonadotropic hypogonadism. Medical conditions causing hypogonadism may include gonadotropin or luteinizing hormone-releasing hormone deficiency; pituitary-hypothalamic injury from tumors, trauma, or radiation;

[a] Fluoxymesterone, methyltestosterone, testosterone enanthate injection, and testosterone pellet implant

cryptorchidism; bilateral torsion; orchitis; vanishing testis syndrome; orchidectomy; Klinefelter syndrome; chemotherapy; and toxic damage from alcohol or heavy metals.

2 METHODS AND MATERIALS

Proprietary drug utilization databases available to the Agency were used to conduct these analyses. Detailed descriptions of the databases are included in **Appendix C**.

2.1 DATA SOURCES USED

The IQVIA, National Sales Perspective™ database was used to obtain the nationally estimated number of packages sold for testosterone products from manufacturers to all U.S. channels of distribution for the year ending August 2017. The IQVIA, Total Patient Tracker™ database was used to provide the nationally estimated number of male patients who received a dispensed prescription for testosterone from U.S. outpatient retail pharmacies from September 2009 through August 2017.

The IQVIA Real-World Data Adjudicated Claims – U.S. Database is an administrative claims database used to obtain the number of unique patients with a pharmacy prescription claim or procedure code for testosterone products from January 2006 through December 2016. This database is a longitudinal patient data source which captures adjudicated medical and pharmacy data, including outpatient prescription claims and procedure codes for a robust sample of commercial health care insurance plans. The patient data were obtained from a sample of approximately 148 million enrollees with at least one month of commercial insurance coverage between January 2006 and December 2016.

Patient selection was based on the presence of at least five testosterone claims. Testosterone claims were identified using National Drug Codes (NDCs) for testosterone within pharmacy claims or Healthcare Common Procedure Coding System (HCPCS) codes for testosterone within outpatient medical facility claims. **Tables B1 and B2** in **Appendix B** show the NDCs and HCPCS codes for testosterone included in this review. A final cohort of chronic use patients was identified by examining each patient's testosterone claims patterns per the following criteria:

1. Patients must have five or more testosterone claims, AND
2. Patients meet one of the following criteria:
    a. At least one year between first and last testosterone claim and an overall average of two or more testosterone claims per year, OR
    b. Testosterone episode of one year or greater, where procedure codes were assigned a 30 days' supply, and episodes were created using a 90-day gap allowance, OR
    c. Patient has five or more testosterone episodes, using the episode definition in (b)

Each chronic use patient was assigned an index date—the date of the first testosterone claim. All diagnosis fields were searched in all claims during the 365 days prior to and 60 days following

the index date. All four-digit International Classification of Diseases (ICD)-9 codes present on any claim during this time period were reported for each patient. ICD-10 codes were not included in this analysis due to a lack of validated crosswalk between the differing ICD versions. Results were stratified by patient age: 0-13, 14-17, and 18-19 years old.

3 RESULTS

3.1 SETTINGS OF CARE

Sales data for the year ending August 2017 indicated that approximately 78% of testosterone of bottles or packages were sold to retail pharmacies, followed by 14% to mail order/specialty pharmacies. Approximately 8% were sold to non-retail settings of care.[b] Therefore, only outpatient retail pharmacy and mail order/specialty pharmacy utilization patterns were examined. Non-retail pharmacy data were not included in this review.

3.2 OUTPATIENT UTILIZATION DATA

Table A1 in **Appendix A** shows the annual number of male patients who received dispensed prescriptions for testosterone from outpatient retail pharmacies from September 2009 through August 2017. The annual number of male patients aged 19 years and younger who received testosterone prescriptions increased (b) (4)% from approximately (b) (4) patients in the year ending August 2010 to (b) (4) patients in the year ending August 2017. During the time examined, male patients aged 14-17 years old comprised annually approximately half of all male patients aged19 years and younger who received testosterone prescriptions. The annual number of male patients aged 14-17 years who received testosterone prescriptions increased (b) (4)% from approximately (b) (4) patients in the year ending August 2010 to (b) (4) patients in the year ending August 2017. Approximately (b) (4) male patients aged 13 years or younger received testosterone prescriptions in the year ending August 2017, as well as (b) (4) male patients aged 18-19 years.

3.3 ADMINISTRATIVE CLAIMS DATA

We extracted enrollment and claims data for a total of (b) (4) male patients with a medical or pharmacy claim for testosterone aged 19 years or younger. We excluded 113 patients due to missing or incomplete data. Approximately 30% of testosterone claims were medical claims for the administration of injectable testosterone or placement of testosterone subcutaneous pellet implant. The remaining 70% were outpatient pharmacy claims for dispensed testosterone products. After applying the criteria to define chronic testosterone users, a final sample of (b) (4)

[b] IQVIA, National Sales Perspectives™. Sept 2016 – Aug 2017. Extracted 10/20/2017. File: NSP testosterone in boys 0-19yo 2017-2072.xlsx.

male patients was identified: (b) (4) patients aged 13 years and younger, (b) (4) patients aged 14-17 years, and (b) (4) patients aged 18-19 years.

Table A2 in **Appendix A** displays the top 25 ICD-9 diagnoses codes possibly related to testosterone therapy based on diagnosis claims data captured for male patients aged 14-17 years old. Data for patients in the other age groups was provided for context. The diagnoses results included in this analysis are not mutually exclusive and should not be summed, or patient counts may be overestimated. Each diagnosis should be evaluated independently of other diagnoses. For example, a 15-year old patient may have had claims for testicular hypofunction and claims for Klinefelter syndrome in the 12 months prior to initiating testosterone therapy.

Among the (b) (4) patients 14-17 years old, the most prevalent diagnosis code captured was *other testicular hypofunction* (ICD-9 code 257.2), a diagnosis code present in the claims of (b) (4) ((b) (4)%) patients. This was followed closely by *delay in sexual development and puberty, not elsewhere classified* (ICD-9 code 259.0), seen in (b) (4) ((b) (4)%) patients. *Lack of expected normal physiological development* (ICD-9 code 783.4) was seen in (b) (4) ((b) (4)%) patients, and *Klinefelter syndrome* (ICD-9 code 758.7) was seen in (b) (4) ((b) (4)%) patients.

Among the (b) (4) patients 0-13 years old, the diagnosis of *other testicular hypofunction* was present in the claims of (b) (4) ((b) (4)%) patients, and *delay in sexual development and puberty, not elsewhere classified* was present for (b) (4) ((b) (4)%) patients. Among the (b) (4) patients 18-19 years old, the diagnosis of *other testicular hypofunction* was present in the claims of (b) (4) ((b) (4)%) patients, and *other anterior pituitary disorders* (ICD-9 code 259.0) was present in (b) (4) ((b) (4)%) patients.

4 DISCUSSION

Of all FDA-approved products containing testosterone, two products—testosterone enanthate and testosterone subcutaneous pellet implant—are approved to treat "carefully-selected" adolescent males with "clearly delayed puberty". No testosterone products are currently FDA approved to treat adolescent males on a long-term basis. Based upon outpatient retail pharmacy data, less than (b) (4) adolescent males aged 14-17 years received dispensed testosterone prescriptions annually. However, some patients may receive testosterone only during visits to outpatient medical facilities, such as injections administered in doctor’s offices or clinics. We analyzed pharmacy and medical claims from a sample of male children and adolescents up to 19 years old with commercial insurance who received testosterone from a pharmacy or outpatient medical facility. Of all patients with a testosterone claims, 17% of patients met our definition for long-term use, around half of whom were aged 14-17 years old. However, based on healthcare claims data alone, the reason for long-term use of testosterone was not easily ascertained. The most prevalent conditions captured based on billing data in the patients with claims suggestive of long-term testosterone use were for relatively nonspecific disorders: testicular hypofunction,

delayed puberty, and lack of expected physiological development. Small percentages of patients had claims for conditions such as Klinefelter syndrome, pituitary dwarfism or pituitary neoplasm; conditions that may require testosterone therapy over long periods of time.

Findings from this review should be interpreted in the context of the known limitations of the databases used. We used outpatient pharmacy claims to calculate a national annual estimate of boys and adolescent males who received dispensed testosterone prescriptions. This national annual estimate did not take into account male patients who were administered testosterone only in an outpatient medical facility, such as a clinic or doctor's office. Furthermore, we used commercial administrative claims from a robust sample of commercial healthcare plans to identify possible diagnoses or conditions for which testosterone was dispensed or administered on a long-term basis. These results are not generalizeable to patients who do not have commercial insurance, such as Medicaid patients or patients without health care coverage or pharmacy coverage. Also, the analysis was not designed to determine the one singular diagnosis for which a patient received testosterone. Instead, the analysis evaluated each possible diagnoses independently and determined the number of patients in each age group with that particular diagnosis present in the claims prior or proximal to the start of testosterone therapy. This provides only a crude estimate of the possible indication for the patients who started testosterone therapy. Medical charts were not available to validate the diagnosis or condition for which a patient received testosterone therapy. Furthermore, ICD-9 codes were not mapped to ICD-10 codes due to a lack of access to a validated crosswalk, and therefore the results included only ICD-9 codes. However, ICD-9 codes comprised the vast majority of diagnosis claims in this data.

5 CONCLUSION

Testosterone use was low among adolescent males aged 14-17 years old, and long-term testosterone therapy was present but very low. The reason for long-term testosterone therapy was difficult to ascertain. The most prevalent diagnoses identified in claims data were relatively nonspecific and related to testicular hypofunction and delayed puberty. Small percentages of patients had claims with more specific diagnoses, such as Klinefelter syndrome or panhypopituitarism.

6 APPENDICES

6.1 APPENDIX A. TABLES AND FIGURES

Table A1. Nationally estimated number of male patients with dispensed prescriptions for testosterone from U.S. outpatient retail pharmacies, stratified by age, September 2009 through August 2017, annually.

	Year ending Aug 2010		Year ending Aug 2011		Year ending Aug 2012		Year ending Aug 2013	
	Patients* (N)	*Share (%)*	Patients (N)	*Share (%)*	Patients (N)	*Share (%)*	Patients (N)	*Share (%)*
All male patients								(b) (4)
0-19 years old								
0-13 years old								
14-17 years old								
18-19 years old								
20+ years old								
Unspecified age								

	Year ending Aug 2014		Year ending Aug 2015		Year ending Aug 2016		Year ending Aug 2017	
	Patients (N)	*Share (%)*	Patients (N)	*Share (%)*	Patients (N)	*Share (%)*	Patients (N)	*Share (%)*
All male patients								(b) (4)
0-19 years old								
0-13 years old								
14-17 years old								
18-19 years old								
20+ years old								
Unspecified age								

Source: IQVIA, Total Patient Tracker™. Sept 2009-Aug 2017. File: TPT testosterone in boys 0-19yo 2017-2072 xlsx

* Unique patient counts may not be added across time periods or drug products due to the possibility of double counting those patients who are receiving multiple treatments over multiple periods in the study due to switching or other reasons. Summing across time periods or by drug product is not advisable and will result in overestimates of patient counts.

Table A2. Number of male patients from a sample of a commercially insured population with diagnosis conditions possibly related to testosterone therapy, stratified by age, January 2006 through December 2016, aggregated.

		0-13 years old (n= (b) (4))		14-17 years old (n= (b) (4))		18-19 years old (n= (b) (4))	
ICD-9 code	Diagnosis description	Patients* (N)	*Share (%)*	Patients (N)	*Share (%)*	Patients (N)	*Share (%)*
257.2	Other testicular hypofunction						(b) (4)
259.0	Delay in sexual development and puberty, not elsewhere classified						
783.4	Lack of expected normal physiological development						
758.7	Klinefelter syndrome						
253.2	Panhypopituitarism						
253.4	Other anterior pituitary disorders						
253.3	Pituitary dwarfism						
237.0	Neoplasm of uncertain behavior of pituitary gland and craniopharyngeal duct						
255.4	Corticoadrenal insufficiency						
259.1	Precocious sexual development and puberty, not elsewhere classified						
259.9	Unspecified endocrine disorder						
752.5	Undescended and retractile testicle						
752.8	Other specified congenital anomalies of genital organs						
227.3	Benign neoplasm of pituitary gland and craniopharyngeal duct (pouch)						
608.3	Atrophy of testis						
752.6	Hypospadias and epispadias and other penile anomalies						
253.9	Unspecified disorder of the pituitary gland and its hypothalamic control						
302.8	Other specified psychosexual disorders						
239.7	Neoplasm of unspecified nature of endocrine glands and other parts of nervous system						
253.7	Iatrogenic pituitary disorders						
253.8	Other disorders of the pituitary and other syndromes of diencephalohypophyseal origin						
608.8	Other specified disorder of male genital organs						
257.9	Unspecified testicular dysfunction						
253.1	Other and unspecified anterior pituitary hyperfunction						
315.9	Unspecified delay in development						

Source: IQVIA Real-World Data Adjudicated Claims – U.S. Database. Jan 2006-Dec 2016.

* Unique patient counts may not be added across diagnoses due to the possibility of double counting those patients who had claims for different diagnoses during the time examined. Summing across diagnoses is not advisable and will result in overestimates of patient counts.

6.2 APPENDIX B. NATIONAL DRUG CODES AND HEALTHCARE COMMON PROCEDURE CODING SYSTEM CODES

Table B1. National Drug Codes for testosterone

00002197590	00182306963	00304165156	00418050141	00574046000	00781307470	10719010142	38779004705	47649012905
00003032816	00182307363	00304182959	00418078110	00574046001	00781307471	10719010242	38779005403	47649018105
00003032840	00187020010	00306007810	00418079141	00574046005	00781309270	10719011042	38779005404	47679079230
00003038530	00188818344	00314008310	00418085110	00574046025	00781309370	10974003410	38779005405	47679079330
00007315518	00191004321	00314065270	00418655141	00574046101	00781309670	10974005110	38779016300	47679079430
00007315613	00191004421	00314076870	00418656141	00574046105	00781309770	10974005210	38779016303	47679079530
00009008510	00191004521	00314077170	00418657141	00574046125	00781310270	10974006710	38779016304	47679079730
00009008601	00191005121	00314077270	00427064670	00574082001	00781310570	10974007210	38779016305	49072071110
00009008610	00191005221	00314078670	00427064970	00574082010	00785801310	10974007510	38779016308	49072071710
00009025301	00191005621	00314081570	00427065070	00574082105	00785906710	11289837008	38779016309	49072072710
00009025302	00191008821	00314083570	00427065170	00574082710	00802395717	11289839008	38779016403	49137025610
00009034701	00191011421	00314087570	00436024870	00574091510	00802395719	11289840008	38779016404	49137035610
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00009041702	00217681208	00351048270	00455477010	00588504470	00814770540	11299001013	38779016409	49137071610
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51552002910	51552128305	52406008310	53638008430	54569633700	58597007704	62295290101	63370097025	
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Source: IQVIA Real-World Data Adjudicated Claims – U.S. Database. Jan 2006-Dec 2016.

Table B2. Healthcare Common Procedure Coding System (HCPCS) codes for testosterone

HCPCS code	Description
J0900	Testosterone enanthate to 1cc inj
J1060	Testosterone cypionate to 1ml inj
J1070	Testosterone cypionate to 100mg inj
J1080	Testosterone cypionate 1/200 mg inj
J1090	Testosterone cypionate-1 cc-50 mg
J3120	Testosterone enanthate to 100mg inj
J3130	Testosterone enanthate to 200mg inj
J3140	Testosterone susp to 50 mg inject
J3150	Testosterone propionate to 100mg inj
S0189	Testosterone pellet 75 mg

Source: IQVIA Real-World Data Adjudicated Claims – U.S. Database. Jan 2006-Dec 2016.

6.3 APPENDIX C. DRUG UTILIZATION DATABASE DESCRIPTIONS/LIMITATIONS

IQVIA, National Sales Perspectives™: Retail and Non-Retail
The IQVIA National Sales Perspectives™ measures the volume of drug products, both prescription and over-the-counter, and selected diagnostic products moving from manufacturers into various outlets within the retail and non-retail markets. Volume is expressed in terms of sales dollars, eaches, extended units, and share of market. These data are based on national projections. Outlets within the retail market include the following pharmacy settings: chain drug stores, independent drug stores, mass merchandisers, food stores, and mail service. Outlets within the non-retail market include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings.

IQVIA, Total Patient Tracker™ (TPT)
TPT is a national-level projected service designed to estimate the total number of unique (non-duplicated) patients across all drugs and therapeutic classes in the retail outpatient setting from United States retail pharmacies. Clients get access to all markets and can manipulate the period under study from 1 month to 1 year. Data are available back to January 2002 and are available 20 days after the close of the month. TPT uses the prescription activity as part of its projection and integrates information from pharmacies and payers to eliminate duplicate patients, and multiple prescriptions fills, producing quick and reliable unique patient counts. Prescription coverage is 90%, has a sample of 50,400 pharmacies, and captures about 3.7 billion transactions annually. TPT is projected to the known universe.

IQVIA Real-World Data Adjudicated Claims – U.S. Database
The IQVIA Real-World Data Adjudicated Claims – U.S. Database is a health plan claims database comprised of fully adjudicated medical and pharmacy claims on over 150 million individuals. These are unique, de-identified enrollees with both medical and pharmacy benefits. There are 10+ years of data history at any point in time with data history available to 2006. Data contributors to the database are largely commercial health plans and self-insured employer groups. Additionally, the database has a small set of Commercial Medicare and Commercial Medicaid patients. The database is used in a variety of life sciences and commercial effectiveness studies. It contains a longitudinal view of inpatient and outpatient services, prescription and office/outpatient administered drugs, costs and eligibility information. Over 250 peer reviewed publications have used IQVIA RWD Adjudicated Claims-U.S.

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/s/

CORINNE M WOODS
12/06/2017
Data vendor clearance 12/1

SHEKHAR H MEHTA
12/08/2017

TRAVIS W READY
12/08/2017

GRACE CHAI
12/12/2017

HUMAN FACTORS VALIDATION RESULTS REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	October 18, 2017
Requesting Office or Division:	Division of Bone, Reproductive, and Urologic Products (DBRUP)
Application Type and Number:	NDA 209863
Product Name and Strength:	Xyosted (testosterone enanthate) Injection 50 mg/0.5 mL; 75 mg/0.5 mL; 100 mg/0.5 mL
Product Type:	Combination Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Antares Pharma, Inc.
Submission Date:	December 20, 2016
OSE RCM #:	2016-2905 and 2017-432
DMEPA Primary Reviewer:	Walter Fava, RPh., MSEd.
DMEPA Team Leader:	Lolita White, PharmD.
DMEPA Associate Director for Human Factors:	QuynhNhu Nguyen, MS.

1 REASON FOR REVIEW

The Division of Bone, Reproductive, and Urologic Products (DBRUP) requested that DMEPA evaluate the human factors (HF) study report submitted on December 20, 2016 under NDA 209863. In addition, we provide a review of the Instructions for Use (IFU), carton labeling, device labels, and prescribing information (PI) to determine if it is acceptable from a medication error perspective.

2 PRODUCT INFORMATION

Xyosted (testosterone enanthate) injection is an androgen indicated for testosterone replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone including primary hypogonadism (congenital or acquired) and hypogonadotropic hypogonadism (congenital or acquired). The starting dose is 75 mg administered once a week and the dose can be adjusted based upon pre-dose testosterone trough levels (sample measured 7 days after most recent dose) that are obtained following 6 weeks of dosing. The dose may be increased or decreased by 25 mg for trough levels below or above 350 ng/dL and 650 ng/dL respectively. Xyosted is a single-use, disposable, autoinjector device intended for subcutaneous administration by patients or caregivers in the abdomen only. Xyosted will be available in strengths of 50 mg/0.5 mL; 75 mg/0.5 mL; and 100 mg/0.5 mL.

3 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C
ISMP Newsletters	D (N/A)
FDA Adverse Event Reporting System (FAERS)*	E (N/A)
Other	F (NA)
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

4 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Our assessment of the human factors (HF) validation study results, prescribing information (PI), device labels, carton labeling and Instructions for use (IFU) are as follows:

4.1 HUMAN FACTORS VALIDATION STUDY RESULTS

Antares completed two validation studies to evaluate the safe and effective use of their device and its associated labels and labeling:

- Study CLS-1022-R1- This study was an actual-use HF study conducted with patients and caregivers to evaluate the safety and effectiveness of the device, packaging design, product labeling and Instructions for Use (IFU). The HF evaluation was integrated as part of a clinical trial with protocol reference (QST-16-006) where dedicated HF data collection and analyses were performed.
- Study HSS-1088-R1-A - This study was a simulated use study conducted with healthcare providers (HCPs) only to evaluate the effectiveness of the device, packaging design, product labeling and IFU for mitigating persisting patterns of use-errors or difficulties that could result in harm or impact effective treatment by healthcare practitioners HCPs. The validation also evaluated whether the end-users could use the product effectively without patterns of preventable use-errors or difficulties that could result in harm.

Human Factors Validation Study CLS-1022-R1 Results

Sixty-five (65) representative patients or caregivers participated in the actual use HF validation study with devices containing testosterone. Participants were randomized into trained and untrained groups and randomly assigned to one of three different dose strengths during the study (50 mg/0.5 mL, 75 mg/0.5 mL, and 100 mg/0.5 mL). Sixty-four participants performed their first injection. Fifty-nine participants returned a week later to perform a second injection. The one week learning/training decay interval is representative of the weekly injection schedule for the product. Patient participants performed an injection into their body and caregivers injected into the patient participants with hypogonadism. Tables 2 and 3 provide summary and analyses of results for this study.

Table 2: Summary of Critical Task Use Errors and Close Calls

Critical Tasks Description	1st injection (n=64)		2nd injection (n=59)	
	Use Errors	Close Calls	Use Errors	Close Calls
Remove Auto-Injector cap	1	3	0	1
Do not uncap before ready to use	12		11	

Do not recap before use	3			
Push Auto-Injector down against injection site until “click” is heard	3	5		4
Hold device for 10 seconds	21	2	28	
Check to see if viewing window is blocked	1	1	1	
Dispose of Auto-Injector in a sharps container	26	2	20	1

Table 3: Analyses of Critical Tasks Use Errors and Close Calls for Study CLS-1022-R1

Critical Tasks Description	Description of Use Errors	Description of Close calls	Applicant’s Root Cause Analysis	DMEPA’s Analysis and Recommendation
Remove auto-injector cap	First Injection: 1 Patient did not remove the injection cap.	First Injection: 1 Patient and 2 Caregivers recovered but almost did not remove injection cap. Second Injection: 1 Patient almost did not remove injection cap but recovered when looking back at the IFU	Antares states the device label and IFU indicate that the cap is to be twisted to be removed and additionally, since the cap must be removed to trigger the injection, it becomes evident to the user further in the injection process if the cap is not removed. According to Antares, the clinical impact of this failure to remove the pen cap would be no treatment, a dose omission or a delay in therapy until the end-user referred to the IFU or contacts a healthcare provider for use task clarification. Antares states that no further mitigation is required.	Failure to remove the auto-injector cap would result in delayed therapy. Our review of the instructions for cap removal and the participant subjective feedback provided finds the instructions are acceptable. In particular, we find the IFU instructions to ‘Remove Cap’ is prominent and provides the clear instruction to, ‘Twist the cap to remove (this will also break the red safety seal), and is accompanied by a figure illustrating how to twist the cap to remove. We agree that no additional mitigation is required to address risk of the failure to remove the auto-injector cap.
Do not uncap before ready to use	First Injection:	None	12 participants removed the device cap before being ready to	Our review of the participant subjective feedback and the IFU finds

Table 3: Analyses of Critical Tasks Use Errors and Close Calls for Study CLS-1022-R1				
Critical Tasks Description	**Description of Use Errors**	**Description of Close calls**	**Applicant's Root Cause Analysis**	**DMEPA's Analysis and Recommendation**
	6 Patients and 6 Caregivers removed the device cap before being ready to administer injection. Second Injection: 4 Patients and 7 Caregivers removed the device cap before being ready to administer injection.		administer the injection. Each of the experienced patients report subjective feedback of either curiosity or usual practices. 11 participants removed the cap before ready to inject. One patient wanted to see how it opened. One patient states as soon as I read the instructions I decided to remove the cap. One patient did not believe the order mattered. One patient did not provide feedback. One caregiver did not see a reason for the timing of the step. Two caregivers were observed on video review removing the cap with no subjective feedback collected. One caregiver said it was the first step on the paper. Antares provided a root cause analysis for these errors as information oversight. In addition, Antares provided responses to a questionnaire where forty-six out of fifty-nine participants indicated that the	the step to remove the autoinjector cap may be better presented to decrease risk of medication error of wrong technique. Specifically, the statement that users should not remove the cap until ready to perform the injection is located in the device diagram prior to step 1 and is not prominently placed. We recommend relocating the instruction to increase the prominence and decrease risk of infection and contamination. **We provide specific recommendations to address this concern in section 5.1.**

Table 3: Analyses of Critical Tasks Use Errors and Close Calls for Study CLS-1022-R1				
Critical Tasks Description	**Description of Use Errors**	**Description of Close calls**	**Applicant's Root Cause Analysis**	**DMEPA's Analysis and Recommendation**
			instruction for the step to remove autoinjector cap was clear to very clear. Eleven participants stated they did not see the instruction. Antares did not provide any information about the remaining two participants. Antares states that no further mitigation is required.	
Do not recap before use	First Injection: 2 Patients and 1 Caregiver recapped the device prior to administering the injection.	None	Three participants thought putting the cap back on would reduce contamination of the needle. Antares states the IFU warning to not replace the cap for later use was added prior to the summative study and that no further mitigation is required.	Our review of the IFU finds that step one includes the statement, '**DO NOT** recap for later use'. Since the device has a needle guard, we do not see contamination as a likely occurrence if the device cap is removed too soon during the injection process. We agree that the IFU statements mitigate this use error adequately, and that no further mitigations of these errors are required.
Push Auto-Injector down against injection site until "click" is heard	First Injection: 3 patients did not push auto-injector down against site so first "click" is heard.	First Injection: 3 Patients and 2 Caregivers recovered, but almost did not push auto-injector down against site so first click is heard.	The three participants that experienced use errors indicated that they were unable to actuate the device. Through root cause analysis, the sponsor indicated that devices had irregularly high activation forces and were not able to be activated due to this. The	Regarding the devices with irregularly high activation forces, our internal discussions with the division has provided information that the Phase 3 data shows 93 per cent efficacy and no device-related adverse events. However, we defer to CDRH's review of the device activation force specification.

Table 3: Analyses of Critical Tasks Use Errors and Close Calls for Study CLS-1022-R1				
Critical Tasks Description	**Description of Use Errors**	**Description of Close calls**	**Applicant's Root Cause Analysis**	**DMEPA's Analysis and Recommendation**
	Second Injection: None	Second Injection: 1 Patient and 3 Caregivers recovered, but almost did not push auto-injector down against site so first "click" is heard.	sponsor considered these use errors to be study artifacts. Two injection experienced patients, three injection experienced caregivers and two injection naïve patients recovered but initially thought pressing the top of the device like a button would actuate the device. Antares states that all participants were eventually successful in triggering the device (pushing against the injection site until a click is heard) and that no further mitigation is required.	Our review of the IFU confirms that step 3 entitled, 'Inject and Hold Down', provides the instruction, 'Firmly push Auto-Injector down on the site and continue to hold down after you hear the 'CLICK' (see Figure 7). Furthermore, figure 7 is labeled , '**PUSH (CLICK) HOLD'**. We find that should this type of error occur, it is likely to only occur initially and upon repeated use, the patient or caregiver will hold the auto-injector in place until the click sound is heard. This is evident by the lack of use errors seen in the 2nd injection. As such, we have no recommendations for changes to the IFU to further mitigate these close call errors.
Hold device for 10 seconds	First Injection: 10 Patients and 11 caregivers did not hold device for 10 seconds Second Injection:	First Injection: 2 Caregivers recovered, but almost did not hold the device for 10 seconds Second Injection: No close calls	30 participants that experienced use errors indicated that they thought they held the device for the full 10 seconds. The other 16 participants indicated that they used the viewing window or second click as a guide for the injection time. According to Antares, the device takes 6.3 seconds on average to complete the delivery of the drug	While not holding the auto-injector to the site long enough to inject the drug results in an under dose of testosterone, we do not believe that would result in life threatening or serious harm. Our review of the IFU and the device label determined that the instruction to hold the injection for 10 seconds,

Table 3: Analyses of Critical Tasks Use Errors and Close Calls for Study CLS-1022-R1				
Critical Tasks Description	**Description of Use Errors**	**Description of Close calls**	**Applicant's Root Cause Analysis**	**DMEPA's Analysis and Recommendation**
	14 patients and 14 caregivers did not hold device for 10 seconds		product. In reviewing the injection time, a total of 12 participants in the first injection and 9 in the second injection held the device in place less than 7 seconds. The sponsor reaffirms that if the user chooses to use the auditory click or viewing window as a guide for complete injection it is appropriate. Antares concludes that none of the use-errors observed were attributed to the design of the proposed, intended-to-market device; therefore, no design changes to the device are required for safe and effective use by the intended end-users in the intended use environment. Antares states the risk has been reduced as far as possible through labeling and device design and no further mitigation is required.	(While holding Auto-Injector down, slowly count from 1 to 10 to allow all of the medication to be delivered), is clearly stated and includes a graphic of a clock face depicting 10 seconds. In addition, based on the subjective feedback from participants provided in the results summary which indicated the reason for the short injection was related to confusion of the device cues (i.e. the viewing window changing color and the sound of a second click at different times). Thus, we determined that the use-errors observed were attributed to the user interface of the product. In conversations with the review team, we discussed that although failure to hold the injection in place for 10 seconds as labeled or the critical 6.3 second minimum may lead to under dosing, we agree with Antares and the Division concurs that this has a low potential for physical harm and is not a significant safety concern. As such, no additional mitigation is required.

Table 3: Analyses of Critical Tasks Use Errors and Close Calls for Study CLS-1022-R1				
Critical Tasks Description	**Description of Use Errors**	**Description of Close calls**	**Applicant's Root Cause Analysis**	**DMEPA's Analysis and Recommendation**
Check to see if viewing window is blocked	First Injection: 1 Caregiver did not check the viewing window after injection Second Injection: 1 Caregiver did not check the viewing window after injection	First Injection: 1 Patient recovered, but almost did not check the viewing window after injection. This participant checked the window when asked if they got the complete dose but was able to identify they did not get the dose, because they saw a bubble in the remaining medication	Of the two user errors, one participant indicated that they forgot to check the viewing window. The other participant indicated that they just need to check the viewing window once. During the knowledge assessment, Antares states that 58 out of 59 end-users questioned indicated that it was clear to very clear in the IFU how to check that all the drug was delivered by checking the viewing window. The one exception is the participant who indicated that the instruction to check the viewing window was slightly unclear. Additionally, Antares states the device has a large viewing window on each side that changes from clear to high-contrast orange upon use of the device, and no further mitigation is required.	Without checking the window, the user may be uncertain whether a dose has been delivered. In addition to the window serving as a visual cue, the device has an auditory cue of a 'click', to inform the user that an injection has been complete. Our review of the IFU confirms that step 4 entitled, 'Inspect Viewing Window', is prominent and includes the instruction, 'After injecting, inspect the Viewing Window. (b)(4) however, we find a single occurrence of underdose in this particular product to be clinically insignificant. As such, we have no additional recommendations to further mitigate these errors.

Table 3: Analyses of Critical Tasks Use Errors and Close Calls for Study CLS-1022-R1				
Critical Tasks Description	**Description of Use Errors**	**Description of Close calls**	**Applicant's Root Cause Analysis**	**DMEPA's Analysis and Recommendation**
Dispose of Auto-Injector in a sharps	First Injection: 14 Patients and 12 Caregivers did not dispose of the AI in a sharps container. Second Injection: 11 Patients and 9 Caregivers did not dispose of the AI in a sharps container	First Injection: 2 patients recovered, but initially wanted to dispose the device in the trash due to their prior experience with needles/injections. Second Injection: 1 Caregiver recovered, but almost did not dispose of the AI in the sharps container.	15 participants mentioned they were unsure and did not know how to properly dispose the device. 30 participants disposed the device in the household trash (or recycling) due to personal habit. Antares references the FDA Sharps Disposal website is provided in the disposal section of the IFU. Antares further states that safety of disposal of the device in regular trash is ensured with a locking needle shield and that no further mitigation is required.	Our review of the IFU identified the prominent heading, 'Disposal After Injection' which precedes instructions on how to properly dispose of the device in an FDA-cleared sharps container immediately after use. The clinical impact of improper disposal of the device is the risk of needle stick injuries if the plastic outer needle cover was broken and the needle became exposed. We acknowledge the auto-injector has a locking needle shield and thus we find the risk of needle sticks low. No further mitigation is needed.

Human Factors Validation Study HSS-1088-R1 A

Fifteen (15) health care professionals representative of intended users participated in this simulated use study to evaluate the effectiveness of the device, packaging design, product labeling and IFU. The goal of the study was to mitigate persisting patterns of use-errors or difficulties that could result in harm or impact effective treatment by healthcare practitioners All participants were randomized to administer one of three doses (50 mg, 75 mg, or 100 mg) and asked to choose the correct dose prior to the injection. They were instructed to use the device as they would in their clinics and as if study staff were not present. Each participant performed two injections. There were 25 use errors occurred for the following critical tasks from participants performing two injections:

- Do not uncap until ready to use (n=4)
- Do not recap (n=2)
- Hold injection for 10 seconds (n=19)

Table 4: Analyses of Critical Tasks Use Errors and Close Calls for HSS-1088-R1 A

Critical Tasks Description	Description of Use Errors	Description of Close calls	Applicant's Root Cause Analysis	DMEPA's Analysis and Recommendation
Do not uncap before ready to use	First Injection: 4 participants removed the device cap before being ready to administer injection. Second Injection: None	None	Four participants removed the device cap before being ready to administer the first injection and there were no errors for the second injection. One participant stated they had to go back and look at the directions; one participant stated they were following the steps and knew for the 2nd injection I could bring it and take cap off next to the patient; one participant knew they made a mistake; the fourth participant provided no	Our review of the subjective feedback finds that none of the participants indicated that they were confused or did not understand the instructions for use. The use task failures in the previous Human Factors Validation Study CLS-1022-R1 resulted in 23 failures with this use step. Our review of the IFU notes the warning statement that users should not remove the cap until ready to perform the injection is located with the device diagram prior to step 1. While we see an improvement in the number of failures between the first study and the second study, the error still occurred. We recommend

Table 4: Analyses of Critical Tasks Use Errors and Close Calls for HSS-1088-R1 A				
Critical Tasks Description	**Description of Use Errors**	**Description of Close calls**	**Applicant's Root Cause Analysis**	**DMEPA's Analysis and Recommendation**
			subjective feedback. Antares did not provide a true root cause for these errors. They only indicated that the possible root cause was information oversight.	relocating the instruction to remove the cap task of the IFU to step 1 to increase prominence and to decrease risk of infection and contamination. **We provide specific recommendations in section 5.1.**
Do not recap before use	First Injection: 2 participants recapped the device prior injecting. Second Injection: None	None	One participant decided to look at directions and didn't want to put it down uncovered; One participant stated he was seeing if he had to activate it. Antares documented that one end-user thought putting the cap back on would reduce contamination of the needle and the other recapped the device in an attempt to learn more about the functionality of the injector.	The device has a needle guard that minimized the risk of contamination if the device cap is removed too soon during the injection process. We also note that the number of failures decreased from 4 in the first study to 3 in the second study. We agree that the IFU statements mitigate this use error adequately. We have no additional recommendations for further mitigations of these errors.
Hold device for 10 seconds	First Injection: 9 participants did not hold the device in place for 10 seconds. Second Injection: Ten (10) end-users	None	6 participants withdrew the AI early in response to the window becoming occluded. 3 participants withdrew the AI early secondary to auditory clicks. 10 participants counted for what they thought was 10 seconds.	Our review of the IFU and the device label determined that the instruction to hold the injection for 10 seconds, (While holding Auto-Injector down, slowly count from 1 to 10 to allow all of the medication to be delivered), is clearly stated and includes a graphic of a clock face depicting 10 seconds. Although failure to hold the injection in place for

Table 4: Analyses of Critical Tasks Use Errors and Close Calls for HSS-1088-R1 A				
Critical Tasks Description	**Description of Use Errors**	**Description of Close calls**	**Applicant's Root Cause Analysis**	**DMEPA's Analysis and Recommendation**
	did not hold the device in place for 10 seconds.		None of the feedback obtained from participants during the second injection indicates that the end-users were confused or did not understand the instructions to hold for 10 seconds. Furthermore, according to Antares, the device delivers the drug in 6.3 seconds and the 10 second hold time is intended to provide a factor of safety in the event a user counts quickly. Antares states the risk has been reduced as far as possible through labeling and device design and no further mitigation is required.	10 seconds as labeled or the critical 6.3 second minimum to deliver a complete dose may lead to under dosing, we find this risk acceptable, and the division concurs, due to the low risk of clinical harm to end-users and we have no recommendations to mitigate the risk of these errors and close calls.

4.2 INSTRUCTIONS FOR USE

We reviewed the proposed IFU for risk of medication error and areas of needed improvement. Our review identified the following:

- The warning statement that users should not remove the cap until ready to perform the injection is not prominently placed and may be overlooked. We provide further recommendation in section 5.1 below.

4.3 CARTON LABELING, DEVICE LABEL AND PRESCRIBER INFORMATION

We reviewed the proposed Xyosted labels and labeling for vulnerability to medication error and areas of needed improvement. We note the submitted device labels and carton labeling contain revisions are in response to recommendations that we made during a previous label and labeling review.[a] Our current review of the device label, carton labeling, and prescribing information (PI) for Xyosted finds them acceptable from a medication error perspective. We have no further recommendations at this time.

5 CONCLUSION & RECOMMENDATIONS

We conclude that the human factors validation study results identify a lack of clarity in the task of when to remove the pen cap which may pose risk of medication error of wrong technique leading to product contamination, if removed before the user is ready to inject.

We provide a recommendation to the Applicant to address our concerns to increase the prominence of the use task of do not remove cap until ready to inject. We advise these recommendations are implemented prior to the approval of this application. Please see our recommendation in sections 5.1 below for Antares.

5.1 RECOMMENDATIONS AND COMMENTS FOR ANTARES

The results of your patient and caregiver validation study (CLS-1022-R1) and healthcare provider validation study (HSS-1088-R1A) show use errors with the critical task of uncapping the device before the user is ready to inject. We are concerned with these use errors because they may lead to infection and unintended exposure. We have the following recommendation to further optimize the Instructions for Use (IFU), which do not require additional validation:

1 As currently presented in the IFU, the statement, 'Do not remove cap until ready to inject', is located above the diagram of the device instead of in close proximity to the corresponding use task. The removal of the cap prior to use poses risk of medication error of wrong technique which may result in contamination or infection. Based on the errors

[a] Baugh D. label and Labeling Review for Xyosted (NDA 209863). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 May 12. RCM No.: 2017-432.

noted in the HF validation study and the participant subjective feedback, we recommend adding the same statement to the section titled, “Inspect Autoinjector”, to call the user’s attention that they should not remove the cap until they are ready to inject.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Xyosted that Antares submitted on December 20, 207.

Table 2. Relevant Product Information for Xyosted	
Initial Approval Date	N/A
Active Ingredient	testosterone enanthate
Indication	testosterone replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone including primary hypogonadism (congenital or acquired) and hypogonadotropic hypogonadism (congenital or acquired)
Route of Administration	Subcutaneous
Dosage Form	Injection
Strength	50 mg/0.5 mL; 75 mg/0.5 mL; 100 mg/0.5 mL
Dose and Frequency	The starting dose is 75 mg administered once a week and dose can be adjusted based upon pre-dose testosterone trough levels (sample measured 7 days after most recent dose) that are obtained following 6 weeks of dosing. The dose may be increased or decreased by 25 mg for trough levels below or above 350 ng/dL and 650 ng/dL respectively.
How Supplied/ Container Closure	Carton containing 4 single-use auto-injectors
Storage	68° F to 77°F (20°C to 25°C) Protect from light

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On May 25, 2017, we searched the L:drive and AIMS using the terms, Testosterone enanthate and Xyosted to identify reviews previously performed by DMEPA.

B.2 Results

Our search identified five previous reviews[b],[c],[d],[e],[f], and we confirmed that our previous recommendations communicated to the Applicant thus far have been implemented.

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[b] Fava, W. Label, labeling and human factors usability study review for Testosterone enanthate (IND 116022). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2014 December 15. RCM No.: 2014-2234.

[c] Fava, W. Human Factors Study Protocol for testosterone enanthate (IND 116022). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016 January 11. RCM No.: 2015-1461-1.

[d] Fava, W. Human Factors Validation Study Protocol Review for testosterone enanthate (IND 116022). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016 April 22. RCM No.: 2016-240

[e] Fava, W. Human Factors Validation Study Protocol Review Memo for testosterone enanthate (IND 116022). Silver Spring (MD): FDA, CDER, OSE DMEPA (US); 2017 February 2. RCM No.: 2016-1873

[f] Baugh, D. Label, Labeling, and Packaging Review for Xyosted (NDA 209683). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 MAY 12. RCM #: 2017-432

APPENDIX C. HUMAN FACTORS VALIDATION STUDY RESULTS SUBMISSION

EDR Link: ////CDSESUB1/EVSPROD/NDA209863/209863.enx

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[g] along with postmarket medication error data, we reviewed the following Xyosted labels and labeling submitted by Antares on December 20, 2017, and provided comments in review 2017-432 dated May 12, 2017[h].

- Device label
- Carton labeling
- Instructions for Use
- Prescribing Information (no image)

9 Pages of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

[g] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

[h] Baugh, D. Label, Labeling, and Packaging Review for Xyosted (NDA 209683). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2017 MAY 12. RCM #: 2017-432.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

WALTER L FAVA
10/18/2017

LOLITA G WHITE
10/18/2017

QUYNHNHU T NGUYEN
10/19/2017

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Center for Drug Evaluation and Research
Office of New Drugs
Office of Drug Evaluation IV
Division of Pediatric and Maternal Health
Silver Spring, MD 20993
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M E M O R A N D U M

From:	Jacqueline Spaulding, MD Division of Pediatric and Maternal Health (DPMH) Office of Drug Evaluation IV (ODE IV) Office of New Drugs (OND)
Through:	Mona Khurana, MD, Pediatric Team, DPMH John J. Alexander, MD, MPH. Deputy Director DPMH, ODE IV, OND
To:	Division of Bone, Reproductive, and Urologic Products
Application Number:	NDA 209863/IND 116022
Drug:	Xyosted (testosterone enanthate)
Applicant:	Antares Pharma, Inc.
Proposed Indication:	Testosterone replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone: • Primary hypogonadism (congenital or acquired) • Hypogonadotropic hypogonadism (congenital or acquired)
Proposed Dosage:	75 mg (i.e., one device) once a week. Adjust dose based upon pre- dose testosterone trough concentrations obtained after 6 weeks of Xyosted treatment
Route of Administration:	Subcutaneous injection
Consult Request:	DBRUP consulted DPMH on September 22, 2017 to re-evaluate whether or not a full waiver of required studies under the Pediatric Research Equity Act (PREA), as requested by the applicant in the Agreed initial Pediatric Study Plan (iPSP), is appropriate for this product and for all testosterone replacement therapy (TRT) drug products being developed for hypogonadism.

Materials Reviewed:
Relevant documents submitted in DARRTS under IND 116022

- Applicant's Request for Full Waiver of Pediatric Studies (December 11, 2014)
- Agreed Initial Pediatric Study Plan (iPSP) included FDA Advice Letter (February 9, 2015)

Relevant documents submitted in DARRTS under NDA 209863

- Module 2.2 - Introduction
- Module 2.5 - Clinical Overview

Background
The applicant, Antares Pharma, has developed Xyosted, {also known as QuickShot® Testosterone [QST] (testosterone enanthate) injection} which is a combination product containing a preservative-free testosterone enanthate injection within a disposable pre-filled syringe (PFS) system. [1]

At a pre-investigational new drug application (PIND) meeting on December 5, 2012,[2] DBRUP informed Antares Pharma that the new route of administration of QST would trigger the requirement for a full pediatric assessment under PREA. The applicant stated they intended to submit an iPSP at the time of the End-of-Phase 2 (EOP2) meeting, and this plan would likely include a request for full waiver of pediatric studies in patients less than 17 years of age. The meeting minutes did not capture a discussion of the applicant's rationale for seeking a full pediatric waiver.

The IND 116,022 for QST injection was submitted to the Agency on July 26, 2013 for the proposed indication of testosterone replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone. [1] DBRUP subsequently issued an Agreed iPSP to the applicant on February 9, 2015 in which DBRUP agreed with the applicant's plan to request a full pediatric waiver on the basis that these studies would be impossible or highly impractical and there are too few pediatric patients with the disease/condition to study[3] This approach was also agreed to by the Pediatric Review Committee (PeRC) in 2015. [4] At a Type C Guidance meeting on May 1, 2017[5] the applicant inquired if there was FDA agreement on whether a "waiver of requirements for a pediatric development program [was] appropriate for the QST product for the indication of hypogonadism in adult males."

Notably, the Division of Metabolism and Endocrinology Products (DMEP) has granted full pediatric waivers of PREA requirements on the same basis for the following TRT NDAs:

1. Aveed (NDA 022219)[6]
2. Axiron (NDA 022504)[7]
3. Natesto (NDA 205488)[8] and;
4. Testim (NDA 021454)[9]

[1] NDA 209863, Xyosted, Clinical Overview
[2] Pre-IND Meeting Minutes, IND 116022, December 5, 2012
[3] Agreed iPSP and Advice Letter for NDA 209863 (February 9, 2015)
[4] PeRC Meeting Minutes (February 4, 2015.
[5] IND 116022, Type C Guidance Meeting (May 1, 2014
[6] Aveed, NDA 022219, Approval Letter
[7] NDA 022504 Axiron Approval Letter
[8] NDA 205488 Natesto Approval Letter
[9] NDA 021454 Testim Approval Letter

Table 1 in the Appendix contains a listing of currently approved prescription TRT products in the United States along with PREA requirements issued for these products. On December 20, 2016 the applicant submitted a new drug application (NDA) 209863 for QST injection as a 505(b)(2) relying in part on the safety and effectiveness of listed drug, Delatestryl (testosterone enanthate) injection NDA 009165 and the published literature . The NDA for QST is currently under review in DBRUP and has a PDUFA goal date of October 20, 2017.

On September 20, 2017 DBRUP met with the PeRC to discuss potential issuance of PREA post-marketing requirements (PMRs). DBRUP noted that the Agreed iPSP contained a full pediatric waiver request, but the PeRC did not agree that granting the applicant a full waiver would be appropriate. DMEP colleagues were also present at the PeRC meeting to provide subject matter expertise and advocated for the need for pediatric studies to provide therapies which offer a meaningful benefit over existing treatment. DMEP colleagues noted that adolescent males 14 years to 17 years of age with congenital or pathological causes of hypogonadism requiring chronic replacement therapy may be an appropriate pediatric population which would benefit from being included in development programs for TRT products. DMEP colleagues noted that the current standard of care for this adolescent male population is intramuscular TRT which must be administered by a healthcare provider in a medical setting. DMEP noted that availability of QST may provide a meaningful benefit over IM TRT by reducing patient and caregiver burden by allowing self-administration at home. DMEP noted that the only other available TRT treatments generally accepted for use are testosterone gels and patches, none of which are approved for use in pediatric patients. The PeRC discussion centered on what kinds of studies could be done in this small population to collect interpretable data which could be informative to prescribers and added to product labeling. The PeRC recommended that DBRUP consider a deferred study in adolescent males 14 years to less than 17 years of age and a partial waiver for pediatric patients less than 14 years of age.

Reviewer Comments: The PeRC's recommendation to evaluate TRT therapy in adolescent males for NDA #209863 represents a policy shift in the pediatric development program for other TRT products. Table 1 in the Appendix displays a listing one TRT product under development and currently approved prescription TRT products for the indication of replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone (primary or secondary hypogonadism) and the PREA requirements which were issued and/or waived for these products and the basis for the waiver wherever applicable.

Reconsideration of pediatric development for TRT products must also consider the known safety concerns associated with the use of acute and chronic testosterone therapy. [10] *Testosterone therapy may be associated with an increased risk of serious adverse reactions in older males with certain diseases such as metastatic prostate cancer, breast cancer, undiagnosed prostate nodule or induration, unexplained PSA elevation, erythrocytosis (hematocrit >50%), or unstable severe congestive heart failure. In contrast to older males, young adult men with hypogonadism have been reported to have a low frequency of adverse events with replacement doses of testosterone. Common adverse reactions reported with testosterone therapy include increase in hematocrit, acne, oiliness of skin, and breast tenderness. However, these safety issues have not been used as the basis for granting partial*

[10] Basin, S., Cunningham, G., Hayes, F., Matsomoto, A., Synder, P., Swerdloff, R., et al. (2006). Clinical Guidelines - Testosterone Therapy in Adult Men with Androgen Deficiency Syndrome: An Endocrine Society Clinical Practice Guideline. *The Journal of Clinical Endocrinology and Metabolism*, 1995-2010.

or full pediatric waiver requests for TRT drug products to date.

DPMH Discussion

Based on the PeRC's recommendations, DBRUP convened a meeting with DMEP and DPMH to discuss not only how to proceed with PREA PMRs for NDA 209863 but also for a broader discussion on how to approach pediatric development programs for all TRT drug products in development .[11] DBRUP described their approach to granting full waivers of required pediatric studies for other TRT drug products previously approved for the same indication. DPMH clarified that required studies under PREA would be to support the same indication in pediatric patients as that being sought in adults. DBRUP clarified that the indication being sought by the applicant for NDA 209863 is TRT for treatment of true hypogonadism in adult males.

Discussion then centered on identifying a pediatric subpopulation in whom the same indication would apply. DMEP noted that adolescent males 14 years to 17 years of age represent a pediatric subpopulation which could benefit from TRT drug products and in whom approved TRT drug products are likely being used off-label.

DMEP described the different causes of pediatric hypogonadism requiring chronic testosterone therapy. These include idiopathic causes (including constitutional delay), primary causes due to heritable conditions such as Klinefelter's syndrome, and acquired causes of pituitary-hypothalamic injury due to tumors, trauma, or radiation. DMEP proposed that a PREA assessment for QST may apply to adolescent males with primary or secondary of hypogonadism who would require chronic testosterone replacement therapy. DMEP commented that formal evaluation of TRT may give the Agency and providers a better understanding of the pharmacokinetics (PK) effects of different testosterone formulations; dosing effects, food effects and safety associated with chronic TRT in this adolescent population.

Discussion among DPMH, DBRUP and DMEP on whether adolescent males could benefit from chronic TRT and what type of studies would be feasible to obtain interpretable data to inform product use in this age group. General agreement was reached that further internal discussion was warranted to identify the type of study(ies) which could be conducted. Given the small patient population, there are feasibility concerns with requiring efficacy trials but studies designed to characterize the PK profile of TRT products and to show improvement in a pharmacodynamics marker (e.g. serum testosterone trough concentrations, Tanner stage) could be feasible and should be considered, particularly if efficacy could be extrapolated from adults with hypogonadism. There was general agreement that both short- and long-term safety should also be assessed, particularly if these products are to be given chronically, starting in adolescence.

DPMH conveyed the following two possible approaches to DBRUP for addressing PREA PMRs for NDA 209863:

1) grant the applicant a full pediatric waiver while making it clear to the applicant that FDA is re-visiting pediatric development programs for TRT products and that pediatric studies may be required for QST in the future; or
2) issue the applicant a PREA PMR for deferred studies in adolescent males 14 years to less than 17 years of age pending further internal discussion on how to study TRT drug products in this age group and grant a partial waiver for pediatric study requirements in patients less than 14 years of age on the basis that studies are impossible and highly

[11] DBRUP meeting with DMEP and DPMH (September 29, 2017)

impractical. With regards to option 1, FDA has the authority under the marketed drugs provision [12]to rescind a previously granted waiver when a public health benefit is anticipated as long as FDA explains the grounds under which the waiver was originally granted and justifies why the waiver should no longer be granted.

DPMH is not in favor of the first approach because of the potential legal issues related to conversion of a waiver that has been granted to a requirement to conduct deferred studies.

DPMH Recommendations

1. A partial waiver of pediatric study requirements for all TRT programs in patients less than 14 years of age is reasonable on the basis that studies are impossible and highly impractical. Further discussion is warranted with internal stakeholders regarding the optimal studies to be conducted (b) (4) and whether such studies are feasible.
2. Pending further internal discussion, DPMH recommends issuing a PREA PMR for deferred studies in adolescent males 14 years to less than 17 years of age (see discussion above). If, based on follow-up discussion, there is internal consensus that studies are infeasible in this age group, then the applicant may be released from any PMR in the future.

[12] Food and Drug Administration Amendments Act (FDAAA)

Appendix

Table 1: TRT Product in Development and Approved prescription TRT in the United States

Brand Name NDA or IND	Active Ingredient	Type of Formulation	PREA requirement	Basis for Action	Date of Approval	Indication
[redacted] (b) (4)						
Delatestryl NDA 009165	Testosterone enanthate	Injection	N/A	PREA not triggered	Prior to 01/1982 (per Orange book)	Same as above
Androgel	Testosterone	Transdermal gel	N/A	PREA not triggered	02/28/2000	Same as above
Testim NDA 021454	Testosterone	Gel	Full waiver	Necessary studies impossible or highly impractical	al10/31/ 2002	Same as above
Striant NDA 021543	Testosterone Extended-release	Oral (buccal) tablet	PMC	Continue ongoing studies for at least 2 years	06/19/2003	Same as above
Axiron NDA 022504	Testosterone	Topical solution	Full waiver	Necessary studies impossible or highly impractical.	11/23/2010	Same as above
Fortesta NDA 021463	Testosterone	Transdermal gel	N/A	PREA not triggered	12/29/2010	Same as above
Androderm NDA 020489	Testosterone extended-release	Transdermal film	N/A	PREA not triggered	10/20/2011	Same as above
Aveed NDA 022219	Testosterone undecanoate	Injection	Full waiver	Necessary studies impossible or highly impractical . groups	03/05/2014	Same as above
Natesto	Testosterone	Spray	Full waiver	Necessary	05/28/2014	Same as above

NDA 205488				impossible or highly impractical		
Volgexon NDA 204399	Testosterone	Transdermal gel	N/A	PREA not triggered	06/04/2014	Same as above

Source: Drugs at FDA, Orange Book
N/A = Non-applicable

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/s/

JACQUELINE A SPAULDING
10/12/2017

MONA K KHURANA
10/12/2017

LYNNE P YAO
10/16/2017

M E M O R A N D U M

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: October 5, 2017

To: Hylton V. Joffe, M.D., Director
Division of Bone, Reproductive, and Urologic Products

Through: Dominic Chiapperino, Ph.D., Acting Director
Martin Rusinowitz, M.D., Medical Officer
Silvia Calderon, Ph.D., Pharmacologist
Controlled Substance Staff

From: Alicja Lerner, M.D., Ph.D., Medical Officer
Controlled Substance Staff

Subject: **NDA 209863/IND 116022**
Name: XYOSTED, Testosterone Enanthate Injection, QuickShot™ USP
Indication: For the treatment of adult males with hypogonadism.
Dosage: 100 mg/ mL, 150 mg/mL, and 200 mg/mL at injection volume of 0.5 mL administered subcutaneously delivering 50, 75, or 100 mg of testosterone enanthate once weekly
Sponsor: Antares Pharma, Inc.
PDUFA Goal Date: Oct 20, 2017

Materials Reviewed:

- NDA in DARRTS Dec 20, 2016
- Meeting Minutes Nov 28, 2016
- Response to CSS IR included in 74-day letter from Feb 24, 2017 received April 4, 2017
- Response to IR from July 10, 2017 received July 28, 2017
- Response to IR from Aug 21, 2017 received Aug 29, 2017

Table of Contents

A. SUMMARY

I. BACKGROUND

This memorandum responds to a consult from the Division of Bone, Reproductive, and Urologic Products (DBRUP) requesting Controlled Substance Staff (CSS) to review section 9 of the PI, specifically keeping in mind that the proposed formulation is an injectable for patient self-subcutaneous (SC) administration at home.

Testosterone Enanthate Injection for SC administration, QuickShot™ (QST) NDA (b) (4) with indication for the treatment of adult men with hypogonadism, was submitted as a 505(b)(2) NDA using Delatestryl® Injection as the approved listed drug (LD).

The Sponsor has developed QST as a single-use, pressure-assisted autoinjector prefilled with testosterone solution designed for SC self-administration.

CSS has requested additional information on dependendence, withdrawal, and drug accountability (Information requests letters dated Feb 24, July 10, and Aug 21, 2017).

During the drug development program the Sponsor performed 5 clinical studies for QST ; QST-14-004, QST-13-002, QST-16-006, QST-13-003 and QST-15-005:

- QST-14-004 - Phase 1: open-label, single-dose study of 50 and 100 mg injections via QST in healthy male subjects
- QST-13-002 - Phase 2, bioavailability study of QST (50 and 100 mg SC) versus Delatestryl® 200 mg IM: 3-arm, open-label, randomized, multi-dose parallel group study
- QST-16-006 - Phase 2: open-label, safety and tolerability of 2 single doses of 50 mg, 75 mg, or 100 mg doses ofQST.
- QST-13-003 - Phase 3: double-blind, multiple-dose, 52-week study of efficacy and safety

- QST-15-005 - Phase 3: double-blind, multiple-dose, 6-month safety study of QST

II. CONCLUSIONS

1. Testosterone and, thus, all testosterone containing products are controlled in Schedule III of the Controlled Substances Act (CSA) since 1990.

2. Testosterone products are known to form dependence resulting in a withdrawal syndrome upon drug discontinuation in healthy men and women (athletes, bodybuilders) who take it in supratherapetic doses. However, the data on consequences of testosterone withdrawal in older men with hypogonadism after testosterone replacement therapy (TRT) are very sparse. Therefore, sponsors should continue to acquire reports of adverse events (AEs) indicating these withdrawal signs and symptoms in future clinical studies, to further refine section 9.3 Dependence of testosterone products' labeling (see Recommendations).

3. Review of the safety database for this NDA identified two cases related to suicidality; one of these cases was a "completed suicide," and the second one was coded as "depression" but was in reality a "suicide attempt." The risk of suicidality in testosterone and anabolic steroids abusers was noted already during testosterone TSI # 1351 (4 completed suicides, 6 suicide attempts, and 12 suicidal ideations).

4. Upon identification of the two "suicidality" cases under the current NDA for QST, CSS recommended that the Division consult OSE/DPV to evaluate further this issue, the Division followed up on this request and the corresponding review from OSE can be found in DARRTS (DARRTS, NDA 209863, Author: Kapoor Rachna, 08/30/2017). However, the review states that it is only "high level" review, and a detailed analysis of cases was not performed. However, CSS further reviewed the data and information provided in the OSE/DPV review, and presents some representative cases and provides further comments and recommendations (see Discussion, section on Post-marketing data).

5. Depression in older hypogonadal men has been observed (Barrett-Connor et al. 1999, Shores et al., 2004; Amore et al., 2008; Makhlouf et al., 2008). also depressed men with lower levels of testosterone were shown to be at higher risk of suicide (Sher, 2013). Treatment with testosterone may cause depression as an AE (see labeling). In the current NDA, 15-30% of subjects with the disease condition had a history of depression, and some subjects were discontinued due to AEs of depression. However, suicidality during TRT and upon withdrawal of testosterone has not been evaluated and, therefore, it is recommended in the future studies of TRT that depression and suicidality are evaluated with appropriate questionnaires (see Recommendations). These scales are in common use for other psychoactive drugs in patient populations with a history of depression, current depression, and for drugs known to precipitate depression.

6. Dependence was not systematically evaluated in any of the conducted studies and there is no data on dependence and withdrawal in this NDA. Information on withdrawal AEs were requested twice, in the 74-day letter and in an IR dated July 7, 2017. It appears though that

the Sponsor is confusing the situation where subjects discontinue drug treatment due to AEs (discontinuation AEs) and the situation where drug discontinuation leads to AEs (withdrawal AEs).

7. There was a number of cases where drug accountability discrepancies were reported in the clinical studies QST-13-003 and QST-15-005 and showed that some subjects lost a number of devices, representing 60 % to 80 % of the total amount of devices received by these subjects. These cases may be indicative of drug misuse and/or diversion of the study drug (see Discussion, section on Diversion/Drug Accountability).

8. There were three cases of "above expected testosterone levels" that may be indicative of misuse. Two cases with levels above 1500 ng/dL and one case of 2300 ng/dL 3 hours post dose. As the submission's ISS states (page 18), the maximum C_{trough} values were in the range of 900-1300 ng/dL, with mean values all below 500 ng/dL. .

III. RECOMMENDATIONS

1. Since testosterone is known to be abused and misused, we recommend continuing post-marketing assessment of AEs suggestive of abuse-potential, dependence, and withdrawal. These assessments should be included in the Sponsor's standard Periodic Adverse Event Reports (PADERS).

2. If new clinical studies are conducted with QST, then CSS recommends evaluation of dependence and withdrawal at the end of the trial(s). In order to evaluate potential dependence and withdrawal after discontinuation of therapeutic doses of testosterone, it is recommended that all AEs be collected for at least 4 weeks from drug discontinuation, at weekly intervals. Additionally, we recommend that appropriate depression, suicidality, and insomnia scales be administered (see below).

3. CSS recommends addressing the need for studing the signs and symptoms following discontinuation of testosterone containing product, and we suggest including the following language for sponsors at the time of future Pre-IND or IND submissions:

   A testosterone withdrawal syndrome may last for weeks or months and include the following withdrawal symptoms and signs: depressed mood, major depression, fatigue, craving, restlessness, irritability, anorexia, insomnia, decreased libido and hypogonadotropic hypogonadism. Although a testosterone withdrawal syndrome is known to occur after prolonged use of supra-therapeutic doses of testosterone, withdrawal adverse events after discontinuation of therapeutic doses of testosterone in hypogonadal men have not been evaluated.

   In order to evaluate potential dependence and withdrawal after abrupt discontinuation of therapeutic doses of testosterone, it it recommended that all emerging AEs be collected for at least 4 weeks from drug discontinuation at weekly intervals and that depression, suicidality, and insomnia scales be administered (see below).

- *Columbia-Suicide Severity Rating Scale (C-SSRS)*
- *Depression Scales (any of below listed):*
  - *Hamilton Depression Rating Scale (HDRS)*
  - *Montgomery-Asberg Depression Rating Scale (MADRS)*
  - *Beck Depression Inventory*
  - *Hospital Anxiety and Depression Scale (HADS)*
- *Insomnia scales (any of below listed):*
  - *Pittsburgh Sleep Quality Index (PSQI)*
  - *Leeds Sleep Evaluation Questionnaire (LSEQ)*
  - *Epworth Sleepiness Scale (ESS)*

4. We have the following recommendations for the label changes for all testosterone drugs. Data generated by OSE-DPV and reviewed by CSS indicates there may be a causal relationship of testosterone treatment with: 1) suicidality, especially in patients with pre-existing depression; 2) resolution of suicidality upon testosterone discontinuation; and 3) emergence of withdrawal syndrome with the key adverse events of suicidality and depression. Because of importance of this major safety issue CSS would recommend that OSE-DPV proceeds with the full analysis of the data presented in the OSE-DPV review (Aug 30 2017). CSS recommends the following changes to testosterone product labeling:

   - Add "suicidality" as an adverse events, and possibly consider black box warning based on the outcome of further OSE review of the data
   - Add "suicidality and depression" as withdrawal adverse events in the section 9.3 Dependence (suggested language):

     After the discontinuation of treatment with testosterone emergence of suicidality and depression were observed.

IV. REFERENCES

1. Amore M, Scarlatti F, Quarta AL, Tagariello P. Partial androgen deficiency, depression and testosterone treatment in aging men. Aging Clin Exp Res. 2009 Feb;21(1):1-8. Review.

2. Barrett-Connor E, von Muhlen DG, Kritz- Silverstein D. Bioavailable testosterone and depressed mood in older men: The Rancho Bernardo Study. J Clin Endocrinol Metab 1999; 84(2):573-7.

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5. Sher L. Low testosterone levels may be associated with suicidal behavior in older men while high testosterone levels may be related to suicidal behavior in adolescents and young adults: a hypothesis. Int J Adolesc Med Health. 2013;25(3):263-8.

6. Sher L. Both high and low testosterone levels may play a role in suicidal behavior in adolescent, young, middle-age, and older men: a hypothesis. Int J Adolesc Med Health. 2016 Jun 7.

7. Shores MM, Sloan KL, Matsumoto AM, Moceri VM, Felker B, Kivlahan DR. Increased incidence of diagnosed depressive illness in hypogonadal older men. Arch Gen Psychiatry. 2004 Feb;61(2):162-7.

V. DISCUSSION - Review of the selected topics related to drug abuse potential and dependence

1. CHEMISTRY

1.1 Substance Information

International Nonproprietary Name (INN) - Testosterone enanthate
Chemical names (Mod. 3.2.S.1.1 Nomenclature):

- Androst-4-en-3-one, 17-(1-oxoheptyl)oxy-,(17β)- (CAS)
- (17β)-3-Oxoandrost-4-en-17-yl heptanoate (IUPAC)
- (17β)-17-[(1-Oxoheptyl)oxy]-androst-4-en-3-one
- 17β-Hydroxy-4-androsten-3-one 17-enanthate
- 4-Androsten-17β-ol-3-one 17-enanthate
- Testosterone 17β-heptanoate

Testosterone enanthate is (17β)-17-[(1-Oxoheptyl)oxy]-androst-4-en-3-one or 17 β-Heptanoyloxy-4-androsten-3-one.
Molecular Formula: $C_{26}H_{40}O_3$
Molecular Weight: 400.6 g

Drug Product, Dosage Form and Route of Administration
QuickShot™ Testosterone (QST) contains testosterone enanthate 50 mg, 75 mg, or 100 mg in a pre-filled syringe for SC administration of a fixed volume of 0.5 mL via a pressure-assisted autoinjector device for single use.
The formulation is a preservative free injection in sesame oil.
No antimicrobial preservative is included in the formulation since Testosterone Enanthate Injection USP is a single use product.

Testosterone Enanthate Injection, QuickShot™ USP device from 3.2.P.7 Container Closure System, page 14.

Figure 3: Representative Model Auto-injector Assembly

2. CLINICAL STUDIES

During the drug development the Sponsor performed 5 clinical studies for QuickShot™ Testosterone:

- QST-14-004 - Phase 1: open-label, single-dose study of single-dose injections 50 and 100 mg via QST in healthy male subjects
- QST-13-002 - Phase 2, bioavailability study of QST (50 and 100 mg SC) versus Delatestryl® 200 mg IM: 3-arm, open-label, randomized, multi-dose parallel group study
- QST-16-006 - Phase 2: open-label, safety and tolerability of 2 single doses of 50 mg, 75 mg, or 100 mg doses via QST.
- QST-13-003 - Phase 3: double-blind, multiple-dose, 52-week study of efficacy and safety
- QST-15-005 - Phase 3: double-blind, multiple-dose, 6-month safety study of QST

2.2 Adverse Event Profile Through all Phases of Development

SINGLE DOSE STUDIES IN HEALTHY VOLUNTEERS

1. Study # QST-14-00: An Open-Label Study to Evaluate the Pharmacokinetics of Testosterone Enanthate after Single-Dose Injection via QuickShot® Testosterone in Healthy Male Subjects

- Population: healthy volunteers; completed: N = 12
- Doses:
  - Arm A: single dose of QST 50/0.5 mL mg
  - Arm B: 2 consecutive doses of QST 100/0.5mL mg.

There were no AEs related to abuse potential in this study.

MULTIPLE DOSE STUDIES IN PATIENTS

1. Study # QST-13-002: A Three Arm, Open-label, Randomized, Multidose Parallel Group Study of the Pharmacokinetics, Safety, and Tolerability of Two Dose Levels of a Preservative-Free Formulation of Testosterone Enanthate Administered Subcutaneously via an Autoinjection Device or Intramuscular Testosterone Enanthate in Hypogonadal Adult Males

- Population: randomized: N = 39; completed: N = 38
- Doses:
  - Arm A: 6 weekly SC doses of 100 mg/0.5 mL TE via QST.
  - Arm B: 6 weekly SC doses of 50 mg/0.5 mL TE via QST.
  - Arm C: Single dose of 200 mg/1 mL TE RLD via IM injection.

The AEs related to abuse potential are presented in the Table 1 below, page 9.

2. Study # QST-13-003: A Double-Blind, Multiple-Dose, 52-Week Study to Evaluate the Efficacy and Safety of QuickShot™ Testosterone Administered Subcutaneously Once Each Week to Adult Males with Hypogonadism

- Population1: randomized: 150; completed: 97; discontinued: 52
- Doses:
  - QST 75 mg 1 X per week
  - Dose titration allowed at Week 7 (to 50, 75 or 100 mg).
- The AEs related to abuse potential are presented in the Table 1 below, on the next page.

Selected cases and issues relevant to abuse potential in this study

Suicidality

1. Completed suicide (Patient # (b) (6)) Study # QST-13-003 – the suicide (method unknown) occurred during the withdrawal period on the 13th day of discontinuation, on study day 182 and after 169 days on testosterone.The patient did not have a history of underlying depression or any known history of mental health disorders.

2. Worsening depressive disorder and suicide attempt (Patient (b) (6)) Study # QST-13-003– five days after the first dose of study medication (QST 75 mg), after an argument with his spouse, the patient intentionally ingested 20 to 25 tablets of tramadol 50 mg which were not prescribed to him. This resulted in an emergency room visit followed by the admission to the hospital. It was further revealed that the patiend had suicidal thoughts and ideations. Patient was treated with venlafaxine, the worsening of his depressive disorder resolved with sequelae of ongoing outpatient psychiatric care.

3. Study # QST-15-005 A 6-Month Safety Study of QuickShot™ Testosterone Administered Subcutaneously Once Each Week to Adult Males with Hypogonadism

- Population: randomized: N = 133; completed: N = 113

- Doses:
  - QST 75 mg 1 X per week
  - Dose titration allowed at Weeks 7, 13, 19
  - PK sub-study: Dose adjustment allowed after Week 12

See Table 1, below, for AEs relevant to abuse potential.

4. Study # QST-16-006: An Open-Label Study to Evaluate the Safety of Testosterone Enanthate After Two Single-Dose Injections via QuickShot® Testosterone 50 mg, 75 mg, or 100 mg by Intended Users

- Population: randomized N= 65 patients; completed: N = 59
- Doses: 50, 75, 100 mg testosterone as QST

There were no AEs related to abuse potential in this study.

Table 1. Summary of abuse related adverse events based on Sponsor's Table 14.3.1.4.1, from Study Report QST-13-003 p. 572; Table 14.3.1.2 from Study Report QST-15-005, p 315; and Table 14.3.1.2 from Study Report QST-13-002, p 901.

Adverse Event PT	Study QST-13-003 N=150, n (%)	Study QST-15-005 N=133, n (%)	Study QST-13-002 N=39, n (%)
Subjects with any TEAE	125 (83.3)	87 (65.4)	13 (33.3)
Psychiatric Disorders		7 (5.3)	2 (5.1)
Anxiety	2 (1.2)	2 (1.5)	
Panic attack	1 (0.7)		
Insomnia	1 (0.7)	3 (2.3)	2 (5.1)
Depression	1 (0.7)*	2 (1.5)	
Hypersexuality	1 (0.7)		
Completed Suicide	**1 (0.7)**		
General Disorders			
Fatigue	3 (2.0)	3 (2.3)	

*Depression- it was actually a suicide attempt as described in the study report QST-13-003, page 760.

Conclusions:
During the study in hypogonal patients there were few neuropsychiatric adverse related to abuse potential, including anxiety, insomnia, panic attack and depression. There was suicidality in these studies, one patient committed suicide during the withdrawal period and another had worsening of depression and a suicide attempt. Depression is known as an AE related to testosterone treatment (Testosterone label). Also, both depression and suicidality are known AEs in a population of healhy subjects abusing testosterone and anabolic steroids. Additionally, hypogonal men are known to have a higher risk for depression (Barrett-Connor et al., 1999; Shores, 2004; Makhlouf et al., 2008) . Therefore, it is further recommended that the Division advises sponsors to closely monitor for events of depression and suicidality in future testosterone studies, and to include in future protocols depression scales and the

Columbia Suicide Severity Rating Scale (C-SSRS). These scales are routinely used in the development of psychiatric and neurological drugs known to cause or worsen depressive disorders and suicidality, and inclusion of these scales has been recommended by the Division of Psychiatric Product (DPP) and the Division of Neurology Products (DNP)

Adverse Events Leading to Discontinuation from Clinical Studies
In the study QST-13-003 there were a number of possibly abuse related AEs that lead to discontinuation from the study, including depression/suicide attempt, fatigue.

In the study QST-15-005 the following abuse-related AEs lead to discontinuation from the study: depression (2), one patient had a new onset of depression and did not recover while the second patient's outcome was unknown.There was one AE of insomnia.

3. EVIDENCE OF ABUSE, MISUSE, DIVERSION, OVERDOSE IN CLINICAL TRIALS

3.1 Overdose accidental and intentional

In the response to CSS' inquiry on "above expected" levels of testosterone, the Sponsor stated that "above expected levels" was not a prospectively defined endpoint of any study. However, based on the study # QST-13-002 data, the modelling and simulation exercise predicted no testosterone levels above 1500 ng/dL in patients receiving 75 mg of QST. Thus the Sponsor identified, in the studies # QST-13-003 and QST-15-005, the following cases of blood testosterone levels above 1500 ng/dL:

Study # QST-13-003.

- Patient (b) (6) was a 34 year old Hispanic male with a trough level >1500 ng/dL at his week 38 visit (b) (6)
- Patient (b) (6) was a 46 year White male with a T (testosterone) level >1500 ng/dL obtained at an early withdrawal visit (b) (6) His last dose of study medication was (b) (6)

Study # QST-15-005

- There was a single patient (b) (6) who participated in the PK substudy, with a week 12 Cmax T (testosterone) blood level of 2300 ng/dL 3 hours post dose.

In general the maximum C_{trough} values were in the range of 900-1300 ng/dL, with mean values all below 500 ng/dL (ISS, p 18).

Comment
It is not clear why in these few cases patients had higher levels. One possibility is some peculiar dosing regimen, another is misuse of the drug product.

3.2 Diversion/Drug Accountability

In response to the CSS IR (July 10 2017), the Sponsor provided more information on drug accountability and its location.
The summary of drug accountability data:

- there were a total of 9844 devices dispensed for all 5 studies (Table 1 of the ISS)
- there were no lost devices in studies QST-13-002, QST-14-004, or QST-16-006.
- in the study # QST-13-003: (Table 14.1.1.8, p 187) there were 6502 devices dispensed and there were 55 lost devices (0.84%), generally patients lost 1 or 2 devices but some patients lost 4 to7 devices:
    - patient # (b) (6) received total of 17 devices and lost 4 (~23%)
    - patient # received total of 12 devices and lost 7 (~58%)
    - patient # received total of 25 devices and lost 6 (~24%)
    - patient # received total of 6 devices and lost 4 (~66%)
    - patient # received total of 38 devices and lost 4 (~10%), coincidentally this patient had also higher than expected testosterone trough level >1500 ng/dL

- in the study # QST-15-005 (Table 14.1.1.8, p 128) there were 3215 devices dispensed and 55 lost (~1.7%), generally patients lost 1 or 2 devices but few patients lost 4-5:
    - patient # (b) (6) received total of 5 devices and lost 4 (80%)
    - patient # received total of 5 devices and lost 4 (80%)
    - patient # received total of 17 devices and lost 5 (~29%)

An IR was issued on Aug 21 2017 to provide narrtives for the patients who did not return the devices. The Sponsor's response (Aug 30 2017) mentioned, as the reasons for not returned devices, that they were "lost to follow-up", or "never returned to the site" or the patient was withdrawn from the study after not returning the devices. These cases may suggest misuse/diversion but maybe also represent accidental losses.

Conclusion

There is some loss of the devices during the studies and some patients lost 4-7 devices. As some of these subjects received a total of number of devices ranging from 5 to 38, the loss of 4-7 devices represented in some cases 60-80% loss of the total number of devices that particular subject received, suggesting possible diversion. Some of these patients lost up to 80% of their supply and were withdrawn by the Sponsor from the study, and some never returned to the site.

3.3 Evaluation of Dependence, Tolerance and Rebound in Clinical Studies

Dependence and Withdrawal

Dependence was not systematicallyevaluated in any of the conducted studies and there is no data on dependence and withdrawal in the NDA submission. Information on withdrawal AEs was requested twice, in the 74-day letter and an IR July 7 2017, to clarify the issue of withdrawal AEs. The Sponsor appears to confuse the two situations where subjects discontinue drug treatment due to AEs (discontinuation AEs) and the situation where drug discontinuation leads to AEs (withdrawal AEs).

4. REGULATORY ISSUES AND ASSESSMENT

4.1. Adverse Event Reporting Post-Approval

Post-approval, we recommend continuing post-marketing assessment of those AEs suggestive of abuse-potential, misuse, and overdose as well as AEs related to dependence and withdrawal, see Guidance [1]. These should be included in the standard Periodic Adverse Event Reports (PADERS).

4.2 Recommended Studies or Trials

1. ***Evaluation of dependence and withdrawal in the future testosterone studies or in the new TRT study in hypogonadal men if CR is issued.***

Testosterone products are known to form dependence which results in a withdrawal syndrome upon drug discontinuation in healthy men and women (athletes, bodybuilders) who take them in supra-therapeutic doses. However, the data on consequences of testosterone withdrawal in older men with hypogonadism after TRT is very sparse, therefore Sponsors should continue to acquire such data in future testosterone INDs in order to further refine the label section 9.3 Dependence.
In order to evaluate the potential dependence and withdrawal after therapeutic doses of testosterone all AEs should be collected for at least 4 weeks from drug discontinuation at weekly intervals, and depression, suicidality and insomnia scales should be administered:

- Columbia-Suicide Severity Rating Scale (C-SSRS)
- Depression Scales (any of below listed):
  - Hamilton Depression Rating Scale (HDRS)
  - Montgomery-Asberg Depression Rating Scale (MADRS)
  - Beck Depression Inventory (BDI)
  - Hospital Anxiety and Depression Scale (HADS)
- Sleep scales (any of below listed):
  - Pittsburgh Sleep Quality Index (PSQI)
  - Leeds Sleep Evaluation Questionnaire (LSEQ)
  - Epworth Sleepiness Scale (ESS)

2. ***It is also recommended to monitor depression and suicidality in the future TRT trials.***

5. POST-MARKEING ADVERSE EVENTS RELATED TO SUICIDALITY

5.1 Review of suicidality cases based on OSE/DPV review from Aug 30 2017 by Dr. Rachna Kapoor

The question of suicidality in this NDA was raised by CSS, however DNP staff expressed concerns as well. Therefore, DBRUP requested OSE/DPV consult review to evaluate this issue. However, due to time constraints OSE/DPV provided only "*high level summary of the FAERS cases review*" of suicidality cases without analysis of individual cases and literature search. CSS reviewed the individual cases and provides comments and recommendations below.

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[1] Guidance for Industry for Assessment of Abuse Potential of Drugs Jan 2017
http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf

OSE/DPV identified 74 cases which included 15 cases of completed suicides, 13 cases of suicidal attempt, and 46 cases of suicidal ideation reported with testosterone use and after exclusion of: duplicates, body builders, women, Nebido cases,overdoses and cross sex hormonal therapy. However, it is not clear why Nebido related cases (testosterone undecanoate) were excluded from the analysis, PSUR 2010 shows some suicidality cases: 1 completed suicides, 1 suicide attempt, and 1 case of suicidal depression, and from 2013 also one case of suicidal ideation.

Although there were cases where drug-event causality could not be easily established or there was not enough information, there were many cases where this relationship appears more clear. CSS was quite conservative assigning the causal relationship between testosterone treatment (or withdrawal of testosterone) so likely many more cases from OSE/DPV review could be cited to support the statements below.

There are 3 types of adverse events where there is causal relationship of testosterone treatment (or withdrawal of testosterone) and suicidality, below the cases are presented where the causality was clearer:

1. There are a number of cases where the onset of suicidality is directly related to the start of testosterone therapy or emerges during the treatment.
2. There are a number of cases where the suicidality resolves upon testosterone discontinuation.
3. There are a number of cases where the onset of suicidality is directly related to the withdrawal of testosterone therapy.

Therefore, CSS recommends to add "suicidality" as an adverse event of testosterone therapy, and add "suicidality and depression" as withdrawal adverse event emerging upon testosterone discontinuation in the all testosterone labels.

There is also a quite representative statement from one of the patients (Case ID: 10676706) who experienced depression, suicidal ideation and suicide attempt in the course of testosterone therapy:

""It is important to note that Androgel 1.62%, 4 pumps daily was the only medication I was taking at the time of initial onset of depressive symptoms in the spring (b) (6) ***The depression became worse after the Androgel prescription was increased to 6 pumps daily of the 1.62% concentration*** (b) (6) (b) (6) ***This medication's (Androqel) deadly side effect is not adequately presented to doctors by the manufacturer… I was nearly killed as a result of this side effect."***

Cases presentation:

* in italics are representative patient's statements or third person's statements (wife, physician or other).

1. There are a number of cases where the onset of suicidality is directly related to the start of testosterone therapy, dose increase or emerges during the treatment.
    - Case Id: 5935985, symptoms of suicidal ideation, (page 23), which has same time of onset as "roid rage" due to Androgel.

- Case Id: 6181512, symptoms of suicidal depression, (page 32):…"*Since beginning ANDROGEL, the patient has experienced periodic episodes of suicidal depression, irritability, and low energy*"
- Case Id: 8018820 and Case Id: 8018822, and page 57-61, symptoms of suicidal ideation and aggression in 2 patients with Klinefelter's Syndrome and related to testosterone therapy, in each case symptoms resolved upon discontinuation of testosterone (Radko et al., 2011).
- Case Id: 8663367: (page 83), symptoms of worsening depression and suicidal ideation: "*since using the testosterone, his depression had worsened and he was having bad feeling in his head and suicidal thoughts."*
- Case Id: 8745412: (page 87), symptoms of agitation and suicide attempt: "*He applied the gel as directed and after 3 weeks of use he became increasingly agitated, had volatile anger outbursts, and became suicidal on the evenings* (b) (6) *"*
- *Case Id: 9158659:* (page 96): symptoms of suicidal ideation and anxiety*: "The patient stated the testosterone solution caused him major anxiety and feelings of wanting to commit suicide whilst taking the medication."*
- Case Id: 9410523: (page 112), symptoms of depression and suicide attempt*: "increasingly depressed after 1-2 months start with Testogel, attempted suicide".*
- *Case Id: 9479150: (*page 116), symptoms of suicidal ideation and mood swings: *"Since the patient's ANDROGEL dose was increased to three pumps* (b) (6) (b) (6) *the patient has had severe mood swings. They come and go. The mood swings have included suicidal thoughts with a plan."*
- Case Id: 10555750, (page 139), symptoms of suicidal ideation and worsening depression: "*The patient started ANDROGEL (TESTOSTERONE)* (b) (6) *....., but within two weeks he was feeling very depressed with suicidal ideation".*
- Case Id: 12125692: (page 193), symptoms of suicidal ideation and anxiety after testosterone dose increase.
- Case Id: 13152271: (page 228), symptoms of suicidal ideation after testosterone dose increase.
- Mfr report # TESTO0203002722: (page 241), symptoms of suicidal ideation during testosterone treatment and dose increase
- Mfr report # 190705001/225AE: (page 256), symptoms of suicidal ideation and depression during testosterone treatment
- Mfr report # 2005-04814: (page 257), symptoms of suicidal depression and violent aggression after the start of new testosterone formulation (Androderm patches, previously injections were used)
- Case ID: 9027842: (page 265), symptoms of suicidal ideation and depression after the start of testosterone and resolution of symptoms after drug discontinuation "*A little more than a week after starting Androderm I started getting depressed, but I thought it might just be me feeling down. It continued to get worse. I started thinking bad thoughts like suicide*."

- Case ID: 10524469: (page 261), symptoms of suicidal ideation and worsening depression: "*Patient reported that his depression began to worsen after initiation of testosterone... Symptoms resolved after discontinuation of drug."*
- Case ID: 10676706, (page 272), onset of depression and worsening of depression followed by suicidal ideation and suicidal attempt during testosterone treatment and in particular after the dose increases; symptoms resolved upon drug discontinuation. Patient's statement: "*It is important to note that Androgel 1.62%, 4 pumps daily was the only medication I was taking at the time of initial onset of depressive symptoms in the spring of 2014. The depression became worse after the Androgel prescription was increased to 6 pumps daily of the 1.62% concentration* (b) (6) ***This medication's (Androqel) deadly side effect is not adequately presented to doctors by the manufacturer… I was nearly killed as a result of this side effect."***
- Case ID: 11358782: (page 275), completed suicide: patient's mother*: "My son used Androgel for Low T for about two years. During that time he became more and more depressed, suffered from insomnia, loss of muscle strength, loss of energy. The depression got so bad that he committed suicide."*
- Case ID: 11693245: (page 279), symptoms of depression, anxiety and suicidal ideation that emerged during TRT.
- Case ID: 11934615: (page 284), symptoms of increasing anxiety, depression, suicidal ideation, extreme insomnia, paranoia, and mania emerging upon change of testosterone formulation.

2. There are a number of cases where the suicidality resolves upon testosterone discontinuation.
   - Case Id: 8018820,(page 57), suicidal ideation and aggression in patient with Klinefelter's Syndrome treated with testosterone which resolved after discontinuation of testosterone (Radko et al., 2011)..
   - Case Id: 9292935, (page 107), symptoms of suicidal ideation resolved upon discontinuation of testosterone.
   - Case Id: 10555750, (page 139), symptoms of suicidal ideation and depression resolved upon discontinuation of testosterone.
   - Case Id: 12323980, (page 202), symptoms of suicidal ideation shortly after testosterone start which resolved upon drug discontinuation " *He also experienced suicidal thoughts. …The patient discontinued the Androgel and no medication was prescribed for the events. All events resolved on their own*."
   - Mfr Report 5700, (page 239), symptoms of suicidal ideation and depression resolved upon discontinuation of testosterone
   - Case ID: 9027842: (page 265), resolution of symptoms of suicidal ideation and depression after drug discontinuation
   - Case ID: 10524469: (page 261), symptoms of suicidal ideation and worsening depression resolved after discontinuation of drug.

- Case ID: 10676706, (page 272), resolution of depression and suicidal ideation upon testosterone discontinuation.

3. There are a number of cases where the onset of suicidality is directly related to the withdrawal of testosterone therapy or lowering the dose or level, and in some cases there is reversal of symptomatology by restarting of testosterone treatment:

- Case Id: 6013103, (page 26), symptoms of suicidal ideation after the discontinuation of testosterone therapy.
- Case Id: 6181512, (page 32) symptoms of suicidal depression and irritability "treated" by the patient with the "boost" of Androgel
- Case Id: 6687923, symptoms of suicidal ideation/withdrawal syndrome, (page 42): due to testosterone interruption, symptoms resolved when testosterone restarted again.
- Case Id: 8068948, (page 63), symptoms of suicidal ideation and attempt, depression, anxiety upon discontinuation of testosterone: "*After discontinuing testosterone, the patient experienced suicidal thoughts."*
- Case Id: 10399181: (page 126), symptoms of suicidal ideation and depression upon testosterone withdrawal: "*He reported that since he has been off his Androgel he has felt depressed, sad and had suicidal thoughts*"
- Case Id: 10497771: (page 130), symptoms of suicidality and irritability upon testosterone withdrawal: "*It was reported that the patient was feeling irritable, gaining weight, feeling low and almost suicidal after he stopped taking testosterone cipionate because he no longer had his medication as he ran out of it*."
- Case Id: 10507806: (page 132), symptoms of suicidality upon withdrawal of testosterone: " *The patient stated that if he was without his ANDROGEL he would be suicidal."*
- Case Id: 12089154: page 184, symptoms of suicidality and depression upon withdrawal of testosterone:" *Shortly after he stopped using Androgel he experience as he stated an emotional crash, extreme fatigue where he needed to take 3 naps a day, his depression worsen and had suicidal ideation….. He switched to another insurance that did cover Androgel. When he was able to resume his Androgel therapy his events resolved.*
- *Case Id: 12601094:* symptoms of suicidal ideation and depression upon dose decrease: "*attempt to taper himself off unknown strength Androgel after being on it for five years. The patient experienced confusion, brain fog, suicidal ideation, and deep dark depression."*

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/s/

ALICJA LERNER
10/06/2017

DOMINIC CHIAPPERINO
10/06/2017
Signing also for Silvia Calderon and Martin Rusinowitz

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs

REVIEW DEFERRAL MEMORANDUM

Date:	October 6, 2017
To:	Hylton Joffe, MD Director **Division of Bone, Reproductive and Urologic Products (DBRUP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Marcia Williams, PhD Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Nyedra Booker, PharmD, MPH Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
Subject:	Review Deferred: Patient Package Insert (PPI) and Instructions for Use (IFU)
Drug Name (established name):	testosterone enanthate
Dosage Form and Route:	injection, for subcutaneous use
Application Type/Number:	NDA 209863
Applicant:	Antares Pharma, Inc.

1 INTRODUCTION

On December 20, 2016, Antares Pharma, Inc. submitted for the Agency's review an original New Drug Application (NDA) 209863 for testosterone enanthate injection, for subcutaneous use indicated for testosterone replacement therapy in adult males for the following conditions associated with a deficiency or absence of endogenous testosterone:

- Primary hypogonadism (congenital or acquired)
- Hypogonadotropic hypogonadism (congenital or acquired)

On February 8, 2017, the Division of Bone, Reproductive and Urologic Products (DBRUP) requested that the Division of Medical Policy Programs (DMPP) review the Applicant's proposed Patient Package Insert (PPI) and Instructions for Use (IFU) for testosterone enanthate, injection for subcutaneous use.

This memorandum documents the DMPP review deferral of the Applicant's proposed PPI and IFU for testosterone enanthate, injection for subcutaneous use.

2 CONCLUSIONS

Due to outstanding clinical deficiencies, DBRUP plans to issue a Complete Response (CR) letter. Therefore, DMPP defers comment on the Applicant's patient labeling at this time. A final review will be performed after the Applicant submits a complete response to the Complete Response (CR) letter. Please send us a new consult request at such time.

Please notify us if you have any questions.

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/s/

NYEDRA W BOOKER
10/06/2017

MARCIA B WILLIAMS
10/06/2017

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: October 5, 2017

To: Jeannie Roule, Regulatory Project Manager
Division of Bone, Reproductive and Urologic Products (DBRUP)

From: Jina Kwak, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: NDA 209863
OPDP labeling comments on Testosterone Enanthate Auto Injection

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This memo is in response to DBRUP labeling consult request dated February 8, 2017. Reference is made to the email to OPDP from Jeannie Roule on October 5, 2017 conveying that a Complete Response action will be taken on this application. Therefore, OPDP defers comment on the proposed labeling at this time, and request that DBRUP submit a new consult request during the subsequent review cycle.

If you have any questions, please contact Jina Kwak at (301) 796-4809 or jina.kwak@fda.hhs.gov

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/s/

JINA KWAK
10/05/2017

Food and Drug Administration
Center for Drug Evaluation and Research

CONSULTATION

To:	Jeannie Roule, RPM Division of Bone, Reproductive and Urologic Products (DBRUP)
From:	Ovidiu Galescu, M.D. Clinical Reviewer Division of Metabolism and Endocrinology Products (DMEP)
	Mary Roberts, M.D. Clinical Reviewer DMEP
Through:	James Smith, M.D., M.S. Deputy Division Director DMEP
Date of Request:	September 21, 2017
Re:	NDA 209863 Testosterone enanthate auto injection (QuickShot Testosterone) IND 116022

Basis for Consult

Antares Pharma has developed QuickShot Testosterone (QST) for the treatment of adult male hypogonadism. The NDA was submitted 20 December 2016 and is currently under review in the Division of Bone, Reproductive, and Urologic Products (DBRUP) with a planned PDUFA date of 20 October 2017. QST is a single-use auto-injector prefilled with testosterone enanthate solution and is designed for subcutaneous injection, which is a new route of administration for a testosterone product. This product, therefore, triggers the Pediatric Research Equity Act (PREA), which requires all applications submitted under section 505 of the Act (21 U.S.C. 355) or section 351 of the Public Health Service Act (PHSA) (42 U.S.C. 262) for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration to contain a pediatric assessment unless the applicant has obtained a waiver or deferral (section 505B(a) of the Act).

In order to implement this statutory requirement, sponsors planning to submit an application for a drug subject to PREA need to submit an initial Pediatric Study Plan (iPSP) early in the development process. During QST's development, DBRUP agreed to an iPSP submitted under IND 116022 which granted a full waiver for pediatric studies because "the necessary studies were impossible or highly impracticable and there are too few children with the disease/condition to study" (Advice Letter dated 9 February 2015). However, a formal decision by the Agency about granting a waiver and/or deferral of

required pediatric assessment is not made until approval of the marketing application. Therefore, as part of QST'S NDA review for market approval, DBRUP requested the Division of Metabolism and Endocrinology Products to opine on the following:

PREA assessment [for QST] would apply to adolescent boys with congenital or well-recognized pathological causes of hypogonadism who would require chronic testosterone replacement therapy. Please discuss the following:

- *The estimated size of the population of adolescent boys with congenital or pathological causes of hypogonadism requiring chronic testosterone replacement.*
- *If testosterone therapy were to be evaluated in these boys, what efficacy and safety endpoints would be appropriate?*

Background

Gonadarche results from pulsatile gonadotropin releasing hormone (GnRH) secretion from the hypothalamus. GnRH secretion occurs every 60 to 90 minutes, resulting in LH and FSH release (initially during sleep), which in turn results in gonadal stimulation. LH stimulates Leydig cell hyperplasia in males and subsequent testosterone release. FSH has little effect in males until the onset of spermarche (sperm maturation). Testosterone secretion leads to the development of secondary sexual characteristics. Adequate functioning at all levels of the hypothalamic-pituitary-gonadal axis is necessary for normal gonadal development and subsequent sex steroid production. Deficiencies at any level of the axis can lead to a hypogonadal state.

In boys, hypogonadism can manifest as a complete lack of secondary sexual development or failure of normal pubertal progression. It can cause:

- Decreased development of muscle mass
- Lack of deepening of the voice
- Impaired growth of body hair
- Impaired growth of the penis and testicles
- Excessive growth of the arms and legs in relation to the trunk of the body
- Development of breast tissue (gynecomastia)

Pediatric male hypogonadism can be classified according to localization of cause. Please see Table1.

Table 1. Male Hypogonadism - Causes*

Hypothalamic-pituitary origin (hypogonadotropic syndromes)	Testicular origin	Target Organ Resistance to Sex Steroids
• Constitutional delay of growth and puberty • Idiopathic hypogonadotropic hypogonadism (IHH)	• Congenital and acquired anorchia • Klinefelter Syndrome and variants	• Androgen insensitivity syndrome (partial and complete)

Hypothalamic-pituitary origin (hypogonadotropic syndromes)	Testicular origin	Target Organ Resistance to Sex Steroids
• Kallmann Syndrome • Congenital Adrenal Hypoplasia • Prader-Willi Syndrome • Laurence-Moon-Biedl Syndrome • Pituitary insufficiency (congenital or acquired) • Biologically inactive gonadotropins • Hyperprolactinemia	• Gonadal Dysgenesis • Sertoli-only Syndrome • Significant systemic illness • Deficiencies in enzymes of Testosterone synthesis • Cancer therapy	

*Table adapted from Alan D. Rogol "Pubertal Androgen Therapy in Boys" [1]

Constitutional Delay of Growth and Puberty (CDGP) is not a medical disorder, but a temporary condition. It is probably the most common condition seen by specialists at growth clinics. Although it can produce extreme anxiety, particularly in boys, often because of short stature in comparison with friends of the same age and the apparent lack of genital development, the appropriate initial approach is reassurance and watchful waiting[2]. Given the transitory and benign nature of this disorder, it will not be the focus of this review and it should not be the intended patient population for this product.

Estimated size of the population of adolescent boys with congenital or pathological causes of hypogonadism requiring chronic testosterone replacement

Chronic male hypogonadism has a multifactorial etiology that includes genetic conditions, anatomic abnormalities, infection, tumor, and injury. Hypogonadism can begin during fetal development, before puberty or during adulthood. Pediatric hypogonadism may be unrecognized and underdiagnosed, making it difficult to provide an overall estimate of population size (See Table 2).

Table 2. Chronic Male pediatric hypogonadism incidence/prevalence

Etiology	Type	Incidence/Prevalence	Comments
Klinefelter syndrome	Hypergonadotropic hypogonadism	1:500-1000 live newborn males[3, 4]	In 2008 it was estimated that approximately 250,000 men in the United States have Klinefelter syndrome[5] However, Klinefelter syndrome is often undiagnosed in young males. Less than 10% of patients are diagnosed before puberty. Diagnosis frequently occurs in adulthood with a mean age of diagnosis ~30 years [6].
Genetic causes (SF-1, DAX-1, FGFR1, GPR54,	Hypogonadotropic hypogonadism	Rare but part of IHH (1:10000 men) prior to mutation	

Etiology	Type	Incidence/Prevalence	Comments
Prop-1, Hesx-1, LEP. LEPR)		discovery.	
KAL-1 (X-linked R)	Hypogonadotropic hypogonadism	1:30000 males[7]	
Traumatic Brain injury	Hypogonadotropic hypogonadism	41.6% in the acute phase to 7.7% at 12 months[8] 100-300 /100000/year[9]	Male:female 2-4:1 OR 1.1-2.36/100/year with prevalence ~30%[10]
Central nervous system tumors	Hypogonadotropic hypogonadism	13% prior to therapy 20-80% post therapy[11-15]	In the United States, based upon data from the Central Brain Tumor Registry of the United States (CBTRUS), the estimated incidence of primary nonmalignant and malignant CNS tumors is 5.6 cases per 100,000 person-years for children and adolescents ≤19 years of age[16]
Prader Willi Syndrome	Hypogonadotropic hypogonadism	1:15000 births, 1:1 male:female	~100% hypogonadal, 80-90% males have cryptorchidism[17]
Congenital Adrenal Hypoplasia (SF1, DAX1)	Hypogonadotropic hypogonadism	1:12500 live births X-linked with male preponderance.	Overlaps with the other genetic causes
Noonan Syndrome (PTPN11 mutation)	Hypogonadotropic hypogonadism	1:1000-1:2500 live births 76% of patients have cryptorchidism and resulting hypogonadism	
Testicular regression sequence	Hypergonadotropic hypogonadism	As many as 1:1250 males may be affected[18]	5% of cryptorchidism cases [19] (cryptorchidism occurs in 3% of full term neonates, 33% in premature infants)[20]
Chemotherapy and Radiation	Hypergonadotropic hypogonadism	Non-HL and ALL treated males 83% primary hypogonadism[21]	Non-Hodgkins Lymphoma >70000 cases (4.3% of all cancers) in 2017, 1.7% <20 years[22] Acute Lympoblastic Leukemia ~6000 cases (0.4% of all cancers) in 2017, 56.1% <20 years [23]
Autoimmune gonadal failure	Hypergonadotropic hypogonadism	Rare	
Drug/alcohol abuse, traumatic injury, illness (mumps)	Hypergonadotropic hypogonadism	Unquantified	

In an effort to provide context for the numbers of children presenting with delayed puberty that could ultimately be a result of chronic hypogonadism, a literature search yielded a large case series of patients (n=232) who had been seen for delayed puberty at an tertiary referral center over a roughly 3.5 year period[24]. In this retrospective medical record review, patients with abnormal progression of puberty were excluded. Included were girls with lack of breast development by age 13 years and boys with lack of testicular enlargement (testis size<2.5 cm in length or <4mL in volume) by 14 years. The case series included 158 boys (mean age 15.1 years) and 74 girls (mean age 14.5). Among the 158 boys, 14 (9%) were diagnosed with permanent hypogonadotropic hypogonadism, and 11 (7%) with permanent hypergonadotropic hypogonadism; in 2 (1%) the etiology was not classifiable. Although, the most common cause of delayed puberty in boys in this case series was constitutional delay of growth and puberty (63% of boys) a transient benign variant of typical pubertal development, this report suggests there is a small group of male pediatric patients with chronic hypogonadism who present in adolescence and after appropriate evaluation and work-up would be treated with testosterone[25].

Study Endpoints

Any specifics regarding a study design which may yield informative data in this population is beyond the scope of this consult given the limited time for completion and the paucity of experience with pediatric studies in this therapeutic area. In our opinion, the design and conduct of a clinical trial would depend on several considerations such as the primary question the investigation hopes to address, the type of study design most likely to answer the question, the appropriate population to study (given the heterogeneity of the underlying conditions associated with hypogonadism) as well as the population size and accessibility to potential clinical trial sites. Furthermore, the efficacy and safety endpoints chosen would impact study duration and would be subject to technical complexities (e.g. testosterone assays, assessment of pubertal stage, reading bone age films) that require additional consideration. These, and potentially other unknown factors, may impact the feasibility and utility of a clinical investigation.

However, with the aim of addressing the specific consult question regarding study endpoints, an investigation of testosterone therapy in male pediatric patients with chronic hypogonadism could include the following: pharmacokinetic profiles of total and free testosterone, and total dihydrotestosterone; evidence of testosterone effects such as changes in phallic size, pubic hair (Tanner stage), testicular volume, muscle mass, deepening voice, erections, libido, and tempo of pubertal development. Quality of life or behavior assessments, such as status of psychosocial relationships or aggression, could also be explored. Broadly, safety measurements should include an assessment of linear growth and bone age advancement, hematology, liver, and lipid profiles, and vital signs.

Given the PDUFA goal date for the QST product and the late reconsideration of the need for pediatric studies, one could consider deferring pediatric studies at this time, setting a reasonable milestone for final protocol submission that would allow continued discussion about the appropriate path forward – including feasibility considerations – for evaluating testosterone therapy in boys with congenital and acquired causes of chronic hypogonadism.

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/s/

OVIDIU A GALESCU
10/02/2017

MARY D ROBERTS
10/02/2017

JAMES P SMITH
10/02/2017

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Pharmacovigilance Memo

Date:	August 30, 2017
Reviewer:	Rachna Kapoor, PharmD, MBA Division of Pharmacovigilance II
Team Leader:	Neha Gada, PharmD, BCPS Division of Pharmacovigilance II
Product Name:	Androderm (Testosterone), AndroGel (Testosterone), Aveed (Testosterone Undecanoate), Axiron (Testosterone), Delatestryl (Testosterone Enanthate), Fortesta (Testosterone), Striant (Testosterone), Testim (Testosterone), Testosterone, Vogelxo (Testosterone), Xyosted (testosterone enanthate)
Subject:	Completed Suicide, Suicidal Ideation, Suicide Attempt
Application Type/Number:	NDA 020489, NDA 021015, NDA 022309, NDA 022219, NDA 022504, NDA 009165, NDA 021463, NDA 021543, NDA 021454, NDA 202763, NDA 203098, NDA 204399, NDA 209863
Applicant/Sponsor:	Watson Labs, Abbvie, Endo Pharms Inc., Endo Pharms, Eli Lilly and Co., Auxillium Pharms LLC, Auxillium Pharms, Teva Pharms, Perrigo Israel, Upsher Smith, Antares Pharma Inc.
OSE RCM #:	2017-1637

1 INTRODUCTION

On August 10, 2017, the Division of Bone, Reproductive, and Urologic Products (DBRUP) consulted the Division of Pharmacovigilance II (DPV-II) for an FDA Adverse Event Reporting System (FAERS) high level summary of testosterone replacement therapy, when used in hypogonadal men, and completed suicide, suicidal ideation, or suicidal attempt for consideration in their review of NDA 209863. This memo was prompted by their evaluation of NDA 209863, testosterone enanthate for injection, currently under review and seeking approval in adult males for 1) primary hypogonadism (congenital or acquired) and 2) hypogonadotropic hypogonadism (congenital or acquired). During the pivotal clinical trials, one case each of completed suicide and worsening depressive disorder with suicidal behavior was noted. The purpose of this memorandum is to provide DBRUP with a high level summary of the FAERS cases of suicidal attempt, completed suicide or suicidal ideation, because of the rapid response needed by DBRUP. However, DBRUP will request a full review in the future if they deem the cases require further analysis.

In 2015, DPV completed a FAERS review on testosterone and abuse, misuse and dependence for Tracked Safety Issue (TSI) # 1351 and noted two cases of suicide or suicidal behavior (b) (6) [redacted] In summary, the TSI Decisional Memorandum dated October 21, 2016, summarized the totality of safety data available at that time and concluded, "*Based on very limited evidence and multiple confounding factors, however, it is not possible to attribute suicidal or homicidal intent/behavior to testosterone abuse. The multiple confounders typically present in these situations is particularly notable, and the missing information in these case reports also precludes a determination of drug causality for these specific events.*"

On August 30, 2017, during the Wrap Up meeting for NDA 209863, DBRUP requested DPV-II to provide data mining scores with testosterone and suicide related events. Given that data mining is a hypothesis generating tool, the role of ad hoc data mining queries for signals identified by other sources is limited. Furthermore, we are unable to narrow the focus to testosterone use in hypogonadal cisgender men using data mining. Drug and event causality cannot be inferred from data mining scores.

2 METHODS AND MATERIALS

2.1 CASE DEFINITION

We included cases of completed suicide, suicidal ideation, or suicidal attempt in men assumed to be cisgender, unless otherwise specified. We applied the case definition for *Suicidal Ideation and*

Behavior[1] developed by the Office of Surveillance and Epidemiology (OSE) and separated events into one of three categories: suicidal attempt, completed suicide, and suicidal ideation. The authors of the case definition considered the Columbia-Suicide Severity Rating Scale (C-SSRS) and diagnostic criteria from DSM-5 in the development of the inclusion criteria for each category of events (see **Table 2.1.1**).

We excluded cases noting intentional overdose of testosterone therapy; use of testosterone in body builders or athletes; use for hormone therapy in women; use of Nebido, use in cross sex hormone therapy, and cases lacking clinical information for case assessment.

Table 2.1.1. Inclusion Criteria applied to FAERS cases for Suicidal Attempt, Completed Suicide and Suicidal Ideation reported with Testosterone Therapy

Suicidal Attempt (suicidal behavior)	**Completed Suicide (suicidal behavior)**	**Suicidal Ideation**
Inclusion Criteria • Temporal relationship* to suspect drug initiation or dose increase **AND any one of the following:** • Diagnosis of suicidal behavior from a healthcare provider • Suicide attempt (includes potentially self-injurious behavior, associated with at least some intent to die, as a result of the act) • Preparatory acts toward imminent suicidal behavior (including interrupted or aborted attempt)	**Inclusion Criteria** • Temporal relationship* to suspect drug initiation or dose increase **AND:** • Completed suicide (a self-injurious behavior that resulted in fatality and was associated with at least some intent to die as a result of the act)	**Inclusion Criteria** • Temporal relationship* to suspect drug initiation or dose increase **AND any one of the following:** • Diagnosis of suicidal ideation by a healthcare provider • Passive thoughts about wanting to be dead or wish to fall asleep and not wake up • Active thoughts about wanting to end one's life or commit suicide (see definitions in Section I) ■ Nonspecific; no method, intent or plan ■ Method, but no intent or plan ■ Method and intent, but no plan ■ Method, intent, and plan

* No guidelines or consensus on timeline of temporal relationship between initiation of drug and onset of events

2.2 FAERS Search Strategy

DPV-II searched the FAERS database with the strategy described in Table 2.2.1.

Table 2.2.1. FAERS Search Strategy*	
Date of Search	August 15, 2017
Time Period of Search	All reports through August 15, 2017
Search Type	Quick Query
Product Terms	Active Ingredient: Testosterone phenylacetate; Testosterone enantate benzilic acid hydrazone; Testosterone propionate; Testosterone enanthate; Testosterone undecanoate; Testosterone decanoate; Testosterone isocaproate; Epitestosterone; Testosterone; Methyltestosterone; (1,2,6,7-3H)Testosterone; Chlorodehydromethyltestoterone; Testosterone acetate; Testosterone cypionate; Testosterone ketolaurate; Testosterone phenylpropionate
MedDRA Search Terms (Version 20.0)	PT terms: Columbia suicide severity rating scale abnormal; Columbia suicide severity rating scale; Completed suicide; Suicide attempt; Suicidal ideation; Suicidal behavior; Depression suicidal; Intentional overdose; Intentional self-injury; Poisoning deliberate
* See Appendix A for a description of the FAERS database.	

3 RESULTS

3.1 FAERS Case Selection

The FAERS search retrieved 112 reports. After applying the case definition in Section 2.1 and accounting for duplicate reports, 74 cases were included in the case series of completed suicide, suicidal attempt, or suicidal ideation reported with testosterone use (see Figure 3.1.1).

Figure 3.1.1. FAERS Case Selection

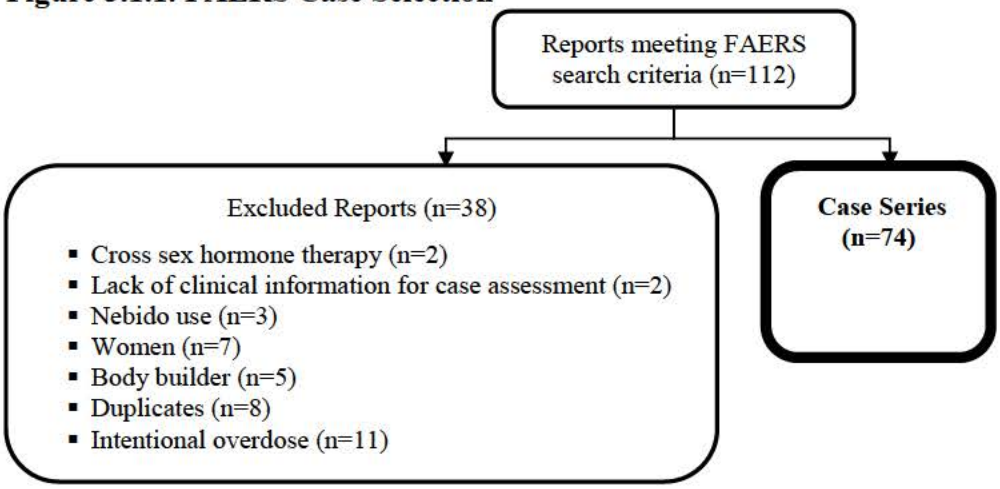

Table 3.1.1. and Table 3.1.2. summarizes the 74 FAERS cases of completed suicide, suicidal attempt, or suicidal ideation reported with testosterone use for this case series.

Appendix B lists all the FAERS case numbers, FAERS version numbers, and Manufacturer Control numbers for the 74 cases in this case series.

Table 3.1.1. Descriptive case characteristics of suicidal attempt, completed suicide, or suicidal ideation reported with testosterone use in cisgender men, received by FDA through August 15, 2017 (N=74)	
Country of report	
Norway	1
Not reported	1
Poland	2
France	2
Denmark	2
Canada	3
USA	63
Report type	
Non-expedited report	8
Direct report	9
Expedited (15-day) report	57
Serious regulatory outcomes[*,†] (n=66)	
Required intervention	1
Disability	7
Life-threatening	10
Death	15
Hospitalization	19
Other serious	38

* For the purposes of this memo, the following outcomes qualify as serious: death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention and other serious important medical events.

† A case may have one or more outcome.

Table 3.1.2. Event-related information for FAERS cases of suicidal attempt, completed suicide, or suicidal ideation reported with testosterone use in cisgender men, received by FDA through August 15, 2017 (N=74)	
Reason for use	
Sexual dysfunction	3
Hypogonadism	11
Low testosterone	23
Not reported	37
Drug used[‡]	
IM testosterone (NOS)	1
Methyltestosterone	1
Fortesta	1
Testopel	1
Testogel	2
Testoderm	2
Testosterone gel	2
Testosterone pellets (NOS)	2
Testosterone (NOS)	4
Androderm	5
Testosterone cypionate	5
Axiron	6
Depo-testosterone	7
Testim	7
AndroGel	43
Suicide category	
Suicidal attempt	13
Completed suicide	15
Suicidal ideation	46
Suicidal Ideation Cases - Dechallenge[§] (n=46)	
Symptoms of suicidal ideation resolved when drug discontinued	7
Not reported	39

‡ A case may have one or more drug used.

§ Of the cases that reported dechallenge, all of them were identified in cases categorized as suicidal ideation.

3.2 FAERS CASES REPORTING SUICIDAL ATTEMPT (N=13)

DPV-II identified 13 cases reporting attempted suicide while taking testosterone therapy. All of the patients were on testosterone therapy for sexual dysfunction (n=2), low testosterone (n=4), hypogonadism (n=4); three cases did not report a reason for use. The details for the suicide attempt in the cases are not reported. Nor is it clear if the patients had a previous history of depression or suicide attempt. When the duration of therapy was reported, the testosterone therapy ranged from one month to six years.

3.3 FAERS CASES REPORTING COMPLETED SUICIDE (N=15)

DPV-II identified 15 cases reporting completed suicide while taking testosterone therapy. The patients in these cases were taking testosterone therapy for sexual dysfunction (n=1), hypogonadism (n=1), or low testosterone (n=5); eight cases did not report a reason for use. A vast majority of these patients had underlying depression and anxiety; additionally, concomitant medications are not reported in a vast majority of the cases. There was one case where the patient shot himself in the head. There was another case where it was reported that the patient was on multiple medications including those for depression (i.e., paroxetine) and pain (i.e., oxycodone hydrochloride) as well as testosterone therapy when the patient completed suicide.

3.4 FAERS CASES REPORTING SUICIDAL IDEATION (N=46)

DPV-II identified 46 cases reporting suicidal thoughts, ideation, and/or worsening depression to the point where they thought about killing themselves, after receiving testosterone therapy. Patients in these cases were on testosterone therapy for hypogonadism (n=6), and low testosterone (n=14); Twenty-six cases did not report a reason for use.

DPV-II identified 7 cases where it was reported that the patients' symptoms of suicidal thoughts and ideation resolved after discontinuation of testosterone. While the patients were on testosterone therapy it was reported that suicidal thoughts occurred and depression got worse, however, when the testosterone was discontinued, the patients went back to baseline or no longer had suicidal thoughts.

4 DISCUSSION

From FAERS, DPV-II identified 13 cases of suicidal attempt, 15 cases of completed suicide, and 46 cases of suicidal ideation with the use of testosterone. Individual reports have not been reviewed to assess for causality between testosterone and completed suicide, suicidal attempt or suicidal ideation given the rapid response needed by DBRUP. More importantly, a vast majority of the cases do not provide necessary information regarding concomitant medications, past medical history, duration of therapy, time-to-onset of suicidal symptoms, and previous history of suicidal attempts to ascertain a drug-event association.

As with all analyses of spontaneous adverse events data, this qualitative summary is subject to several limitations, including, but not limited to:

- FAERS cannot be used to estimate a risk, because the database does not collect information about the total number of persons exposed.
- As reporting by healthcare facilities, practitioners, and patients to the FDA or to manufacturers is entirely voluntary, FDA has observed an overall increase in the annual volume of FAERS reports submitted from all sources in recent years (see Appendix A). At present, over 17 million reports have been collected since 1969.
- Under-reporting of adverse events also prevents the ascertainment of a complete numerator as reporting is voluntary.
- Reporting biases such as the time the drug has been on the market further limit the ability to compare risks between products.

5 CONCLUSION

We identified cases of suicidal attempt, completed suicide, and suicidal ideation reported with the use of testosterone. We are mindful that this memo is a high level summary and the individual cases were not reviewed for drug-event causality given the rapid response needed by DBRUP. However, a vast majority of the cases do not provide necessary information regarding concomitant medications, past medical history, duration of therapy, time-to-onset of suicidal symptoms, and previous history of suicidal attempts to ascertain a drug-event association. This is a limitation of spontaneous data. Additionally, we did not note a specific trend.

6 REFERENCES

[1] Working copy of OSE Case Definition of Suicidal Ideation and Behavior. Last updated May 9, 2017.

7 APPENDICES

7.1 APPENDIX A. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

FDA Adverse Event Reporting System (FAERS)

FAERS is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary.

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

Data Mining of FAERS using Empirica Signal

Empirica Signal refers to the software that OSE uses to perform data mining analyses while using the Multi-item Gamma Poisson Shrinker (MGPS) data mining algorithm. "Data mining" refers to the use of computer algorithms to identify patterns of associations or unexpected occurrences (i.e., "potential signals") in large databases. These potential signals can then be evaluated for intervention as appropriate. In OSE, the FAERS database is utilized for data mining. MGPS analyzes the records in FAERS and then quantifies reported drug-event associations by producing a set of values or scores that indicate varying strengths of reporting relationships between drugs and events. These scores, denoted as Empirical Bayes Geometric Mean (EBGM) values, provide a stable estimate of the relative reporting of an event for a particular drug relative to all other drugs and events in FAERS. MGPS also calculates lower and upper 90% confidence limits for EBGM values, denoted EB05 and EB95, respectively. Because EBGM scores are based on FAERS data, limitations relating to FAERS data also apply to data mining-derived data. Further, drug and event causality cannot be inferred from EBGM scores.

7.2 APPENDIX B. FAERS LINE LISTING OF SUICIDAL ATTEMPT, COMPLETED SUICIDE, OR SUICIDAL IDEATION CASE SERIES (N=74)

FAERS Case #	Version Number	Manufacturer Control #	Age in Years	Country Derived	Reason for Use	Category	Drug	Serious Outcome?	All Outcomes
10040156	1	US-ABBVIE-14P-163-1213912-00	50	USA	low T	suicidal ideation	Androgel	Y	OT
10363745	1	201407069	37	USA	low T	completed suicide	Testim	Y	DE,LT
10399181	1	US-ABBVIE-14P-163-1273643-00	51	USA	NR	suicidal ideation	Androgel	Y	OT
10497771	1	US-PFIZER INC-2014271832	NR	USA	NR	suicidal ideation	Depo-Testosterone	Y	OT
10507806	1	US-ABBVIE-14P-163-1291127-00	NR	USA	NR	suicidal ideation	Androgel	Y	OT
10524469	1		64	USA	NR	suicidal ideation	Androgel	Y	HO,OT
10545194	1	US-ELI_LILLY_AND_COMPANY-US201410006180	30	USA	hypogonadism	suicidal ideation	Axiron	Y	OT

FAERS Case #	Version Number	Manufacturer Control #	Age in Years	Country Derived	Reason for Use	Category	Drug	Serious Outcome?	All Outcomes
10040156	1	US-ABBVIE-14P-163-1213912-00	50	USA	low T	suicidal ideation	Androgel	Y	OT
10555750	2	CA-ABBVIE-14P-028-1302179-00	63.849	CAN	low T	suicidal ideation	Androgel	Y	OT
10557923	1	US-WATSON-2014-23073	47.151	USA	low T	completed suicide	testosterone cypionate	Y	DE
10676706	1		32	USA	low T	suicide attempt	Androgel	Y	DS,HO,LT
10996878	1	CA-JNJFOC-20150400972	14	CAN	hypogonadism	suicide attempt	IM testosterone	Y	HO,OT
11083034	1	US-ABBVIE-14P-163-1309900-00	70	USA	low T	suicidal ideation	Androgel	N	
11130269	2	US-ABBVIE-15P-163-1393742-00	NR	USA	NR	suicide attempt	Androgel, Depo-Testosterone	Y	HO,OT
11358782	1		54	USA	low T	completed suicide	Androgel	Y	DE

FAERS Case #	Version Number	Manufacturer Control #	Age in Years	Country Derived	Reason for Use	Category	Drug	Serious Outcome?	All Outcomes
10040156	1	US-ABBVIE-14P-163-1213912-00	50	USA	low T	suicidal ideation	Androgel	Y	OT
11459348	2	US-PFIZER INC-2015296391	42	USA	hypogonadism	suicidal ideation	Androgel, Depo-Testosterone	Y	DS,HO,OT
11579501	2	US-ABBVIE-15P-163-1472247-00	NR	USA	NR	suicidal ideation	Androgel	Y	DS
11655713	1	CA-ABBVIE-15P-028-1487040-00	52	CAN	low T	suicidal ideation	Androgel	Y	LT
11693245	1		55	USA	NR	suicidal ideation	testosterone cypionate	Y	DS,HO,LT
11934615	1		46	USA	NR	suicidal ideation	testosterone pellets	Y	DS,HO,LT
12045382	3	US-ELI LILLY AND COMPANY-US201602001192	53.0486	USA	hypogonadism	completed suicide	Androgel, Axiron, testosterone cypionate	Y	DE,HO,OT
12089154	3	US-ABBVIE-16P-163-1559493-00	NR	USA	hypogonadism	suicidal ideation	Androgel, testosterone pellets	Y	OT

FAERS Case #	Version Number	Manufacturer Control #	Age in Years	Country Derived	Reason for Use	Category	Drug	Serious Outcome?	All Outcomes
10040156	1	US-ABBVIE-14P-163-1213912-00	50	USA	low T	suicidal ideation	Androgel	Y	OT
12113842	1	US-WEST-WARD PHARMACEUTICALS CORP.-US-H14001-16-00309	47.518	USA	low T	completed suicide	Androgel, testosterone cypionate	Y	DE
12125692	1	US-ABBVIE-15P-163-1472625-00	60.35	USA	low T	suicidal ideation	Androgel	N	
12225860	1	US-ENDO PHARMACEUTICALS INC.-2015-005244	45.125	USA	hypogonadism	suicide attempt	Androgel, Depo-Testosterone	Y	DS,HO,OT
12323980	1	US-ABBVIE-15P-163-1449992-00	36.46817	USA	NR	suicidal ideation	Androgel	N	
12324544	1	US-ABBVIE-15P-163-1468048-00	NR	USA	NR	suicidal ideation	Androgel	N	

FAERS Case #	Version Number	Manufacturer Control #	Age in Years	Country Derived	Reason for Use	Category	Drug	Serious Outcome?	All Outcomes
10040156	1	US-ABBVIE-14P-163-1213912-00	50	USA	low T	suicidal ideation	Androgel	Y	OT
12386543	1	US-ENDO PHARMACEUTICALS INC.-2016-001479	40.08487	USA	hypogonadism	suicide attempt	Testim, Androgel, testosterone cypionate	Y	HO
12434752	2	US-ENDO PHARMACEUTICALS INC.-2016-003589	55.77823	USA	NR	suicide attempt	Androderm, Androgel, Testim	Y	DS,HO,OT
12601094	1	US-ABBVIE-16P-163-1686412-00	NR	USA	NR	suicidal ideation	Androgel	Y	OT
12708660	1	US-ENDO PHARMACEUTICALS INC.-2016-005404	55	USA	NR	completed suicide	Testopel	Y	DE
13152271	1	US-ALLERGAN-1702559US	57	USA	NR	suicidal ideation	Androderm, Androgel, testosterone	Y	OT

FAERS Case #	Version Number	Manufacturer Control #	Age in Years	Country Derived	Reason for Use	Category	Drug	Serious Outcome?	All Outcomes
10040156	1	US-ABBVIE-14P-163-1213912-00	50	USA	low T	suicidal ideation	Androgel	Y	OT
13324218	1	US-ABBVIE-17P-163-1896471-00	66	USA	NR	suicidal ideation	Androgel	Y	OT
13665923	1	US-ABBVIE-17P-163-2006691-00	56.91992	USA	NR	suicidal ideation	Androgel	Y	OT
3407382	1	5700	43	NULL	NR	suicidal ideation	Testoderm	Y	HO
4015122	3	TEST00203002722	13	USA	hypogonadism	suicidal ideation	testosterone gel	Y	HO
4150773	1	KII-2002-0010355	55	USA	NR	completed suicide	Testoderm	Y	DE
4843586	1	22585635	54	USA	sexual dysfunction	completed suicide	Depo-Testosterone	Y	DE,OT
5022217	1	27285635	NR	USA	sexual dysfunction	suicide attempt	Depo-Testosterone	N	
5860250	1	190705001/225 AE	41	USA	hypogonadism	suicidal ideation	Testim	Y	RI
5935985	1	US-SOLVAY-00205003776	57.26489	USA	low T	suicidal ideation	Androgel	Y	LT
5954475	2	2005-04814	54	USA	low T	suicidal ideation	Androderm	Y	OT

FAERS Case #	Version Number	Manufacturer Control #	Age in Years	Country Derived	Reason for Use	Category	Drug	Serious Outcome?	All Outcomes
10040156	1	US-ABBVIE-14P-163-1213912-00	50	USA	low T	suicidal ideation	Androgel	Y	OT
6013103	1	US-SOLVAY-00206000968	51.16667	USA	low T	suicidal ideation	Androgel	Y	OT
6102030	2	US-SOLVAY-00206002504	NR	USA	NR	completed suicide	Androgel	Y	DE
6138877	1	2006-BP-10602RO	NR	USA	NR	completed suicide	Androgel	Y	DE
6181512	1	US-SOLVAY-00206003928	56.5	USA	low T	suicidal ideation	Androgel	Y	OT
6594197	1	US-PFIZER INC-2008024010	NR	USA	NR	suicidal ideation	testosterone	Y	OT
6601304	3	US-SOLVAY-00208001176	45	USA	low T	suicidal ideation	Androgel	Y	OT
6687923	1	US-SOLVAY-00208002832	61.91667	USA	NR	suicidal ideation	Androgel	Y	OT
6918830	1	US-SOLVAY-00209000862	40	USA	low T	completed suicide	Androgel	Y	DE

FAERS Case #	Version Number	Manufacturer Control #	Age in Years	Country Derived	Reason for Use	Category	Drug	Serious Outcome?	All Outcomes
10040156	1	US-ABBVIE-14P-163-1213912-00	50	USA	low T	suicidal ideation	Androgel	Y	OT
7049227	2	US-SOLVAY-00209003609	NR	USA	NR	completed suicide	Androgel	Y	DE
7084353	2	US-PFIZER INC-2009252454	NR	USA	NR	completed suicide	Depo-Testosterone	Y	DE
7096924	1	US-SOLVAY-00209004708	53.33333	USA	NR	suicidal ideation	Androgel	Y	OT
7546458	1	201004025	46	USA	low T	suicidal ideation	Testim	Y	HO
7916353	1		59	USA	NR	completed suicide	Testim	Y	DE,LT
8018820	1	PL-WATSON-2011-09550	19	POL	NR	suicidal ideation	testosterone	Y	HO
8018822	1	PL-WATSON-2011-09560	17	POL	NR	suicidal ideation	testosterone	Y	HO
8068948	2	US-ELI LILLY AND COMPANY-US201107006856	59	USA	hypogonadism	suicide attempt	Axiron	Y	OT

FAERS Case #	Version Number	Manufacturer Control #	Age in Years	Country Derived	Reason for Use	Category	Drug	Serious Outcome?	All Outcomes
10040156	1	US-ABBVIE-14P-163-1213912-00	50	USA	low T	suicidal ideation	Androgel	Y	OT
8346620	1	PHHY2012FR004078	27	FRA	NR	suicide attempt	methyltestosterone	Y	OT
8353615	2	DK-ABBOTT-12P-044-0896679-00	14.16	DNK	hypogonadism	suicidal ideation	Testogel	Y	OT
8399641	1	NO-ABBOTT-12P-122-0902925-00	43	NOR	NR	completed suicide	testosterone gel	Y	DE
8406354	1	US-ELI LILLY AND COMPANY-US201201004602	77	USA	NR	suicidal ideation	Axiron	Y	OT
8525529	1		52	USA	NR	suicidal ideation	Androgel	Y	OT
8663367	1	US-ELI LILLY AND COMPANY-US201207001059	47	USA	low T	suicidal ideation	Axiron	Y	OT
8745412	1		45.232	USA	low T	suicide attempt	Androgel	Y	HO,LT,OT
9027842	1		56	USA	NR	suicidal ideation	Androderm, Testim	Y	LT

FAERS Case #	Version Number	Manufacturer Control #	Age in Years	Country Derived	Reason for Use	Category	Drug	Serious Outcome?	All Outcomes
10040156	1	US-ABBVIE-14P-163-1213912-00	50	USA	low T	suicidal ideation	Androgel	Y	OT
9128763	1	US-ABBOTT-13P-163-1046638-00	51.877	USA	low T	suicidal ideation	Androgel	N	
9130115	1	US-ABBOTT-13P-163-1046622-00	NR	USA	NR	suicidal ideation	Androgel	N	
9158659	1	US-ELI_LILLY_AND_COMPANY-US201303001018	35	USA	low T	suicidal ideation	Axiron	Y	OT
9163244	1	FR-ROCHE-1201576	NR	FRA	sexual dysfunction	suicide attempt	Androgel	Y	OT
9241510	2	US-ENDO PHARMACEUTICALS INC.-FORT20130111	29	USA	low T	suicide attempt	Fortesta, Androderm	Y	HO,OT
9292935	1	US-ABBOTT-13P-163-1088871-00	52.89	USA	NR	suicidal ideation	Androgel	Y	OT

FAERS Case #	Version Number	Manufacturer Control #	Age in Years	Country Derived	Reason for Use	Category	Drug	Serious Outcome?	All Outcomes
10040156	1	US-ABBVIE-14P-163-1213912-00	50	USA	low T	suicidal ideation	Androgel	Y	OT
9410523	1	DK-ABBOTT-13P-044-1122561-00	38.916	DNK	low T	suicide attempt	Testogel	Y	HO,LT
9479150	1	US-ABBOTT-13P-163-1136347-00	61	USA	NR	suicidal ideation	Androgel	Y	OT
9721702	4	US-ABBVIE-13P-163-1153267-00	35.337	USA	NR	suicidal ideation	Androgel	N	

*As per 21 CFR 314.80, the regulatory definition of serious is any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect, and other serious important medical events. This outcome should not be confused with the clinical outcome of the reported adverse drug experience. Those which are blank were not marked as serious (per the previous definition) by the reporter, and are coded as non-serious. A report may have more than one serious outcome.
Abbreviations: DE=Death, HO=Hospitalization, LT= Life-threatening, DS= Disability, OT=Other medically significant

7.3 APPENDIX C. FAERS CASE REPORTS (N=74)

See attached 74 cases of suicidal attempt, completed suicide, or suicidal ideation case series

FDA Adverse Event Reporting System (FAERS)

Batch Printing Report for Cases

Run by: SAHOOS

Date - Time: AUG-30-2017 10:07 AM

Disclaimer:

Submission of a safety report does not constitute an admission that medical personnel, user facility, importer, distributor, manufacturer or product caused or contributed to the event. The information in these reports has not been scientifically or otherwise verified as to a cause and effect relationship and cannot be used to estimate the incidence of these events.

Esub Case ID(s) Printed:

5935985	6013103	6102030	6181512	6594197	6601304	6687923
6918830	7049227	7084353	7096924	8018820	8018822	8068948
8346620	8353615	8399641	8406354	8525529	8663367	8745412
9128763	9130115	9158659	9163244	9241510	9292935	9410523
9479150	9721702	10040156	10399181	10497771	10507806	10545194
10555750	10557923	10996878	11083034	11130269	11459348	11579501
11655713	12045382	12089154	12113842	12125692	12225860	12323980
12324544	12386543	12434752	12601094	12708660	13152271	13324218
13665923						

Total number of cases (Esub) = 57

Total number of cases (Non-Esub) = 17

Total Cases = 74

Reference ID: 4146835

FDA - Adverse Event Reporting System (FAERS)

Batch Printing Report for Cases

Case Information:

Case Id: 5935985 **Version:** 1 **Case Type:** 15-DAY **eSub:** Yes **HP:** Y **Country:** USA **Outcome(s):** LT

FDA Rcvd. Date: 06-Dec-2005 **Init FDA Rcvd. Date:** 06-Dec-2005 **Mfr Rcvd. Date:** 29-Nov-2005 **Application Type:** NDA **Application #:** 021015

Mfr. Control #: US-SOLVAY-00205003776

Patient Information:

Patient ID: (b) (6) **Age:** (b) (6) DAY **Age in Years:** 57 (b) (6) Y **Sex:** Male **Weight:** 92 KG **DoB:** (b) (6)

Suspect Products:

#	Product Name	Dose/Frequency	Route	Dosage Text	Indication(s)	Start Date	End Date	Interval 1st Dose to Event	ReC	DeC
1	ANDROGEL	5 GM/	TDER	Daily dose: 5 gram(s) via pump	BLOOD TESTOSTERONE DECREASED	03-Oct-2005	03-Nov-2005	13 Day	NA	Yes

#	Product Name	Lot#	Exp Date	NDC #	Labeler	OTC
1	ANDROGEL					

Event Information:

MedDRA © PreferredTerm	Start Date	End Date	Outcomes	Highlighted Terms	ReC
Anger	15-Oct-2005	03-Nov-2005	RECOVERED/ RESOLVED	Y	NA
Memory Impairment	15-Oct-2005	03-Nov-2005	RECOVERED/ RESOLVED	N	NA
Suicidal Ideation	15-Oct-2005	08-Nov-2005	RECOVERED/ RESOLVED	Y	NA

Event/Problem Narrative:

A physician report was received via a company sales representative regarding a male of unknown age on ANDROGEL, 5 g daily, for low testosterone, start date of therapy unknown. He used ANDROGEL for three weeks and during this time experienced violent roid rage or steroid rage. He does not remember the incident. The physician was able to rule out a brain tumor and he discontinued the ANDROGEL on an unknown date. As of 09 NOV 2005, the patient is no longer experiencing steroid rage and he no longer uses ANDROGEL therapy. The reporter assessed the causal relationship of the adverse events to ANDROGEL as "possible." ***ADDITIONAL INFORMATION RECEIVED ON 29 NOV 2005: Patient demographics were provided. The adverse event of "roid rage" was changed to "rage attack." A start and stop date was provided for the adverse event of "rage attack" and the adverse event of "suicidal ideation" was also added. The patient's physician considered the seious events to be life-threatening. The patient was using the ANDROGEL pump and therapy dates were provided. Another indication for the use of ANDROGEL was provided.Concomitant medications were given and treatment for the events was provided. Medical history was also provided and the reported causality was changed. The patient is a 54-year-old male

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who was treated with ANDROGEL, 5 g daily via pump, from 03 OCT 2005 to 03 NOV 2005. The adverse event of "rage attacks" started on 15 OCT 2005 and ended on 03 NOV 2005. The adverse event of "suicidal ideation" started on 15 OCT 2005 and ended on 08 NOV 2005. The patient's physician reported that the patient has had a long-standing low severity depression for many years, which has been treated with Norpramin 100 mg daily. On 03 OCT 2005, the patient had a testosterone level that was low and he was subsequently started on ANDROGEL. After several days, he became actively suicidal and developed rage attacks. He was treated with Zyprexa and his Norpramin was increased. ANDROGEL was discontinued on 03 NOV 2005 and he recovered completely. The physician assessed the events of rage attacks and suicidal indeation as serious events. The physician assessed the causal relationship for the adverse events to ANDROGEL as "highly probable."

Relevant Medical History:

Date Unknown:This patient has a history of sublingual cancer and kidney problems. ***ADDITIONAL INFORMATION RECEIVED ON 29 NOV 2005: The patient had palate cancer in 1996 and kidney cancer in 2000. He had surgery on a deep vein thrombosis in 2003. In addition, he has a history of benign prostatic hypertrophy, hypertension, coronary artery disease, increased cholesterol and mild depression. Allergies include Levaquin, Allegra and EES.

Disease/Surgical Procedure	Start Date	End Date	Continuing?	Comment

Medical History Product(s)	Start Date	End Date	Indication(s)	MedDRA Preferred Term(s)

Relevant Laboratory Data:

Test Date	Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail Y/N

Concomitant Products:

#	Product Name	Dose/Frequency	Route	Dosage Text	Indication(s)	Start Date	End Date	Interval 1st Dose to Event
1	NORVASC	5 MG/	PO	Daily dose: 5 milligram(s)	ILL-DEFINED DISORDER			
2	NORPRAMIN	100 MG/	PO	Daily dose: 100 milligram(s)	DEPRESSION		Oct-2005	
3	TRICOR	145 MG/	PO	Daily dose: 145 milligram(s)	ILL-DEFINED DISORDER			
4	PREVACID	30 MG/	PO	Daily dose: 30 milligram(s)	ILL-DEFINED DISORDER			
5	ASA	325 MG/	PO	Daily dose: 325 milligram(s)	ILL-DEFINED DISORDER			
6	DIOVAN	160 MG/	PO	Daily dose: 160 milligram(s)	ILL-DEFINED DISORDER			

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	Product Name	Dose/Frequency	Route	Dosage Text	Indication(s)	Start Date	End Date	Interval 1st Dose to Event
7	SPIRIVA	1 /	PO	Daily dose: 1 dosage form	ILL-DEFINED DISORDER			
8	ZOCOR	40 MG/	PO	Daily dose: 40 milligram(s)	ILL-DEFINED DISORDER			
9	NORPRAMIN	/	PO	Daily dose: unknown		Oct-2005		

Reporter Source:

Study Report:	Study Name:	Study Type:	Sponsor Study:	Protocol	IND #:
No					

Literature Text:

Country of Event: USA **Sender MFR:** SOLVAY

Reporter Name: (b) (6)
Reporter Org.:
Reporter Street:
Reporter City:
Reporter Zip:
Health Prof.: YES
Occupation: PHYSICIAN

Reporter Type: Health Professional,
Reporter Email:
Reporter Phone:
Reporter State: (b) (6)
Reporter Country: UNITED STATES
Sent To:
Identity Disclosed:

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FDA - Adverse Event Reporting System (FAERS)

Batch Printing Report for Cases

Case Information:

Case Id: 6013103 **Version:** 1 **Case Type:** 15-DAY **eSub:** Yes **HP:** N **Country:** USA **Outcome(s):** OT

FDA Rcvd. Date: 28-Mar-2006 **Init FDA Rcvd. Date:** 28-Mar-2006 **Mfr Rcvd. Date:** 22-Mar-2006 **Application Type:** NDA **Application #:** 021015

Mfr. Control #: US-SOLVAY-00206000968

Patient Information:

Patient ID: (b) (6) **Age:** (b) (6) MTH **Age in Years:** 51. (b) (6) Y **Sex:** Male **Weight:** 63.5 KG **DoB:** (b) (6)

Suspect Products:

#	Product Name	Dose/Frequency	Route	Dosage Text	Indication(s)	Start Date	End Date	Interval 1st Dose to Event	ReC	DeC
1	ANDROGEL	5 GM/	TDER	Daily dose: 5 gram(s)	BLOOD TESTOSTERONE DECREASED	1999	Sep-2005	7 Year	NA	NA
2	ANDROGEL	5 GM/	TDER	Daily dose: 5 gram(s)		Oct-2005	Dec-2005	7 Year	NA	NA

#	Product Name	Lot#	Exp Date	NDC #	Labeler	OTC
1	ANDROGEL					
2	ANDROGEL					

Event Information:

MedDRA © PreferredTerm	Start Date	End Date	Outcomes	Highlighted Terms	ReC
Blood Testosterone Decreased	01-Jan-2006		UNKNOWN	Y	NA
Suicidal Ideation	01-Jan-2006		UNKNOWN	N	NA

Event/Problem Narrative:

A consumer report was received regarding a 51 year-old male on ANDROGEL, 5 g QD, for low testosterone. He began ANDROGEL therapy in 1999, and interrupted therapy in SEP 2005, due to insurance issues. His testosterone level during therapy interruption was 75. He resumed ANDROGEL therapy in OCT 2005, but in DEC 2005, his physician discontinued therapy for an unknown reason. In JAN 2006, his testosterone level was tested at 300. He had a return of his low testosterone symptoms, which he described to his psychologist as: he was not able to function; he did not look healthy, he had no energy, and would come home and go straight to bed. He mentioned to his psychologist that he wanted to kill himself but had not figured out how to do it yet. On (b) (6) the psychologist instructed him to go to the emergency room (ER) to get testosterone patches. The consumer was held for 6 hours in the ER for testing. As of 22 MAR 2006, the consumer is not using ANDROGEL therapy and it is unknown if the symptoms of low testosterone continue. This case has been medically judged as

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serious by Solvay Pharmaceuticals. The reporter assessed the causal relationship of the return of low testosterone symptoms to ANDROGEL as "possible."

Relevant Medical History:

The consumer has a history of osteoporosis (since 1999), depression (since 1999), memory loss (2005), and has used testosterone injections in the past.

Disease/Surgical Procedure	Start Date	End Date	Continuing?	Comment

Medical History Product(s)	Start Date	End Date	Indication(s)	MedDRA Preferred Term(s)

Relevant Laboratory Data:

Test Date	Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail Y/N

Concomitant Products:

#	Product Name	Dose/Frequency	Route	Dosage Text	Indication(s)	Start Date	End Date	Interval 1st Dose to Event
1	KLONOPIN	1 MG/	PO	Daily dose: .5 milligram(s)	SLEEP DISORDER			
2	AMBIEN CR	13 MG/	PO	Daily dose: 12.5 milligram(s)	SLEEP DISORDER			

Reporter Source:

Study Report:	Study Name:	Study Type:	Sponsor Study:	Protocol	IND #:
No					

Literature Text:

Country of Event: USA **Sender MFR:** SOLVAY

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FDA - Adverse Event Reporting System (FAERS)

Batch Printing Report for Cases

Reporter Name:	(b) (6)	**Reporter Type:**	
Reporter Org.:		**Reporter Email:**	
Reporter Street:		**Reporter Phone:**	
Reporter City:		**Reporter State:**	(b) (6)
Reporter Zip:		**Reporter Country:**	UNITED STATES
Health Prof.:	NO	**Sent To:**	
Occupation:	CONSUMER OR OTHER NON HEALTH PROFESSIONAL	**Identity Disclosed:**	

***Age in Years displays a mid-value where the Age Unit in the report is in DECADE**

FDA - Adverse Event Reporting System (FAERS)

Batch Printing Report for Cases

Case Information:

Case Id: 6102030 **Version:** 2 **Case Type:** 15-DAY **eSub:** Yes **HP:** Y **Country:** USA **Outcome(s):** DE

FDA Rcvd. Date: 25-Aug-2006 **Init FDA Rcvd. Date:** 09-Aug-2006 **Mfr Rcvd. Date:** 23-Aug-2006 **Application Type:** NDA **Application #:** 021015

Mfr. Control #: US-SOLVAY-00206002504

Patient Information:

Patient ID: (b) (6) **Age:** **Age in Years:** **Sex:** Male **Weight:** **DoB:**

Suspect Products:

#	Product Name	Dose/Frequency	Route	Dosage Text	Indication(s)	Start Date	End Date	Interval 1st Dose to Event	ReC	DeC
1	ANDROGEL	/	TDER	Daily dose: unknown	DEPRESSION	Nov-2005	01-Aug-2006	9 Month	NA	NA
2	LITHIUM	/	PO	Daily dose: unknown	DEPRESSION				NA	NA

#	Product Name	Lot#	Exp Date	NDC #	Labeler	OTC
1	ANDROGEL					
2	LITHIUM					

Event Information:

MedDRA © PreferredTerm	Start Date	End Date	Outcomes	Highlighted Terms	ReC
Completed Suicide	(b) (6)	(b) (6)	FATAL	Y	NA

Event/Problem Narrative:

A physician report was received via a company sales representative regarding a male patient of unknown age on ANDROGEL, dose unknown, for depression. The patient was also taking Lithium, for depression, which is also suspect in this case. On an unknown date, the patient committed suicide. Additional information has been requested. The reporter assessed the causal relationship of the adverse event to ANDROGEL as "possible." ***ADDITIONAL INFORMATION RECEIVED ON 23 AUG 2006: The patient's demographics, therapy dates, adverse event dates, date of death, relevant history and reported causality have been updated. The patient began ANDROGEL therapy in NOV 2005, and did not discontinue it prior to his death. The physician reported the patient died on (b) (6) The patient had a history of previous suicide attempts. The reporter assessed the causal relationship of the adverse event to ANDROGEL as "unrelated."

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Relevant Medical History:

Depression. ***ADDITIONAL INFORMATION RECEIVED ON 23 AUG 2006: The patient had a history of previous suicide attempts.

Disease/Surgical Procedure	Start Date	End Date	Continuing?	Comment

Medical History Product(s)	Start Date	End Date	Indication(s)	MedDRA Preferred Term(s)

Relevant Laboratory Data:

Test Date	Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail Y/N

Concomitant Products:

#	Product Name	Dose/Frequency	Route	Dosage Text	Indication(s)	Start Date	End Date	Interval 1st Dose to Event

Reporter Source:

Study Report:	Study Name:	Study Type:	Sponsor Study:	Protocol	IND #:
No					

Literature Text:

Country of Event: USA **Sender MFR:** SOLVAY

***Age in Years displays a mid-value where the Age Unit in the report is in DECADE**

FDA - Adverse Event Reporting System (FAERS)

Batch Printing Report for Cases

Reporter Name:	(b) (6)	**Reporter Type:**	Health Professional,
Reporter Org.:		**Reporter Email:**	
Reporter Street:		**Reporter Phone:**	
Reporter City:		**Reporter State:**	(b) (6)
Reporter Zip:		**Reporter Country:**	UNITED STATES
Health Prof.:	YES	**Sent To:**	
Occupation:	PHYSICIAN	**Identity Disclosed:**	

***Age in Years displays a mid-value where the Age Unit in the report is in DECADE**

FDA - Adverse Event Reporting System (FAERS)

Batch Printing Report for Cases

Case Information:

Case Id: 6181512 **Version:** 1 **Case Type:** 15-DAY **eSub:** Yes **HP:** Y **Country:** USA **Outcome(s):** OT

FDA Rcvd. Date: 08-Dec-2006 **Init FDA Rcvd. Date:** 08-Dec-2006 **Mfr Rcvd. Date:** 30-Nov-2006 **Application Type:** NDA **Application #:** 021015

Mfr. Control #: US-SOLVAY-00206003928

Patient Information:

Patient ID: (b) (6) **Age:** (b) (6) MTH **Age in Years:** 56.(b) (6) YR **Sex:** Male **Weight:** 105.5 KG **DoB:** (b) (6)

Suspect Products:

#	Product Name	Dose/Frequency	Route	Dosage Text	Indication(s)	Start Date	End Date	Interval 1st Dose to Event	ReC	DeC
1	ANDROGEL	/	TDER	Daily dose: 2.5 gram(s)		2005		0 Month	NA	NA
2	ANDROGEL	8 GM/	TDER	Daily dose: 7.5 gram(s)	BLOOD TESTOSTERONE DECREASED	Nov-2005		0 Month	NA	NA

#	Product Name	Lot#	Exp Date	NDC #	Labeler	OTC
1	ANDROGEL					
2	ANDROGEL					

Event Information:

MedDRA © PreferredTerm	Start Date	End Date	Outcomes	Highlighted Terms	ReC
Asthenia	01-Nov-2005		NOT RECOVERED/ NOT RESOLVED	Y	NA
Depression Suicidal	01-Nov-2005		NOT RECOVERED/ NOT RESOLVED	Y	NA
Irritability	01-Nov-2005		NOT RECOVERED/ NOT RESOLVED	Y	NA

Event/Problem Narrative:

A physician report was received regarding a 57-year-old male on ANDROGEL, 7.5 g daily, for low testosterone. The patient began ANDROGEL therapy in NOV 2005. Since beginning ANDROGEL, the patient has experienced periodic episodes of suicidal depression, irritability, and low energy; the last recorded episodes were 30 SEP 2006 and 24 NOV 2006. Within 30 minutes of symptom onset, the patient uses 2.5 g of ANDROGEL. After one hour of using this "boost" of ANDROGEL, the symptoms resolve. The patient also has a history of unstabilized testosterone levels on testosterone injections; lab results, date of onset and therapy dates are unknown. As of 30 NOV 2006, the patient continues on ANDROGEL and the periodic suicidal depression, periodic irritability, and periodic low energy persists. The reporter assessed the causal relationship of the

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adverse events to ANDROGEL as "possible." ***ADDITIONAL INFORMATION RECEIVED ON 01 DEC 2006: The relevant history and relevant tests were updated. The physician reported she ran a testosterone level on the patient approximately 15 months ago (MAR 2005) and it was zero. The patient was having suicidal depression symptoms at that time and testosterone treatment helped; specific therapy details not given. An endocrinologist is currently seeing the patient. The endocrinologist ran testosterone levels recently however, these results are unknown to the physician reporter.

Relevant Medical History:

The consumer has a history of depression, high cholesterol, COPD, asbestos exposure, osteoporosis, GERD, insomnia, posttraumatic stress syndrome, foot compression, lumbar compressions, several fractures, Agent Orange exposure in the navy, unstabilized testosterone levels on testosterone injections, and nicotine use. He had myositis as a result of a Zocor reaction. His risk factor includes nicotine use. ***ADDITIONAL INFORMATION RECEIVED ON 01 DEC 2006: Suicidal depression, onset unknown.

Disease/Surgical Procedure	Start Date	End Date	Continuing?	Comment

Medical History Product(s)	Start Date	End Date	Indication(s)	MedDRA Preferred Term(s)

Relevant Laboratory Data:

Test Date	Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail Y/N

Concomitant Products:

#	Product Name	Dose/Frequency	Route	Dosage Text	Indication(s)	Start Date	End Date	Interval 1st Dose to Event
1	OMACOR	4 GM/	PO	Daily dose: 4 gram(s)	HYPERCHOLESTEROLAEMIA			
2	PROVIGIL	/	PO	Daily dose: unknown	ILL-DEFINED DISORDER			
3	NALTREXONE	10 UG/	PO	Daily dose: 30 microgram(s)	ILL-DEFINED DISORDER			
4	ASPIRIN	81 MG/	PO	Daily dose: 81 milligram(s)	ILL-DEFINED DISORDER			
5	TEMAZEPAM	/	PO	Daily dose: 30 milligrams three times a week	ILL-DEFINED DISORDER			
6	METHADONE HYDROCHLORIDE	20 MG/	PO	Daily dose: 40 milligram(s)	ILL-DEFINED DISORDER			

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FDA - Adverse Event Reporting System (FAERS)

Batch Printing Report for Cases

Reporter Source:

Study Report:	Study Name:	Study Type:	Sponsor Study:	Protocol	IND #:
No					

Literature Text:

Country of Event: USA **Sender MFR:** SOLVAY

Reporter Name:	(b) (6)	**Reporter Type:**	Health Professional,
Reporter Org.:		**Reporter Email:**	
Reporter Street:		**Reporter Phone:**	
Reporter City:		**Reporter State:**	(b) (6)
Reporter Zip:		**Reporter Country:**	UNITED STATES
Health Prof.:	YES	**Sent To:**	
Occupation:	PHYSICIAN	**Identity Disclosed:**	

***Age in Years displays a mid-value where the Age Unit in the report is in DECADE**

FDA - Adverse Event Reporting System (FAERS)

Batch Printing Report for Cases

Case Information:

Case Id: 6594197 **Version:** 1 **Case Type:** 15-DAY **eSub:** Yes **HP:** Y **Country:** USA **Outcome(s):** OT

FDA Rcvd. Date: 26-Mar-2008 **Init FDA Rcvd. Date:** 26-Mar-2008 **Mfr Rcvd. Date:** 14-Mar-2008 **Application Type:** NDA **Application #:** 021928

Mfr. Control #: US-PFIZER INC-2008024010

Patient Information:

Patient ID: UNKNOWN **Age:** **Age in Years:** **Sex:** Male **Weight:** **DoB:**

Suspect Products:

#	Product Name	Dose/Frequency	Route	Dosage Text	Indication(s)	Start Date	End Date	Interval 1st Dose to Event	ReC	DeC
1	CHANTIX	/							NA	Yes
2	TESTOSTERONE	/							NA	Yes

#	Product Name	Lot#	Exp Date	NDC #	Labeler	OTC
1	CHANTIX					
2	TESTOSTERONE					

Event Information:

MedDRA © PreferredTerm	Start Date	End Date	Outcomes	Highlighted Terms	ReC
Abnormal Behaviour			RECOVERED/ RESOLVED	N	NA
Abnormal Dreams			RECOVERED/ RESOLVED	N	NA
Agitation			RECOVERED/ RESOLVED	N	NA
Amnesia			RECOVERED/ RESOLVED	N	NA
Anger			RECOVERED/ RESOLVED	N	NA
Anxiety			RECOVERED/ RESOLVED	N	NA
Disturbance In Attention			RECOVERED/ RESOLVED	N	NA
Feeling Abnormal			RECOVERED/ RESOLVED	N	NA
Frustration Tolerance Decreased			RECOVERED/ RESOLVED	N	NA
Suicidal Ideation			RECOVERED/ RESOLVED	N	NA

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Event/Problem Narrative:

This physician reported to a Pfizer sales representative that a male patient began on Chantix (varenicline) unknown dose, for the treatment of an unknown indication, on an unknown date; and testosterone, unknown dose, for an unknown indication, from an unknown date. Relevant medical history included an unspecified HIV condition from an unknown date. Relevant concomitant medication included Norvir (ritonavir) from an unknown date. On an unknown date, while on Chantix, the patient experienced exacerbated periods of anxiety, rage, extreme agitation, got mad at people in public places, due to which he was frustrated as he had never misbehaved in that manner. He also experienced suicidal ideation, loss of short term memory, loss of memory retention, for example: he lost his keys 5 times in a month. He felt crazy, helpless, could not concentrate, and had bizarre dreams which were sexual and non-sexual at times. He dreamt whatever he watched prior to sleeping; and after he woke up he still felt trapped in the dream. His physician suspected that the above symptoms were caused by testosterone. Hence, he took the patient off the testosterone therapy on an unknown date. However, all these symptoms worsened after discontinuation of testosterone. Due to this, he took the patient off Chantix on an unknown date. The patient took Chantix only for a period of 9 weeks and had successfully quit smoking. Relevant lab data was unknown. At the time of the report, the patient was not taking Chantix and testosterone. At the time of the report, the patient had recovered from the events. Company Clinical Evaluation: A possible contributory role of the subject drug varenicline cannot be excluded in this HIV patient taking medications ritonavir and testosterone. Based on the information provided in the case, this individual report would not seem to modify the risk-benefit profile of the subject drug.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?	Comment
HIV INFECTION				

Medical History Product(s)	Start Date	End Date	Indication(s)	MedDRA Preferred Term(s)

Relevant Laboratory Data:

Test Date	Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail Y/N

Concomitant Products:

#	Product Name	Dose/Frequency	Route	Dosage Text	Indication(s)	Start Date	End Date	Interval 1st Dose to Event
1	NORVIR	/			HIV INFECTION			

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FDA - Adverse Event Reporting System (FAERS)

Batch Printing Report for Cases

Reporter Source:

Study Report:	Study Name:	Study Type:	Sponsor Study:	Protocol	IND #:
No					

Literature Text:

Country of Event: USA

Sender MFR: PFIZER

Reporter Name: (b) (6)
Reporter Org.:
Reporter Street:
Reporter City:
Reporter Zip:
Health Prof.: YES
Occupation: PHYSICIAN

Reporter Type: Health Professional,
Reporter Email:
Reporter Phone:
Reporter State: (b) (6)
Reporter Country: UNITED STATES
Sent To:
Identity Disclosed:

***Age in Years displays a mid-value where the Age Unit in the report is in DECADE**

FDA - Adverse Event Reporting System (FAERS)

Batch Printing Report for Cases

Case Information:

Case Id: 6601304 **Version:** 3 **Case Type:** 15-DAY **eSub:** Yes **HP:** N **Country:** USA **Outcome(s):** OT

FDA Rcvd. Date: 09-Jun-2008 **Init FDA Rcvd. Date:** 31-Mar-2008 **Mfr Rcvd. Date:** 03-Jun-2008 **Application Type:** NDA **Application #:** 021015

Mfr. Control #: US-SOLVAY-00208001176

Patient Information:

Patient ID: (b) (6) **Age:** 45 YR **Age in Years:** 45 YR **Sex:** Male **Weight:** 101.5 KG **DoB:** (b) (6)

Suspect Products:

#	Product Name	Dose/Frequency	Route	Dosage Text	Indication(s)	Start Date	End Date	Interval 1st Dose to Event	ReC	DeC
1	ANDROGEL	5 GM/	TDER	Daily dose: 5 gram(s) via pump	BLOOD TESTOSTERONE DECREASED	Dec-2007			NA	NA

#	Product Name	Lot#	Exp Date	NDC #	Labeler	OTC
1	ANDROGEL					

Event Information:

MedDRA © PreferredTerm	Start Date	End Date	Outcomes	Highlighted Terms	ReC
Suicidal Ideation	01-Feb-2008		NOT RECOVERED/ NOT RESOLVED	Y	NA
Feeling Abnormal			NOT RECOVERED/ NOT RESOLVED	Y	NA

Event/Problem Narrative:

A consumer report was received regarding a 45-year-old male on ANDROGEL, 5 g daily via pump since DEC 2007, for low testosterone. The consumer reported that his wife says he "is different" and "not like himself." He was not able to explain further. Three weeks ago, in FEB 2008, the consumer had suicide thoughts which resolved on an unknown date. As of 17 MAR 2008, the consumer is continuing to use ANDROGEL. The event of "different and not like himself" is ongoing and the event of "suicide thoughts" has resolved. This case has been medically judged as serious. The reporter assessed the causal relationship for the adverse event to ANDROGEL as "possible." ***ADDITIONAL INFORMATION RECEIVED ON 25 APR 2008: Physician information was provided. The outcome for suicidal thoughts was updated. Treatment information was provided, and an additional dosing regimen for Cymbalta was added. The consumer reported that the event of suicide thoughts is ongoing. He also reported that his physician increased the dosage of concomitant medication Cymbalta to 90 mg daily on an unknown date in 2008. ***ADDITIONAL INFORMATION RECEIVED ON 03 JUN 2008: The field "medically confirmed" was updated. The reporter causality for suicidal thoughts and "different/not like himself" was updated. Additional relevant history was added. The physician assessed the causal relationship of suicidal thoughts and "different/not like

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himself" to ANDROGEL as "unrelated." The patient has no prior history of suicide attempts.

Relevant Medical History:

The consumer has had depression for years. He has had high blood pressure since 1982, acid reflux since 1998, spinal disc degeneration since 2005, and pain due a spinal fusion in 2006. ***ADDITIONAL INFORMATION RECEIVED ON 03 JUN 2008: The physician reported that the patient has no prior history of suicide attempts.

Disease/Surgical Procedure	Start Date	End Date	Continuing?	Comment
DEPRESSION			UNKNOWN	
GASTROOESOPHAGEAL REFLUX DISEASE			UNKNOWN	
HYPERTENSION			UNKNOWN	
SPINAL FUSION SURGERY			UNKNOWN	
SPINAL OSTEOARTHRITIS			UNKNOWN	

Medical History Product(s)	Start Date	End Date	Indication(s)	MedDRA Preferred Term(s)

Relevant Laboratory Data:

Test Date	Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail Y/N

Concomitant Products:

#	Product Name	Dose/Frequency	Route	Dosage Text	Indication(s)	Start Date	End Date	Interval 1st Dose to Event
1	PERCOCET	/	PO	Daily dose: 10/325 PRN	PAIN	2007		
2	CYMBALTA	/	PO	Daily dose: unknown	DEPRESSION			
3	NEXIUM	/	PO	Daily dose: unknown	GASTROOESOPHAGEAL REFLUX DISEASE			

***Age in Years displays a mid-value where the Age Unit in the report is in DECADE**

FDA - Adverse Event Reporting System (FAERS)

Batch Printing Report for Cases

	Product Name	Dose/Frequency	Route	Dosage Text	Indication(s)	Start Date	End Date	Interval 1st Dose to Event
4	METHADONE HYDROCHLORIDE	20 MG/	PO	Daily dose: 60 milligram(s)	PAIN	2007		
5	PRILOSEC	/	PO	Daily dose: unknown	GASTROOESOPHAGEAL REFLUX DISEASE	1998		
6	CYMBALTA	/	PO	Daily dose: 90 milligram(s)		2008		
7	SOMA	/	PO	Daily dose: 350 mg PRN	PAIN	2007		
8	METOPROLOL	/	PO	Daily dose: unknown	HYPERTENSION	1982		
9	IBUPROFEN	/	PO	Daily dose: 800 mg PRN	PAIN			

Reporter Source:

Study Report:	Study Name:	Study Type:	Sponsor Study:	Protocol	IND #:
No					

Literature Text:

Country of Event: USA **Sender MFR:** UNIMED

Reporter Name: (b) (6)
Reporter Org.:
Reporter Street:
Reporter City:
Reporter Zip:
Health Prof.: YES
Occupation: PHYSICIAN

Reporter Type: Health Professional,
Reporter Email:
Reporter Phone:
Reporter State: (b) (6)
Reporter Country: UNITED STATES
Sent To:
Identity Disclosed:

***Age in Years displays a mid-value where the Age Unit in the report is in DECADE**

FDA - Adverse Event Reporting System (FAERS)

Batch Printing Report for Cases

Reporter Name:	(b) (6)	**Reporter Type:**	
Reporter Org.:		**Reporter Email:**	
Reporter Street:		**Reporter Phone:**	
Reporter City:		**Reporter State:**	(b) (6)
Reporter Zip:		**Reporter Country:**	UNITED STATES
Health Prof.:	NO	**Sent To:**	
Occupation:	CONSUMER OR OTHER NON HEALTH PROFESSIONAL	**Identity Disclosed:**	

***Age in Years displays a mid-value where the Age Unit in the report is in DECADE**

FDA - Adverse Event Reporting System (FAERS)

Batch Printing Report for Cases

Case Information:

Case Id: 6687923 **Version:** 1 **Case Type:** 15-DAY **eSub:** Yes **HP:** N **Country:** USA **Outcome(s):** OT

FDA Rcvd. Date: 01-Jul-2008 **Init FDA Rcvd. Date:** 01-Jul-2008 **Mfr Rcvd. Date:** 26-Jun-2008 **Application Type:** NDA **Application #:** 021015

Mfr. Control #: US-SOLVAY-00208002832

Patient Information:

Patient ID: (b) (6) **Age:** (b) (6) MTH **Age in Years:** 61. (b) (6) Y **Sex:** Male **Weight:** 118 KG **DoB:** (b) (6)

Suspect Products:

#	Product Name	Dose/Frequency	Route	Dosage Text	Indication(s)	Start Date	End Date	Interval 1st Dose to Event	ReC	DeC
1	ANDROGEL	5 GM/	TDER	Daily dose: 5 gram(s) via pump	ANDROGEN REPLACEMENT THERAPY	2002	Aug-2006	4 Year	NA	NA
2	ANDROGEL	5 GM/	TDER	Daily dose: 5 gram(s) via pump		Sep-2006		4 Year	NA	NA

#	Product Name	Lot#	Exp Date	NDC #	Labeler	OTC
1	ANDROGEL					
2	ANDROGEL					

Event Information:

MedDRA © PreferredTerm	Start Date	End Date	Outcomes	Highlighted Terms	ReC
Depression	01-Aug-2006	01-Sep-2006	RECOVERED/ RESOLVED	Y	NA
Fatigue	01-Aug-2006	01-Sep-2006	RECOVERED/ RESOLVED	Y	NA
Suicidal Ideation	01-Aug-2006	01-Sep-2006	RECOVERED/ RESOLVED	Y	NA
Withdrawal Syndrome	01-Aug-2006	01-Sep-2006	RECOVERED/ RESOLVED	N	NA

Event/Problem Narrative:

A consumer report was received from a male who is currently 63-years-old on ANDROGEL, 5 g daily via pump for testosterone replacement. The consumer began ANDROGEL therapy in 2002. In AUG 2006, he was unable to purchase ANDROGEL; therefore, his therapy was interrupted for 30 days. During the absence of testosterone replacement, he experienced being "extremely depressed, exhausted, and had suicidal thoughts." In SEP 2006, ANDROGEL 5 g daily was restarted and the reported adverse events resolved in approximately five days. He has a history of depression that stopped in 2002; onset date unknown. After starting testosterone therapy (injections and ANDROGEL), he was able to stop anti-

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depressant therapy; dates are unknown. As of 26 JUN 2008, the consumer remains on ANDROGEL and the reported adverse events have resolved. This case has been medically judged as serious by Solvay Pharmaceuticals. The reporter assessed the causal relationship of the adverse events to ANDROGEL as "possible."

Relevant Medical History:

History of depression; onset date unknown and stop date 2002. After starting testosterone therapy (injections and ANDROGEL), he was able to stop anti-depressant therapy; dates are unknown.

Disease/Surgical Procedure	Start Date	End Date	Continuing?	Comment
DEPRESSION			UNKNOWN	

Medical History Product(s)	Start Date	End Date	Indication(s)	MedDRA Preferred Term(s)

Relevant Laboratory Data:

Test Date	Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail Y/N

Concomitant Products:

#	Product Name	Dose/Frequency	Route	Dosage Text	Indication(s)	Start Date	End Date	Interval 1st Dose to Event

Reporter Source:

Study Report:	Study Name:	Study Type:	Sponsor Study:	Protocol	IND #:
No					

Literature Text:

Country of Event: USA **Sender MFR:** UNIMED

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FDA - Adverse Event Reporting System (FAERS)

Batch Printing Report for Cases

Reporter Name:	(b) (6)	**Reporter Type:**	
Reporter Org.:		**Reporter Email:**	
Reporter Street:		**Reporter Phone:**	
Reporter City:		**Reporter State:**	(b) (6)
Reporter Zip:		**Reporter Country:**	UNITED STATES
Health Prof.:	NO	**Sent To:**	
Occupation:	CONSUMER OR OTHER NON HEALTH PROFESSIONAL	**Identity Disclosed:**	

***Age in Years displays a mid-value where the Age Unit in the report is in DECADE**

FDA - Adverse Event Reporting System (FAERS)

Batch Printing Report for Cases

Case Information:

Case Id: 6918830 **Version:** 1 **Case Type:** 15-DAY **eSub:** Yes **HP:** Y **Country:** USA **Outcome(s):** DE

FDA Rcvd. Date: 25-Feb-2009 **Init FDA Rcvd. Date:** 25-Feb-2009 **Mfr Rcvd. Date:** 13-Feb-2009 **Application Type:** NDA **Application #:** 021015

Mfr. Control #: US-SOLVAY-00209000862

Patient Information:

Patient ID: UNKNOWN **Age:** 40 YR **Age in Years:** 40 YR **Sex:** Male **Weight:** **DoB:**

Suspect Products:

#	Product Name	Dose/Frequency	Route	Dosage Text	Indication(s)	Start Date	End Date	Interval 1st Dose to Event	ReC	DeC
1	ANDROGEL	/	TDER	Daily dose: unknown	BLOOD TESTOSTERONE DECREASED	06-Feb-2009		Day	NA	Unk

#	Product Name	Lot#	Exp Date	NDC #	Labeler	OTC
1	ANDROGEL					

Event Information:

MedDRA © PreferredTerm	Start Date	End Date	Outcomes	Highlighted Terms	ReC
Completed Suicide	(b) (6)	(b) (6)	FATAL	Y	NA

Event/Problem Narrative:

A physician report was received via company sales representative concerning a 40-years-old-male who committed suicide while being treated with ANDROGEL. ANDROGEL (daily dose unknown) was started on 06 FEB 2009 for low testosterone. The patient had a history of depression requiring anti-depressant medication use "for years", exact medications and date of use was unknown. The patient was also a paraplegic, onset date was unknown. The patient called his physician during the week of (b) (6) and reported that he had difficulty applying the ANDROGEL and he was interested in switching to the patch therapy. The physician was then notified approximately (b) (6) to (b) (6) that the patient had committed suicide on an unknown date during the week of (b) (6) As of (b) (6) the patient was not on ANDROGEL therapy and the reported suicide was fatal. Outcome: Died. The reporter assessed the causal relationship between ANDROGEL and adverse event as 'possible'.

Relevant Medical History:

Unknown date to (b) (6) : Depression (the patient had used anti-depressant medications "for years") and paraplegia.

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Disease/Surgical Procedure	Start Date	End Date	Continuing?	Comment
DEPRESSION			UNKNOWN	
PARAPLEGIA			UNKNOWN	

Medical History Product(s)	Start Date	End Date	Indication(s)	MedDRA Preferred Term(s)

Relevant Laboratory Data:

Test Date	Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail Y/N

Concomitant Products:

#	Product Name	Dose/Frequency	Route	Dosage Text	Indication(s)	Start Date	End Date	Interval 1st Dose to Event
1	UNKNOWN ANTI-DEPRESSANTS	/	PO	Daily dose: unknown	DEPRESSION			

Reporter Source:

Study Report:	Study Name:	Study Type:	Sponsor Study:	Protocol	IND #:
No					

Literature Text:

Country of Event: USA **Sender MFR:** UNIMED

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FDA - Adverse Event Reporting System (FAERS)

Batch Printing Report for Cases

Reporter Name:	(b) (6)	**Reporter Type:**	Health Professional,
Reporter Org.:		**Reporter Email:**	
Reporter Street:		**Reporter Phone:**	
Reporter City:		**Reporter State:**	(b) (6)
Reporter Zip:		**Reporter Country:**	UNITED STATES
Health Prof.:	YES	**Sent To:**	
Occupation:	PHYSICIAN	**Identity Disclosed:**	

***Age in Years displays a mid-value where the Age Unit in the report is in DECADE**

FDA - Adverse Event Reporting System (FAERS)

Batch Printing Report for Cases

Case Information:

Case Id: 7049227 **Version:** 2 **Case Type:** 15-DAY **eSub:** Yes **HP:** Y **Country:** USA **Outcome(s):** DE

FDA Rcvd. Date: 21-Sep-2009 **Init FDA Rcvd. Date:** 14-Jul-2009 **Mfr Rcvd. Date:** 09-Sep-2009 **Application Type:** NDA **Application #:** 021015

Mfr. Control #: US-SOLVAY-00209003609

Patient Information:

Patient ID: UNKNOWN **Age:** **Age in Years:** **Sex:** Male **Weight:** **DoB:**

Suspect Products:

#	Product Name	Dose/Frequency	Route	Dosage Text	Indication(s)	Start Date	End Date	Interval 1st Dose to Event	ReC	DeC
1	ANDROGEL	/	TDER	Daily dose: 7.5 gram(s) via pump	PRODUCT USED FOR UNKNOWN INDICATION				NA	Unk

#	Product Name	Lot#	Exp Date	NDC #	Labeler	OTC
1	ANDROGEL					

Event Information:

MedDRA © PreferredTerm	Start Date	End Date	Outcomes	Highlighted Terms	ReC
Completed Suicide	(b) (6)		FATAL	Y	NA

Event/Problem Narrative:

A physician report was received via a company sales representative regarding an adult male who committed suicide while on ANDROGEL; dosage and therapy dates are unknown. On an unknown date, the patient committed suicide. Additional information has been requested. The reporter assessed the causal relationship of the adverse event to ANDROGEL as "possible." ***ADDITIONAL INFORMATION RECEIVED ON 09 SEP 2009: Adverse event onset date was added along with daily dosage of ANDROGEL. The physician reported that the patient was taking ANDROGEL, six pumps (7.5 g) daily. The start date for ANDROGEL was not provided. The physician reported that the cause of death was "? suicide claimed/alleged by family." The date of died was reported as (b) (6) The physician reported the causal relationship of the adverse event to ANDROGEL as "unrelated." However, this case is suspect by Solvay Pharmaceuticals Inc. ***09 SEP 2009: Attempted to call the physician for additional information and clarification. The office was closed. Additional information has been requested via letter.

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Relevant Medical History:

None reported.

Disease/Surgical Procedure	Start Date	End Date	Continuing?	Comment

Medical History Product(s)	Start Date	End Date	Indication(s)	MedDRA Preferred Term(s)

Relevant Laboratory Data:

Test Date	Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail Y/N

Concomitant Products:

#	Product Name	Dose/Frequency	Route	Dosage Text	Indication(s)	Start Date	End Date	Interval 1st Dose to Event

Reporter Source:

Study Report:	Study Name:	Study Type:	Sponsor Study:	Protocol	IND #:
No					

Literature Text:

Country of Event: USA **Sender MFR:** UNIMED

***Age in Years displays a mid-value where the Age Unit in the report is in DECADE**

FDA - Adverse Event Reporting System (FAERS)

Batch Printing Report for Cases

Reporter Name:	(b) (6)	**Reporter Type:**	Health Professional,
Reporter Org.:		**Reporter Email:**	
Reporter Street:		**Reporter Phone:**	
Reporter City:		**Reporter State:**	(b) (6)
Reporter Zip:		**Reporter Country:**	UNITED STATES
Health Prof.:	YES	**Sent To:**	
Occupation:	PHYSICIAN	**Identity Disclosed:**	

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FDA - Adverse Event Reporting System (FAERS)

Batch Printing Report for Cases

Case Information:

Case Id: 7084353 **Version:** 2 **Case Type:** 15-DAY **eSub:** Yes **HP:** N **Country:** USA **Outcome(s):** DE

FDA Rcvd. Date: 01-Oct-2009 **Init FDA Rcvd. Date:** 18-Aug-2009 **Mfr Rcvd. Date:** 21-Sep-2009 **Application Type:** ANDA **Application #:** 085635

Mfr. Control #: US-PFIZER INC-2009252454

Patient Information:

Patient ID: UNKNOWN **Age:** **Age in Years:** **Sex:** Male **Weight:** **DoB:**

Suspect Products:

#	Product Name	Dose/Frequency	Route	Dosage Text	Indication(s)	Start Date	End Date	Interval 1st Dose to Event	ReC	DeC
1	DEPO-TESTOSTERONE	/							Unk	Unk

#	Product Name	Lot#	Exp Date	NDC #	Labeler	OTC
1	DEPO-TESTOSTERONE				PFIZER	

Event Information:

MedDRA © PreferredTerm	Start Date	End Date	Outcomes	Highlighted Terms	ReC
Completed Suicide			FATAL		Unk

Event/Problem Narrative:

This is a spontaneous report from a contactable lawyer. This lawyer, representing insurance in coverage dispute, reported that a male consumer while was on testosterone cipionate (DEPO-TESTOSTERONE) burned down house and committed suicide. His wife made claim to insurance for coverage of damage cause by husband, but the insurance company denied claim because of intentional act exclusion. Wife stated that his husband did not act intentionally because he was on testosterone injections. No other information was provided. Follow-up status: case closed (21Sep2009)

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?	Comment

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FDA - Adverse Event Reporting System (FAERS)

Batch Printing Report for Cases

Medical History Product(s)	Start Date	End Date	Indication(s)	MedDRA Preferred Term(s)

Relevant Laboratory Data:

Test Date	Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail Y/N

Concomitant Products:

#	Product Name	Dose/Frequency	Route	Dosage Text	Indication(s)	Start Date	End Date	Interval 1st Dose to Event

Reporter Source:

Study Report:	Study Name:	Study Type:	Sponsor Study:	Protocol	IND #:
No					

Literature Text:

Country of Event: USA

Sender MFR: PFIZER

Reporter Name: (b) (6)

Reporter Org.:

Reporter Street:

Reporter City: (b) (6)

Reporter Zip:

Health Prof.: NO

Occupation:

Reporter Type:

Reporter Email:

Reporter Phone:

Reporter State: (b) (6)

Reporter Country: UNITED STATES

Sent To:

Identity Disclosed:

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FDA - Adverse Event Reporting System (FAERS)

Batch Printing Report for Cases

Case Information:

Case Id: 7096924 **Version:** 1 **Case Type:** 15-DAY **eSub:** Yes **HP:** Y **Country:** USA **Outcome(s):** OT

FDA Rcvd. Date: 26-Aug-2009 **Init FDA Rcvd. Date:** 26-Aug-2009 **Mfr Rcvd. Date:** 20-Aug-2009 **Application Type:** NDA **Application #:** 021015

Mfr. Control #: US-SOLVAY-00209004708

Patient Information:

Patient ID: UNKNOWN **Age:** (b) (6) MTH **Age in Years:** 53. (b) (6) Y **Sex:** Male **Weight:** 124.5 KG **DoB:**

Suspect Products:

#	Product Name	Dose/Frequency	Route	Dosage Text	Indication(s)	Start Date	End Date	Interval 1st Dose to Event	ReC	DeC
1	ANDROGEL	/	TDER	Daily dose: unknown	PRODUCT USED FOR UNKNOWN INDICATION				NA	Unk
2	ARICEPT	/	UNK	Daily dose: unknown	PRODUCT USED FOR UNKNOWN INDICATION				NA	Unk
3	PLAVIX	/	UNK	Daily dose: unknown	PRODUCT USED FOR UNKNOWN INDICATION				NA	Unk
4	SORAFENIB	400 MG/	PO	Daily dose: 800 milligram(s); Total dose: 32800 mg	RENAL CELL CARCINOMA	13-Apr-2009	24-May-2009	0 Year	NA	Yes
5	SUNITINIB	50 MG/	PO	Daily dose: 50 milligram(s); Total dose: 1400 mg	RENAL CELL CARCINOMA	13-Apr-2009	09-May-2009	0 Year	NA	Yes

#	Product Name	Lot#	Exp Date	NDC #	Labeler	OTC
1	ANDROGEL					
2	ARICEPT					
3	PLAVIX					
4	SORAFENIB					
5	SUNITINIB					

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FDA - Adverse Event Reporting System (FAERS)

Batch Printing Report for Cases

Event Information:

MedDRA © PreferredTerm	Start Date	End Date	Outcomes	Highlighted Terms	ReC
Psychotic Disorder	01-May-2009	22-May-2009	RECOVERED/ RESOLVED	Y	NA
Suicidal Ideation	01-May-2009	22-May-2009	RECOVERED/ RESOLVED	N	NA
Depression	15-May-2009	22-May-2009	RECOVERED/ RESOLVED	Y	NA

Event/Problem Narrative:

This report was provided by Pfizer. A health professinal report concerning a 53-year-old male patient who experience psychosis and depression while being treated with five suspect drugs: (b) (6), (b) (6), (b) (6), (b) (6) and (b) (6) The patient participated in a non-Pfizer sponsored interventional study source, IIR Clinical Trial, Protocol # (b) (6) patient ID (b) (6) The patient was enrolled in above study and started to receive (b) (6) (b) (6) mg (b) (6) and (b) (6) mg (b) (6) of weeks (b) (6) on (b) (6) for (b) (6) (b) (6) One cycle equaled to (b) (6) days and max contained (b) (6) cycles. The primary site of disease was the kidney, which was initially diagnosed in Feb2009. The last administered dates of (b) (6) and (b) (6) were (b) (6) and (b) (6) respectively. The total dose administered of the study drugs were (b) (6) mg of (b) (6) and (b) (6) mg of (b) (6) The baseline performance status at initiation of protocol-ECOG/Zubrod scale was 0. Prior therapy included surgery performed in (b) (6) The patient had a history of depression. Other medications included (b) (6) (b) (6) and (b) (6). On 04 MAY 2009, the patient was seen by doctor and he complained of unusual thoughts. He stated that he has nightmares while awake. On 22 May 2009, he was seen again by the physician assistant (PA). He reported that he had been extremely depressed the week prior. He reported he thought he had a suicidal ideation, however, he did not have any plan and had no intention of actually harming himself. He did have a history of depression, but did not take any medications to treat this. He was offered antidepressant treatment and he refused. He did reassure the PA that he did not have any desire to harm himself or others. He was encouraged to talk with someone he trusts, if he starts to feel those symptoms return. He stated his understanding. The reported serious adverse events were psychosis (hallucinations/delusions) grade 2 and mood alteration: depression, grade 4. The start date of primary adverse event was 15 MAY 2009. The event psychosis, exact date was unknown. The patient reported this on 04 MAY 2009, but it was not reported when it started. For event mood alteration: depression, exact onset date was unknown. The patient was seen on 22 MAY 2009 and reported that the event began the week prior. Action taken with study drugs was not provided. The patient was recovered without sequelae from the events on 22 MAY 2009. Outcome: Recovered completely. The reporter considered that there was a reasonable possibility that both events were possibly related to the study drugs (b) (6) and (b) (6) Depression was also possibly related to the drugs (b) (6) (b) (6) and (b) (6) and (b) (6) Psychosis was unrelated to (b) (6) and (b) (6) and unlikely related to (b) (6) and (b) (6) Eisai's Company evaluation: There was no investigator opinion since this report of (b) (6) was considered to be a solicited report. Sponsor's Opinion: In the absence of important medical information such as (b) (6) therapy dates, action taken for (b) (6) dechallenge/rechallenge information, we classify the events as 'Not Assessable" at this time. Additional information will be requested. Case Comment: A reasonable possibility that psychosis (hallucinations/delusions) and mood alteration: depression was related to the blinded study drug, possibly including (b) (6) cannot be excluded. Concomitant administration of donepezil may have contributed to

mood alteration: depression.

Relevant Medical History:

Unknown date: Depression; (b) (6) : (b) (6)

Disease/Surgical Procedure	Start Date	End Date	Continuing?	Comment
DEPRESSION			UNKNOWN	
RENAL CELL CARCINOMA			UNKNOWN	

Medical History Product(s)	Start Date	End Date	Indication(s)	MedDRA Preferred Term(s)

Relevant Laboratory Data:

Test Date	Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail Y/N

Concomitant Products:

#	Product Name	Dose/Frequency	Route	Dosage Text	Indication(s)	Start Date	End Date	Interval 1st Dose to Event

Reporter Source:

Study Report:	Study Name:	Study Type:	Sponsor Study:	Protocol	IND #:
No					

Literature Text:

Country of Event: USA **Sender MFR:** UNIMED

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FDA - Adverse Event Reporting System (FAERS)

Batch Printing Report for Cases

Reporter Name:	PRIVACY	**Reporter Type:**	Health Professional,
Reporter Org.:		**Reporter Email:**	
Reporter Street:		**Reporter Phone:**	
Reporter City:		**Reporter State:**	
Reporter Zip:		**Reporter Country:**	UNITED STATES
Health Prof.:	YES	**Sent To:**	
Occupation:		**Identity Disclosed:**	

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FDA - Adverse Event Reporting System (FAERS)

Batch Printing Report for Cases

Case Information:

Case Id: 8018820 **Version:** 1 **Case Type:** 15-DAY **eSub:** Yes **HP:** Y **Country:** POL **Outcome(s):** HO

FDA Rcvd. Date: 01-Jul-2011 **Init FDA Rcvd. Date:** 01-Jul-2011 **Mfr Rcvd. Date:** 16-Jun-2011 **Application Type:** ANDA **Application #:** 086029

Mfr. Control #: PL-WATSON-2011-09550

Patient Information:

Patient ID: AB **Age:** 19 YR **Age in Years:** 19 YR **Sex:** Male **Weight:** **DoB:**

Suspect Products:

#	Product Name	Dose/Frequency	Route	Dosage Text	Indication(s)	Start Date	End Date	Interval 1st Dose to Event	ReC	DeC
1	TESTOSTERONE CYPIONATE	/	IM	UNK	KLINEFELTER'S SYNDROME				NA	Yes

#	Product Name	Lot#	Exp Date	NDC #	Labeler	OTC
1	TESTOSTERONE CYPIONATE	UNCONFIRMED			WATSON	

Event Information:

MedDRA © PreferredTerm	Start Date	End Date	Outcomes	Highlighted Terms	ReC
Aggression			NOT RECOVERED/ NOT RESOLVED		NA
Confabulation			NOT RECOVERED/ NOT RESOLVED		NA
Disinhibition			NOT RECOVERED/ NOT RESOLVED		NA
Dysphoria			RECOVERED/ RESOLVED		NA
Impulse-Control Disorder			RECOVERED/ RESOLVED		NA
Irritability			RECOVERED/ RESOLVED		NA
Mood Altered			RECOVERED/ RESOLVED		NA
Suicidal Ideation			RECOVERED/ RESOLVED		NA

Event/Problem Narrative:

Date of initial report: 16-JUN-2011 A literature report from the journal Polish Psychiatry, entitled "Iatrogenic influence of testosterone supplementation therapy in persons with Klinefelter Syndrome," describes a 19 year old male patient (Patient Initials: AB) who experienced suicidal thoughts, verbally and physically abusive, sexual disinhibition, dysphoria, irritability, mood changes, told false facts about his life, contacts, leisure activities and false accusations against his family, and lack of impulse control. Testosterone was discontinued and symptoms resolved, except for confabulation and single incidents of

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aggressive behavior accompanied by sexual disinhibition. See article for details. Related cases: 2011-09550 and 2011-09560

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?	Comment

Medical History Product(s)	Start Date	End Date	Indication(s)	MedDRA Preferred Term(s)

Relevant Laboratory Data:

Test Date	Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail Y/N

Concomitant Products:

#	Product Name	Dose/Frequency	Route	Dosage Text	Indication(s)	Start Date	End Date	Interval 1st Dose to Event

Reporter Source:

Study Report:	Study Name:	Study Type:	Sponsor Study:	Protocol	IND #:
No					

Literature Text: Radko M, Lucka I, Ziolkowski J. Iatrogenic influence of testosterone supplementation therapy in persons with Klinefelter Syndrome. Poish Psychiatry. 2011;45 (1):87-95

Country of Event: POL **Sender MFR:** WATSON

FDA - Adverse Event Reporting System (FAERS)

Batch Printing Report for Cases

Reporter Name:	Magdalena Radko	**Reporter Type:**	Health Professional,
Reporter Org.:		**Reporter Email:**	
Reporter Street:	Prof. T. Bilikiewicz Memorial Regional Psychiatric Hospital in Gdansk	**Reporter Phone:**	
Reporter City:		**Reporter State:**	
Reporter Zip:		**Reporter Country:**	POLAND
Health Prof.:	YES	**Sent To:**	
Occupation:		**Identity Disclosed:**	

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FDA - Adverse Event Reporting System (FAERS)

Batch Printing Report for Cases

Case Information:

Case Id: 8018822 **Version:** 1 **Case Type:** 15-DAY **eSub:** Yes **HP:** Y **Country:** POL **Outcome(s):** HO

FDA Rcvd. Date: 01-Jul-2011 **Init FDA Rcvd. Date:** 01-Jul-2011 **Mfr Rcvd. Date:** 16-Jun-2011 **Application Type:** ANDA **Application #:** 086029

Mfr. Control #: PL-WATSON-2011-09560

Patient Information:

Patient ID: ER **Age:** 17 YR **Age in Years:** 17 YR **Sex:** Male **Weight:** **DoB:**

Suspect Products:

#	Product Name	Dose/Frequency	Route	Dosage Text	Indication(s)	Start Date	End Date	Interval 1st Dose to Event	ReC	DeC
1	TESTOSTERONE CYPIONATE	/	IM	every 3-4 weeks	KLINEFELTER'S SYNDROME				NA	Yes

#	Product Name	Lot#	Exp Date	NDC #	Labeler	OTC
1	TESTOSTERONE CYPIONATE	UNCONFIRMED			WATSON	

Event Information:

MedDRA © PreferredTerm	Start Date	End Date	Outcomes	Highlighted Terms	ReC
Aggression			RECOVERED/ RESOLVED		NA
Agitation			RECOVERED/ RESOLVED		NA
Anger			RECOVERED/ RESOLVED		NA
Dysphoria			RECOVERED/ RESOLVED		NA
Headache			RECOVERED/ RESOLVED		NA
Impulsive Behaviour			RECOVERED/ RESOLVED		NA
Irritability			RECOVERED/ RESOLVED		NA
Sleep Disorder			UNKNOWN		NA
Suicidal Ideation			RECOVERED/ RESOLVED		NA
Tension			RECOVERED/ RESOLVED		NA
Vomiting			RECOVERED/ RESOLVED		NA

***Age in Years displays a mid-value where the Age Unit in the report is in DECADE**

Event/Problem Narrative:

Date of initial report: 16-JUN-2011 A literature report from the journal Polish Psychiatry, entitled "Iatrogenic influence of testosterone supplementation therapy in persons with Klinefelter Syndrome," describes a 17 year old male patient (Patient Initials: ER) who experienced suicidal thoughts, verbally and physically abusive, dysphoria, irritability, agitated, tense, impulsive, disturbed sleep, headache, vomiting, and enraged while receiving testosterone for Klinefelter's syndrome. Testosterone injections were discontinued and the patient was discharged in a balanced mental condition. See article submitted with case 2011-09550 for details Related cases: 2011-09550 and 2011-09560

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?	Comment

Medical History Product(s)	Start Date	End Date	Indication(s)	MedDRA Preferred Term(s)

Relevant Laboratory Data:

Test Date	Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail Y/N

Concomitant Products:

#	Product Name	Dose/Frequency	Route	Dosage Text	Indication(s)	Start Date	End Date	Interval 1st Dose to Event

Reporter Source:

Study Report:	Study Name:	Study Type:	Sponsor Study:	Protocol	IND #:
No					

Literature Text: Radko M, Lucka I, Ziolkowski J. Iatrogenic influence of testosterone supplementation therapy in persons with Klinefelter Syndrome. Polish Psychiatry. 2011;45 (1):87-95

Country of Event: POL **Sender MFR:** WATSON

***Age in Years displays a mid-value where the Age Unit in the report is in DECADE**

FDA - Adverse Event Reporting System (FAERS)

Batch Printing Report for Cases

Reporter Name:	Magdalena Radko	**Reporter Type:**	Health Professional,
Reporter Org.:		**Reporter Email:**	
Reporter Street:	Prof. T. Bilikiewicz Memorial Regional Psychiatric Hospital in Gdansk	**Reporter Phone:**	
Reporter City:		**Reporter State:**	
Reporter Zip:		**Reporter Country:**	POLAND
Health Prof.:	YES	**Sent To:**	
Occupation:		**Identity Disclosed:**	

***Age in Years displays a mid-value where the Age Unit in the report is in DECADE**

FDA - Adverse Event Reporting System (FAERS)

Batch Printing Report for Cases

Case Information:

Case Id: 8068948 **Version:** 2 **Case Type:** 15-DAY **eSub:** Yes **HP:** N **Country:** USA **Outcome(s):** OT

FDA Rcvd. Date: 07-Sep-2011 **Init FDA Rcvd. Date:** 04-Aug-2011 **Mfr Rcvd. Date:** 29-Aug-2011 **Application Type:** NDA **Application #:** 022504

Mfr. Control #: US-ELI_LILLY_AND_COMPANY-US201107006856

Patient Information:

Patient ID: **Age:** 59 YR **Age in Years:** 59 YR **Sex:** Male **Weight:** 81.63 KG **DoB:**

Suspect Products:

#	Product Name	Dose/Frequency	Route	Dosage Text	Indication(s)	Start Date	End Date	Interval 1st Dose to Event	ReC	DeC
1	AXIRON	60 MG/	TDER	UNK, one pump per axilla qd	HYPOGONADISM MALE	23-Jun-2011			Unk	Yes

#	Product Name	Lot#	Exp Date	NDC #	Labeler	OTC
1	AXIRON				ELI LILLY AND CO	

Event Information:

MedDRA © PreferredTerm	Start Date	End Date	Outcomes	Highlighted Terms	ReC
Aggression			UNKNOWN	N	Unk
Anger			UNKNOWN	N	Unk
Anxiety			UNKNOWN	N	Unk
Delusion			UNKNOWN	N	Unk
Depression			UNKNOWN	N	Unk
Mood Swings			UNKNOWN	N	Unk
Paranoia			UNKNOWN	N	Unk
Suicide Attempt			RECOVERED/ RESOLVED	N	Unk

Event/Problem Narrative:

This spontaneous case, reported by a physician assistant via a sales representative, with additional information from physician, concerns a 59 year old male patient of unknown origin. Medical history included an allergy to codeine and penicillin's, history of aggressive behaviour, and previous suicide attempts. Patient had a family history of osteoporosis, coronary artery disease, diabetes mellitus, thalassemia, parkinsons disease, Hypercholesterolemia and hypertension. It was also reported that the patient was sexually abused by a family friend from ages of 6 to 7. Concomitant medication included

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clonazepam for the treatment of anxiety and depression, alfuzosin hydrochloride, bupropion, atorvastatin calcium, clopidogrel bisulfate, ropinirole hydrochloride, nicotinic acid, atenolol, ranitidine hydrochloride, calcium carbonate with vitamin D, fish oil and acetylsalicylic acid. The patient received testosterone topical solution 2% (Axiron) 60mg, one pump per axilla daily for the treatment of hypogonadism testicular, remature ejaculation and inhibited sexual desire beginning on 23Jun2011. Within three days of initiating testosterone therapy, the patient became very angry and borderline violent, to the point that his wife had to leave the house. After three weeks patient discontinued testosterone therapy. Patient noted an increase in drive and desire and started increase in ability to obtain erections but not fully. This became frustrating as he cannot have sexual intercourse and became aggressive. He was very anxious and then depressed. After discontinuing testosterone, the patient experienced suicidal thoughts. On an unknown date from commencing treatment patient took 13 pills of clonazepam one night when he became angry with his wife for spending time with another man, considered serious for medically significant reasons. Patient had to have his stomach pumped. Patient was very anxious and jittery and developed anxiety, depression, mood swings, paranoid thoughts and delusions. The patient's baseline testosterone levels were 100, and several days after discontinuing testosterone therapy the patient's testosterone levels were back at 100. The patient's testosterone levels during treatment with testosterone were not provided. Patients examination showed the presents of fatigue and lethargy, abdominal pain (suprapubic), impotence and nocturia (2x). back pain, radiculopathy symptoms, decreased range of motion and joint pain, change in sleeping pattern, disorientation, fearful, frequent crying, nervousness, panic attack and trouble sleeping. It was unknown if the patient received any corrective treatment. Event outcome of suicide attempt by intentional overdose on clonazepam was recovered and very angry, borderline violent/ increase in aggression, anxiety, depression, mood swings, paranoid thoughts and delusions was unknown. The reporting physician assistant stated that the suicide attempt by intentional overdose on clonazepam, patient's anger, borderline violence and anxiety were not related to testosterone therapy, however sufficient reason/explicit statement was not provided hence the as determined relatedness was changed to yes. The reporting physician did not offer an opinion of relatedness of depression, mood swings, paranoid thoughts and delusions to testosterone treatment. Update 05Sep2011: Additional information received on 29Aug2011 from physician. Updated patient demographics, medical/family history and concomitant medication. Updated suspect drug information, after three weeks patient discontinued therapy. Updated serious event of suicidal ideation to suicide attempt by intentional overdose of clonazepam, separated event of anger/ violent/ aggression to event of anger and event of violent/ aggression, added non serious events of anxiety, depression, paranoid thoughts, delusions, updated listedness and causality, added increase in drive and desire, this became frustrating and became aggressive, patient had to have his stomach pumped, added patients examination, event outcomes, corrective treatment. Fields and narrative updated.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?	Comment
AGGRESSION			UNKNOWN	

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HYPERSENSITIVITY	UNKNOWN	codeine and penicillins

Medical History Product(s)	Start Date	End Date	Indication(s)	MedDRA Preferred Term(s)

Relevant Laboratory Data:

Test Date	Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail Y/N
	Testosterone					Y

Concomitant Products:

#	Product Name	Dose/Frequency	Route	Dosage Text	Indication(s)	Start Date	End Date	Interval 1st Dose to Event
1	KLONOPIN	1 MG/	PO	0.5 mg, bid	DEPRESSION			
2	LIPITOR	40 MG/	PO	40 mg, every other day				
3	LIPITOR	20 MG/	PO	20 mg, every other day				
4	CALTRATE WITH VITAMIN D	/	PO	UNK				
5	UROXATRAL	10 MG/	UNK	10 mg, qd		23-Jun-2011		
6	ZANTAC	150 MG/	PO	150 mg, qd				
7	FISH OIL	1000 MG/	PO	1000 mg, qd				
8	REQUIP	0 MG/	PO	0.25 mg, at bed time				
9	NIASPAN	1000 MG/	PO	1000 mg, qd				
10	ATENOLOL	13 MG/	PO	12.5 mg, qd				
11	ASPIRIN	81 MG/	PO	81 mg, qd				
12	PLAVIX	75 MG/	PO	75 mg, qd				
13	WELLBUTRIN SR	200 MG/	PO	200 mg, qd				

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FDA - Adverse Event Reporting System (FAERS)

Batch Printing Report for Cases

Reporter Source:

Study Report:	Study Name:	Study Type:	Sponsor Study:	Protocol	IND #:
No					

Literature Text:

Country of Event: USA **Sender MFR:** ELI LILLY AND CO

Reporter Name:	(b) (6)	**Reporter Type:**	Health Professional,
Reporter Org.:		**Reporter Email:**	
Reporter Street:		**Reporter Phone:**	
Reporter City:		**Reporter State:**	(b) (6)
Reporter Zip:		**Reporter Country:**	UNITED STATES
Health Prof.:	YES	**Sent To:**	
Occupation:	PHYSICIAN	**Identity Disclosed:**	

Reporter Name:	(b) (6)	**Reporter Type:**	
Reporter Org.:		**Reporter Email:**	
Reporter Street:		**Reporter Phone:**	
Reporter City:		**Reporter State:**	
Reporter Zip:		**Reporter Country:**	UNITED STATES
Health Prof.:	NO	**Sent To:**	
Occupation:	CONSUMER OR OTHER NON HEALTH PROFESSIONAL	**Identity Disclosed:**	

***Age in Years displays a mid-value where the Age Unit in the report is in DECADE**

FDA - Adverse Event Reporting System (FAERS)

Batch Printing Report for Cases

Case Information:

Case Id: 8346620 **Version:** 1 **Case Type:** 15-DAY **eSub:** Yes **HP:** Y **Country:** FRA **Outcome(s):** OT

FDA Rcvd. Date: 20-Jan-2012 **Init FDA Rcvd. Date:** 20-Jan-2012 **Mfr Rcvd. Date:** 13-Jan-2012 **Application Type:** ANDA **Application #:** 075049

Mfr. Control #: PHHY2012FR004078

Patient Information:

Patient ID: -- **Age:** 27 YR **Age in Years:** 27 YR **Sex:** Male **Weight:** **DoB:**

Suspect Products:

#	Product Name	Dose/Frequency	Route	Dosage Text	Indication(s)	Start Date	End Date	Interval 1st Dose to Event	ReC	DeC
1	FLUOXETINE	/							Unk	Unk
2	METHYLTESTOSTERONE	/							NA	Unk

#	Product Name	Lot#	Exp Date	NDC #	Labeler	OTC
1	FLUOXETINE				NOVARTIS	
2	METHYLTESTOSTERONE					

Event Information:

MedDRA © PreferredTerm	Start Date	End Date	Outcomes	Highlighted Terms	ReC
Aggression			UNKNOWN		Unk
Suicide Attempt			UNKNOWN		Unk

Event/Problem Narrative:

Case number PHHY2012FR004078 is an initial literature report received on 13 Jan 2012. The author discussed about the prescribed drugs and violence: a case/ noncase study in the French PharmacoVigilance Database. This case referred to a 27-year-old male patient (Tab 1, Pat 53). The patient's medical history included depression without psychotic antecedent. Concomitant medications were unknown. The patient started treatment with fluoxetine and methyltestosterone (manufacturer, route and dose were unknown for both drugs) for an unknown indication from an unreported date. It was reported that on an unreported date, the patient developed aggressiveness (killed his wife) and attempted suicide. Treatment received in response to the events was unknown. The outcome of the event was not reported. The author assessed causality as possibly related to suspect drugs.

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Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?	Comment
DEPRESSION			UNKNOWN	

Medical History Product(s)	Start Date	End Date	Indication(s)	MedDRA Preferred Term(s)

Relevant Laboratory Data:

Test Date	Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail Y/N

Concomitant Products:

#	Product Name	Dose/Frequency	Route	Dosage Text	Indication(s)	Start Date	End Date	Interval 1st Dose to Event

Reporter Source:

Study Report:	Study Name:	Study Type:	Sponsor Study:	Protocol	IND #:
No					

Literature Text:

Country of Event: FRA **Sender MFR:** SANDOZ

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Reporter Name:	PRIVACY	**Reporter Type:**	Health Professional,
Reporter Org.:		**Reporter Email:**	
Reporter Street:		**Reporter Phone:**	
Reporter City:		**Reporter State:**	
Reporter Zip:		**Reporter Country:**	FRANCE
Health Prof.:	YES	**Sent To:**	
Occupation:		**Identity Disclosed:**	

Reporter Name:	Nadege Rouve	**Reporter Type:**	Health Professional,
Reporter Org.:	CENTRE HOSPITALIER UNIVERSITAIRE DE TOULOUSE	**Reporter Email:**	
Reporter Street:	Centre Midi-Pyreneesde PharmacoVigilance, de Pharmacoepidemiologieet d'Information sur les Medicam	**Reporter Phone:**	
Reporter City:		**Reporter State:**	TOULOUSE
Reporter Zip:		**Reporter Country:**	FRANCE
Health Prof.:	YES	**Sent To:**	
Occupation:		**Identity Disclosed:**	

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FDA - Adverse Event Reporting System (FAERS)

Batch Printing Report for Cases

Case Information:

Case Id: 8353615 **Version:** 2 **Case Type:** 15-DAY **eSub:** Yes **HP:** Y **Country:** DNK **Outcome(s):** OT

FDA Rcvd. Date: 23-Jul-2012 **Init FDA Rcvd. Date:** 25-Jan-2012 **Mfr Rcvd. Date:** 13-Jun-2012 **Application Type:** NDA **Application #:** 021015

Mfr. Control #: DK-ABBOTT-12P-044-0896679-00

Patient Information:

Patient ID: (b) (6) **Age:** 14. (b) (6) YR **Age in Years:** 14. (b) (6) YR **Sex:** Male **Weight:** 138 KG **DoB:** (b) (6)

Suspect Products:

#	Product Name	Dose/Frequency	Route	Dosage Text	Indication(s)	Start Date	End Date	Interval 1st Dose to Event	ReC	DeC
1	TESTOSTERONE	/			ANORCHISM			240 Day	Unk	NA
2	TESTOSTERONE	/	TDER	Gel	HYPOGONADISM	05-Jan-2008		240 Day	Unk	NA

#	Product Name	Lot#	Exp Date	NDC #	Labeler	OTC
1	TESTOSTERONE					
2	TESTOSTERONE					

Event Information:

MedDRA © PreferredTerm	Start Date	End Date	Outcomes	Highlighted Terms	ReC
Penile Size Reduced	01-Sep-2008		NOT RECOVERED/ NOT RESOLVED	N	Unk
Suicidal Ideation			UNKNOWN	N	Unk

Event/Problem Narrative:

Case received on 19 Jul 2012 from Besins, reference number 2012-0081-SPO. Case report received from authorities: This case was reported by a consumer/other non health professional via the Danish Authorities (DK-DKMA-ADR-21358300) and concerns a 14 year-old male patient who reported penile size reduced and suicidal ideation whilst using with TESTOGEL (TESTOSTERONE). The medical history of the patient was only provided in local language. The patient's concomitant medication was not reported at the time of the event. On 05 June 2008, the patient was treated with TESTOGEL (TESTOSTERONE) for unspecified testicular dysfunction. On 01 September 2008, the patient experienced penile size reduced. On a date as yet unspecified, he experienced suicidal ideation. The continuation of the treatment with TESTOGEL (TESTOSTERONE) was unknown at the time of the report. This case is considered as serious (other medically significant). At the time of reporting, the outcome of the events was: not recovered for penile size reduced, unknown for suicidal ideation.

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The causal relationship as assessed by the reporter between TESTOGEL (TESTOSTERONE) and the events was not reported. The company considered the causal relationship between ANDROGEL 1% and the event as unlikely. Additional information received on 13 June 2012 from the Danish Authorities. The patient's relevant medical history included obesity, hypogonadism and anorchism. The patient was on no concomitant drugs at the time of the events. Evaluation of penile size in obese subjects are subject to large variability. In this case a measurement of approximately 3 cm in October 2004 by one doctor is not considered significantly different to a measure of approximately 4 cm by another doctor in February 2011. Penis was measured by a ruler which is difficult because of obesity (hidden penis). The Danish Authorities were informed retrospectively of suicidal thoughts by the father. The patient had an MR scan. The patient hadblood samples repeatedly as part of his hypogonadism. Anorchism itself may lead to micropenis and depression in left untreated. Testosterone normalizes these symptoms, and micropenis is therefore not a side effect to Testogel. Pharmacovigilance Comments Penile size reduced: this condition is usually the result of a defect in the hypothalamic-pituitary-gonadal axis, although iatrogenic causes are identified infrequently.

Relevant Medical History:

Concurrent Disease: Obesity (??/??/??) (Continuing: Yes) Hypogonadism (??/??/??) (Continuing: Yes) Anorchism (??/??/??) (Continuing: Yes)

Disease/Surgical Procedure	Start Date	End Date	Continuing?	Comment
ANORCHISM				
HYPOGONADISM				
OBESITY				

Medical History Product(s)	Start Date	End Date	Indication(s)	MedDRA Preferred Term(s)

Relevant Laboratory Data:

Test Date	Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail Y/N
	Body height	184	CM			
	Weight	138	KG			

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Concomitant Products:

#	Product Name	Dose/Frequency	Route	Dosage Text	Indication(s)	Start Date	End Date	Interval 1st Dose to Event

Reporter Source:

Study Report:	Study Name:	Study Type:	Sponsor Study:	Protocol	IND #:
No					

Literature Text:

Country of Event: DNK **Sender MFR:** ABBOTT

Reporter Name: Unknown
Reporter Org.:
Reporter Street:
Reporter City:
Reporter Zip:
Health Prof.: YES
Occupation:

Reporter Type: Health Professional,
Reporter Email:
Reporter Phone:
Reporter State:
Reporter Country: DENMARK
Sent To:
Identity Disclosed:

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FDA - Adverse Event Reporting System (FAERS)

Batch Printing Report for Cases

Case Information:

Case Id: 8399641 **Version:** 1 **Case Type:** 15-DAY **eSub:** Yes **HP:** Y **Country:** NOR **Outcome(s):** DE

FDA Rcvd. Date: 10-Feb-2012 **Init FDA Rcvd. Date:** 10-Feb-2012 **Mfr Rcvd. Date:** 31-Jan-2012 **Application Type:** NDA **Application #:** 021015

Mfr. Control #: NO-ABBOTT-12P-122-0902925-00

Patient Information:

Patient ID: UNK **Age:** 43 YR **Age in Years:** 43 YR **Sex:** Male **Weight:** **DoB:**

Suspect Products:

#	Product Name	Dose/Frequency	Route	Dosage Text	Indication(s)	Start Date	End Date	Interval 1st Dose to Event	ReC	DeC
1	TESTOSTERONE	/	TDER		PRODUCT USED FOR UNKNOWN INDICATION				NA	NA

#	Product Name	Lot#	Exp Date	NDC #	Labeler	OTC
1	TESTOSTERONE					

Event Information:

MedDRA © PreferredTerm	Start Date	End Date	Outcomes	Highlighted Terms	ReC
Completed Suicide			FATAL	N	NA

Event/Problem Narrative:

Case received from Besins; reference number: 2012-0266-SPO Case received from partner: This case was reported by Norway regulatory authority {NO-NOMAADVRE-RELISN-2011-12658} via Besins Healthcare partner and concerned a 43 - year-old male who committed suicide whilst using testosterone gel. No information on patient's medical and drug history and concurrent medications was given. On an unspecified date, the patient applied Testosterone Gel (Testosterone). It was unknown whether Testosterone Gel was used previously. On an unspecified date the patient accomplished SUICIDE which resulted in death. The SUICIDE was assessed as possibly related to treatment with Testosterone Gel. No further informations were provided. The company considered the causal relationship between testosterone gel and the suicide as not assessable (insufficient information). Besins Company Remarks: Case to be documented. At that point, asking literature, no relation has been showed between testosterone and suicide attempts Perez-Rodriguez MM, Lopez-Castroman J, Martinez-Vigo M. Diaz-Sastre C. Ceverino A, Nunez-Beltran A, Saiz-Ruiz J, de Leon J, Baca-Garcia E. Lack of association between testosterone and suicide attempts. Neuropsychobiology. 2012;63(2) ,125-30. Epub 2010 Dec 30.

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Relevant Medical History:

Unknown

Disease/Surgical Procedure	Start Date	End Date	Continuing?	Comment

Medical History Product(s)	Start Date	End Date	Indication(s)	MedDRA Preferred Term(s)

Relevant Laboratory Data:

Test Date	Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail Y/N

Concomitant Products:

#	Product Name	Dose/Frequency	Route	Dosage Text	Indication(s)	Start Date	End Date	Interval 1st Dose to Event

Reporter Source:

Study Report:	Study Name:	Study Type:	Sponsor Study:	Protocol	IND #:
No					

Literature Text:

Country of Event: NOR **Sender MFR:** ABBOTT

***Age in Years displays a mid-value where the Age Unit in the report is in DECADE**

FDA - Adverse Event Reporting System (FAERS)

Batch Printing Report for Cases

Reporter Name:	Unknown	**Reporter Type:**	Health Professional,
Reporter Org.:		**Reporter Email:**	
Reporter Street:		**Reporter Phone:**	
Reporter City:		**Reporter State:**	
Reporter Zip:		**Reporter Country:**	NORWAY
Health Prof.:	YES	**Sent To:**	
Occupation:		**Identity Disclosed:**	

***Age in Years displays a mid-value where the Age Unit in the report is in DECADE**

FDA - Adverse Event Reporting System (FAERS)

Batch Printing Report for Cases

Case Information:

Case Id: 8406354 **Version:** 1 **Case Type:** 15-DAY **eSub:** Yes **HP:** N **Country:** USA **Outcome(s):** OT

FDA Rcvd. Date: 15-Feb-2012 **Init FDA Rcvd. Date:** 15-Feb-2012 **Mfr Rcvd. Date:** 03-Feb-2012 **Application Type:** NDA **Application #:** 021427

Mfr. Control #: US-ELI_LILLY_AND_COMPANY-US201201004602

Patient Information:

Patient ID: (b) (6) **Age:** 77 YR **Age in Years:** 77 YR **Sex:** Male **Weight:** **DoB:**

Suspect Products:

#	Product Name	Dose/Frequency	Route	Dosage Text	Indication(s)	Start Date	End Date	Interval 1st Dose to Event	ReC	DeC
1	AXIRON	30 MG/	TOP	30 mg, unknown					NA	Unk
2	CYMBALTA	20 MG/		20 mg, every fourth day					NA	NA
3	CYMBALTA	20 MG/		20 mg, every fifith day					NA	NA
4	CYMBALTA	20 MG/		20 mg, every third day					NA	NA
5	CYMBALTA	20 MG/		20 mg, weekly (1/W)					NA	NA
6	CYMBALTA	30 MG/		30 mg, unknown	DEPRESSION	Dec-2011			NA	NA
7	CYMBALTA	20 MG/		20 mg, qd		13-Jan-2012			NA	NA
8	CYMBALTA	20 MG/		20 mg, qod					NA	NA
9	CYMBALTA	20 MG/		20 mg, every sixth day					NA	NA

#	Product Name	Lot#	Exp Date	NDC #	Labeler	OTC
1	AXIRON	1413385				
2	CYMBALTA				ELI LILLY AND CO	
3	CYMBALTA				ELI LILLY AND CO	
4	CYMBALTA				ELI LILLY AND CO	
5	CYMBALTA				ELI LILLY AND CO	

***Age in Years displays a mid-value where the Age Unit in the report is in DECADE**

#	Product Name	Dose/Frequency	Route	Dosage Text	Indication(s)	Start Date	End Date	Interval 1st Dose to Event	ReC	DeC
#	Product Name	Lot#	Exp Date		NDC #	Labeler		OTC		
6	CYMBALTA					ELI LILLY AND CO				
7	CYMBALTA					ELI LILLY AND CO				
8	CYMBALTA					ELI LILLY AND CO				
9	CYMBALTA					ELI LILLY AND CO				

Event Information:

MedDRA © PreferredTerm	Start Date	End Date	Outcomes	Highlighted Terms	ReC
Blindness			UNKNOWN	N	NA
Crying			UNKNOWN	N	NA
Drug Ineffective			UNKNOWN	N	NA
Irritability			UNKNOWN	N	NA
Suicidal Ideation			UNKNOWN	N	NA
Vision Blurred			UNKNOWN	N	NA

Event/Problem Narrative:

This spontaneous case, reported by a consumer, who contacted the company to report adverse events, concerns a 77 years old male patient of unknown origin. The patients medical history included being deaf, legally blind, optic ischaemic neruopathy, a previous suicide attempt, weight loss and lack of drug effect with historical use of escitalopram oxalate and sertaline hydrochloride. The patient received duloxetine hydrochloride (Cymbalta) 30 mg, once daily for the treatment of anxiety and depression, beginning on an unspecified date described as being three weeks ago (approx late Dec2011). The patient also received testosterone solution (Axiron) 30 mg, applied topically to the underarm for an unspecified indication, at an unknown frequency and start date; however, the reporter stated the patient had been using the product for 18 days. On unknown date, while receiving the medications, the patient experienced blurred vision. In addition, the patient also conceded that his blindness was getting worse after taking duloxetine and that he had since lost his eyesight and therefore, did not want to live. Adverse event chronology was imprecise relative to product exposure. The events of blindness getting worse/lost eyesight and does not want to live were considered serious by the company for medical significance. The patient added that he was not going to harm himself. On an unknown date, duloxetine was tapered for an unknown reason, to a dosage of 20 mg, once daily, then once every other day, once every third day and so forth, until duloxetine was taken only once weekly. On unknown dates, the patient experienced crying every day, was depressed and cranky. The patient also inquired how long it would take for the testosterone solution to start to work (lack of drug effect). Diagnostic ophthalmic testing results were not provided. Corrective treatment for the events was not reported. At the time of the report, the event outcomes were unknown.

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It was not known if duloxetine or testosterone solution therapy were continued. Update 09-Feb-2012: Upon review on 09-Feb-2012, it was determined that Case US201202002513 is follow-up to this report; therefore, it will be deleted from the database. All information from Case US201202002513 has been captured in this case. Update 09Feb2012: Additional information was received on 03FEb2012 from the initial consumer reporter. Added additional historical medication. Added additional dose tabs to duloxetine to represent tapering scheme. Added Axiron as a suspect medication. Added the serious adverse events of does not want to live and blindness is getting worse/ has lost his eyesight. Added the non-serious events of crying every day, cranky and how long will the medicine start to work (lack of drug efficacy). Updated patient history, the events assessments tab, case narrative and regenerated the PSUR comment.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?	Comment
BLINDNESS	1995			In right eye in 1995 In left eye in 2010
DEAFNESS			UNKNOWN	He is blind and deaf..was blind and deaf before starting Axiron and it has not worsened.
SUICIDE ATTEMPT			UNKNOWN	
WEIGHT DECREASED			UNKNOWN	32 pounds

Medical History Product(s)		Start Date	End Date	Indication(s)	MedDRA Preferred Term(s)
ZOLOFT	/USA/			PRODUCT USED FOR UNKNOWN INDICATION	Drug ineffective
LEXAPRO				PRODUCT USED FOR UNKNOWN INDICATION	Drug ineffective

Relevant Laboratory Data:

Test Date	Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail Y/N

Concomitant Products:

#	Product Name	Dose/Frequency	Route	Dosage Text	Indication(s)	Start Date	End Date	Interval 1st Dose to Event

***Age in Years displays a mid-value where the Age Unit in the report is in DECADE**

FDA - Adverse Event Reporting System (FAERS)

Batch Printing Report for Cases

Reporter Source:

Study Report:	Study Name:	Study Type:	Sponsor Study:	Protocol	IND #:
No					

Literature Text:

Country of Event: USA **Sender MFR:** ELI LILLY AND CO

Reporter Name: (b) (6)
Reporter Org.:
Reporter Street:
Reporter City:
Reporter Zip:

Reporter Type:
Reporter Email:
Reporter Phone:
Reporter State: (b) (6)
Reporter Country: UNITED STATES

Health Prof.: NO
Occupation: CONSUMER OR OTHER NON HEALTH PROFESSIONAL

Sent To:
Identity Disclosed:

***Age in Years displays a mid-value where the Age Unit in the report is in DECADE**

FDA - Adverse Event Reporting System (FAERS)

Batch Printing Report for Cases

Case Information:

Case Id: 8525529 **Version:** 1 **Case Type:** DIRECT **eSub:** Yes **HP:** Y **Country:** USA **Outcome(s):** OT

FDA Rcvd. Date: 23-Apr-2012 **Init FDA Rcvd. Date:** 23-Apr-2012 **Mfr Rcvd. Date:** **Application Type:** **Application #:**

Mfr. Control #: US-FDA-8304310

Patient Information:

Patient ID: (b) (6) **Age:** 52 YR **Age in Years:** 52 YR **Sex:** Male **Weight:** 87.09 KG **DoB:** (b) (6)

Suspect Products:

#	Product Name	Dose/Frequency	Route	Dosage Text	Indication(s)	Start Date	End Date	Interval 1st Dose to Event	ReC	DeC
1	ANDROGEL	/QD	TOP	2 pumps	PRIMARY HYPOGONADISM	01-Oct-2011	11-Mar-2012		NA	NA

#	Product Name	Lot#	Exp Date	NDC #	Labeler	OTC
1	ANDROGEL	90056	20140430	0051-8462-33	ABBOTT	

Event Information:

MedDRA © PreferredTerm	Start Date	End Date	Outcomes	Highlighted Terms	ReC
Affective Disorder					NA
Depression					NA
Dizziness					NA
Hypertension					NA
Suicidal Ideation					NA
Visual Impairment					NA

Event/Problem Narrative:

Used Androgel 1.62% and had gradual increase in blood pressure to point of uncontrolled hypertension, then experienced mood disorder: depression, anxiety, suicidal thoughts, developed visual changes, dizziness, and light headedness. Other Concomitant Medical Product Description: ANDROGEL 10/1/11 TO 3/11/12 Triage Quality Control: (b) (6) |*********| 2012-04-23-08.37.23 |*********| USFDAMWVOLUNTARY_205496_17653_20120421.xml Route To: AERS : Electronic

***Age in Years displays a mid-value where the Age Unit in the report is in DECADE**

Relevant Medical History:

Was treated of hypogonadism. History of hypothyroidism and TSH was normal.

Disease/Surgical Procedure	Start Date	End Date	Continuing?	Comment

Medical History Product(s)	Start Date	End Date	Indication(s)	MedDRA Preferred Term(s)

Relevant Laboratory Data:

Test Date	Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail Y/N

Concomitant Products:

#	Product Name	Dose/Frequency	Route	Dosage Text	Indication(s)	Start Date	End Date	Interval 1st Dose to Event
1	ANDROGEL	/						

Reporter Source:

Study Report:	Study Name:	Study Type:	Sponsor Study:	Protocol	IND #:
No					

Literature Text:

Country of Event: USA **Sender MFR:**

***Age in Years displays a mid-value where the Age Unit in the report is in DECADE**

FDA - Adverse Event Reporting System (FAERS)

Batch Printing Report for Cases

Reporter Name:	(b) (6)	**Reporter Type:**	Health Professional,
Reporter Org.:		**Reporter Email:**	(b) (6)
Reporter Street:		**Reporter Phone:**	
Reporter City:		**Reporter State:**	
Reporter Zip:		**Reporter Country:**	UNITED STATES
Health Prof.:	YES	**Sent To:**	
Occupation:		**Identity Disclosed:**	Y

***Age in Years displays a mid-value where the Age Unit in the report is in DECADE**

FDA - Adverse Event Reporting System (FAERS)

Batch Printing Report for Cases

Case Information:

Case Id: 8663367 **Version:** 1 **Case Type:** 15-DAY **eSub:** Yes **HP:** N **Country:** USA **Outcome(s):** OT

FDA Rcvd. Date: 13-Jul-2012 **Init FDA Rcvd. Date:** 13-Jul-2012 **Mfr Rcvd. Date:** 03-Jul-2012 **Application Type:** NDA **Application #:** 022504

Mfr. Control #: US-ELI_LILLY_AND_COMPANY-US201207001059

Patient Information:

Patient ID: (b) (6) **Age:** 47 YR **Age in Years:** 47 YR **Sex:** Male **Weight:** **DoB:** (b) (6)

Suspect Products:

#	Product Name	Dose/Frequency	Route	Dosage Text	Indication(s)	Start Date	End Date	Interval 1st Dose to Event	ReC	DeC
1	AXIRON	60 MG/		60 mg, qd	BLOOD TESTOSTERONE DECREASED	May-2012			NA	NA

#	Product Name	Lot#	Exp Date	NDC #	Labeler	OTC
1	AXIRON	1450237			ELI LILLY AND CO	

Event Information:

MedDRA © PreferredTerm	Start Date	End Date	Outcomes	Highlighted Terms	ReC
Blood Testosterone Decreased	20-Jun-2012		RECOVERED/ RESOLVED	N	NA
Blood Testosterone Increased	28-Jun-2012		UNKNOWN	N	NA
Anger	03-Jul-2012		UNKNOWN	N	NA
Insomnia	03-Jul-2012		RECOVERED/ RESOLVED	N	NA
Asthenia			UNKNOWN	N	NA
Confusional State			UNKNOWN	N	NA
Depression			UNKNOWN	N	NA
Dizziness			UNKNOWN	N	NA
Dysarthria			UNKNOWN	N	NA
Emotional Disorder			UNKNOWN	N	NA
Fatigue			UNKNOWN	N	NA
Feeling Abnormal			UNKNOWN	N	NA
Libido Decreased			UNKNOWN	N	NA

***Age in Years displays a mid-value where the Age Unit in the report is in DECADE**

MedDRA © PreferredTerm	Start Date	End Date	Outcomes	Highlighted Terms	ReC
Migraine			UNKNOWN	N	NA
Somnolence			UNKNOWN	N	NA
Suicidal Ideation			UNKNOWN	N	NA
Vertigo			UNKNOWN	N	NA
Visual Acuity Reduced			UNKNOWN	N	NA

Event/Problem Narrative:

This case, reported by a consumer who contacted the company to ask a medical question, concerns a 46 year old male patient (ethnicity not provided). Medical history included a motor vehicle accident with a head injury in the 1980's, vertigo, depression, and the use of another manufacturer's testosterone (both oral and injectable). Concomitant medications were not provided. The patient testosterone solution (Axiron) 60 mg or two pumps under each armpit via disposable applicator for the treatment of low testosterone beginning in May2012 (reported as one and a half months ago). Since starting testosterone, time to onset not provided, he had experienced dizziness, feeling like "crap", being tired, a lack of energy, no libido, sleeping a lot, slurred speech, not making sense to family members, being very emotional, vertigo, and migraines. He reported the dizziness and vertigo were weird and with migraines. He was so tired that he would have to lie down by 2:00 PM and was very tired by 6:00-7:00 PM every night. He saw a neurologist for the vertigo and was told he had vertical proximately disorder. Also since using the testosterone, his depression had worsened and he was having bad feeling in his head and suicidal thoughts. The suicidal thoughts were considered serious for other reason medical by the company. He stated he had depression and all the other symptoms before taking testosterone (unclear if they had worsened), but never suicidal thought. He did not have the thoughts all of the time. The suicidal thoughts began gradually. He also had experienced a rapid change in his vision and had changed glasses five times (unclear if before or after starting testosterone solution). On 20Jun2012, he had his blood testosterone level taken (had not taken his testosterone that morning), and it was 58 (units not provided) (reference range 300-1050). He was supposed to return on 22Jun2012, to have his blood testosterone level drawn again but could not due to dizziness. He stated he was unable to drive more than ten miles due to the dizziness. On 28Jun2012, he again had his blood testosterone level drawn (had taken his testosterone that morning), and it was 1153 (units not provided). He was concerned because it was high, but his physician's nurse told him this was high normal. On 03Jul2012, at 3:00 AM, he awoke with anger. He was awake until 4:30 AM when he took some diphenhydramine hydrochloride and was able to return to sleep. He had scheduled an appointment or 09Jul2012 to discuss the suicidal thoughts with his physician. He recovered from the low testosterone and inability to sleep; the outcomes of the remaining events were not provided. The testosterone solution was continued.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?	Comment

***Age in Years displays a mid-value where the Age Unit in the report is in DECADE**

DEPRESSION	UNKNOWN	
HEAD INJURY	UNKNOWN	in the 1980's
ROAD TRAFFIC ACCIDENT	UNKNOWN	in the 1980's
VERTIGO	UNKNOWN	

Medical History Product(s)	Start Date	End Date	Indication(s)	MedDRA Preferred Term(s)
TESTOSTERONE	Jan-2011		BLOOD TESTOSTERONE DECREASED	Drug ineffective
ANDROGEL	Mar-2012		BLOOD TESTOSTERONE DECREASED	Drug ineffective

Relevant Laboratory Data:

Test Date	Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail Y/N
20-Jun-2012	Testosterone	58	unk	300	1050	N
28-Jun-2012	Testosterone	1153	unk	300	1050	N
	Testosterone	185	unk	300	1050	N
	Testosterone	177	unk	300	1050	N

Concomitant Products:

#	Product Name	Dose/Frequency	Route	Dosage Text	Indication(s)	Start Date	End Date	Interval 1st Dose to Event

Reporter Source:

Study Report:	Study Name:	Study Type:	Sponsor Study:	Protocol	IND #:
No					

Literature Text:

Country of Event: USA **Sender MFR:** ELI LILLY AND CO

***Age in Years displays a mid-value where the Age Unit in the report is in DECADE**

FDA - Adverse Event Reporting System (FAERS)

Batch Printing Report for Cases

Reporter Name:	(b) (6)	**Reporter Type:**	
Reporter Org.:		**Reporter Email:**	
Reporter Street:		**Reporter Phone:**	
Reporter City:		**Reporter State:**	(b) (6)
Reporter Zip:		**Reporter Country:**	UNITED STATES
Health Prof.:	NO	**Sent To:**	
Occupation:	CONSUMER OR OTHER NON HEALTH PROFESSIONAL	**Identity Disclosed:**	

***Age in Years displays a mid-value where the Age Unit in the report is in DECADE**

FDA - Adverse Event Reporting System (FAERS)

Batch Printing Report for Cases

Case Information:

Case Id: 8745412 **Version:** 1 **Case Type:** DIRECT **eSub:** Yes **HP:** N **Country:** USA **Outcome(s):** HO,LT,OT

FDA Rcvd. Date: 22-Sep-2011 **Init FDA Rcvd. Date:** 22-Sep-2011 **Mfr Rcvd. Date:** **Application Type:** **Application #:**

Mfr. Control #: US-FDA-7768216

Patient Information:

Patient ID: UNSPECIFIED **Age:** 45.(b) (6) YR **Age in Years:** 45 (b) (6) YR **Sex:** Male **Weight:** 104.32 KG **DoB:** (b) (6)

Suspect Products:

#	Product Name	Dose/Frequency	Route	Dosage Text	Indication(s)	Start Date	End Date	Interval 1st Dose to Event	ReC	DeC
1	ANDROGEL	/	TDER	6 PUMPS OF GEL ONCE A DAY	LOW TESTERONE, BLOOD TESTOSTERONE DECREASED	21-Aug-2011	10-Sep-2011		NA	NA

#	Product Name	Lot#	Exp Date	NDC #	Labeler	OTC
1	ANDROGEL	DONTKNOW				

Event Information:

MedDRA © PreferredTerm	Start Date	End Date	Outcomes	Highlighted Terms	ReC
Adverse Drug Reaction					NA
Agitation					NA
Anger					NA
Hormone Level Abnormal					NA
Intentional Self-Injury					NA
Loss Of Consciousness					NA
Mental Impairment					NA
Suicide Attempt					NA

***Age in Years displays a mid-value where the Age Unit in the report is in DECADE**

Event/Problem Narrative:

Around Aug 21, 2011, My husband was prescribed AndroGel at 6 pumps pe[(b)] day by his family doctor after his bloodwork showed his testerone level was low. He applied the gel as directed and after[(6)] weeks of use he became increasingly agitated, had volatile anger outbursts, and became suicidal on the evenings of [(b) (6)]. On [(b) (6)] he agreed to go to the hospital ER for treatment, he was given Ativan in the ER, and then transported by ambulance to [(b) (6)] Hospital in [(b) (6)] and was admitted to their behavioral health floor and was treated by Dr. [(b) (6)] a psychiatrist. My husband's mental health continued to decline that night to the point he was hitting himself and head-butting the wall so hard he lost consciousness for a short time. Dr. [(b) (6)] continued the Ativan and also prescribed klonipin. By Tuesday, my husband was improving. Wednesday afternoon he was released from the hospital with a referral to a local psychiatrist and anger management counseling. The last day my husband used the AndroGel was Sept. 10th, and Dr. [(b) (6)] advised that he felt that my husband had an adverse reaction to the AndroGel, that it had tipped the balance of levels of hormones in his brain, and resulted in my husband's very near death suicide attempts on [(b) (6)] [(b) (6)] : |*********| 2011-09-22-08.50.20 |*********| USFDAMWVOLUNTARY_192997_6904_20110922.xml Route To: AERS : Electronic

Relevant Medical History:

High blood press and cholesterol controlled by medication Type 2 diabetes, improving and controlled by oral medication Depression, prescr bed Paxil by his family doctor, which he has taken for at least 10 years Smokes 2 packs of cigarettes a day Moderate drinker - drinks beer 4-5 times a week, [(b) (6)] was inpatient for alcoholism rehab at [(b) (6)] Center in [(b) (6)] Caucasian Not previously treated by a psychiatrist

Disease/Surgical Procedure	Start Date	End Date	Continuing?	Comment

Medical History Product(s)	Start Date	End Date	Indication(s)	MedDRA Preferred Term(s)

Relevant Laboratory Data:

Test Date	Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail Y/N
01-Aug-2011	BLOODWORK					
[(b) (6)]	BLOODWORK					
	URINEALYSIS					
	CT SCAN OF HEAD					

Concomitant Products:

#	Product Name	Dose/Frequency	Route	Dosage Text	Indication(s)	Start Date	End Date	Interval 1st Dose to Event

*Age in Years displays a mid-value where the Age Unit in the report is in DECADE

FDA - Adverse Event Reporting System (FAERS)

Batch Printing Report for Cases

Reporter Source:

Study Report:	Study Name:	Study Type:	Sponsor Study:	Protocol	IND #:
No					

Literature Text:

Country of Event: USA

Sender MFR:

Reporter Name: (b) (6)
Reporter Org.:
Reporter Street:
Reporter City:
Reporter Zip:

Health Prof.: NO

Occupation:

Reporter Type:
Reporter Email: (b) (6)
Reporter Phone:
Reporter State:
Reporter Country: UNITED STATES

Sent To:

Identity Disclosed:

***Age in Years displays a mid-value where the Age Unit in the report is in DECADE**

FDA - Adverse Event Reporting System (FAERS)

Batch Printing Report for Cases

Case Information:

Case Id: 9128763 **Version:** 1 **Case Type:** PERIODIC **eSub:** Yes **HP:** **Country:** USA **Outcome(s):**

FDA Rcvd. Date: 28-Feb-2013 **Init FDA Rcvd. Date:** 28-Feb-2013 **Mfr Rcvd. Date:** 02-Feb-2013 **Application Type:** NDA **Application #:** 022309

Mfr. Control #: US-ABBOTT-13P-163-1046638-00

Patient Information:

Patient ID: (b) (6) **Age:** 51 (b) (6) YR **Age in Years:** 51 (b) (6) R **Sex:** Male **Weight:** KG **DoB:** (b) (6)

Suspect Products:

#	Product Name	Dose/Frequency	Route	Dosage Text	Indication(s)	Start Date	End Date	Interval 1st Dose to Event	ReC	DeC
1	ANDROGEL	/		2 pumps a day	Product used for unknown indication	Oct-2012	Nov-2012	0 Day	NA	Yes
2	ANDROGEL	/		Alternate 2 pumps every other day with 1 pump		Nov-2012	20-Dec-2012	0 Day	NA	Yes

#	Product Name	Lot#	Exp Date	NDC #	Labeler	OTC
1	ANDROGEL	UNKNOWN				
2	ANDROGEL	UNKNOWN				

Event Information:

MedDRA © PreferredTerm	Start Date	End Date	Outcomes	Highlighted Terms	ReC
Agitation	01-Oct-2012	23-Dec-2012	RECOVERED/ RESOLVED	N	NA
Aggression	01-Nov-2012	01-Nov-2012	RECOVERED/ RESOLVED	N	NA
Blood Testosterone Increased	01-Nov-2012	01-Dec-2012	RECOVERED/ RESOLVED	N	NA
Crying	01-Dec-2012	23-Dec-2012	RECOVERED/ RESOLVED	N	NA
Depressed Mood	01-Dec-2012	23-Dec-2012	RECOVERED/ RESOLVED	N	NA
Depression	01-Dec-2012	23-Dec-2012	RECOVERED/ RESOLVED	N	NA
Fatigue	01-Dec-2012	23-Dec-2012	RECOVERED/ RESOLVED	N	NA
Loss Of Consciousness	01-Dec-2012	23-Dec-2012	RECOVERED/ RESOLVED	N	NA
Suicidal Ideation	01-Dec-2012	23-Dec-2012	RECOVERED/ RESOLVED	N	NA
Vomiting	01-Dec-2012	23-Dec-2012	RECOVERED/ RESOLVED	N	NA

***Age in Years displays a mid-value where the Age Unit in the report is in DECADE**

MedDRA © PreferredTerm	Start Date	End Date	Outcomes	Highlighted Terms	ReC
Adrenal Disorder	20-Dec-2012		UNKNOWN	N	NA

Event/Problem Narrative:

Spontaneous report from the USA by a consumer of a 51 year old male with events of non-serious AGITATION, LOST TEMPER, FIGHTING, SADNESS, CRYING, BLACKING OUT, THROWING UP, SUICIDAL, ADRENAL GLANDS LOW, HIGH TESTOSTERONE LEVEL, TIRED and DEPRESSION with ANDROGEL (TESTOSTERONE).

In October 2012, the patient experienced AGITATION. In November 2012, the patient experienced LOST TEMPER, FIGHTING and HIGH TESTOSTERONE LEVEL. In November 2012, the LOST TEMPER and FIGHTING resolved. In December 2012, the patient experienced SADNESS, CRYING, BLACKING OUT, THROWING UP, SUICIDAL, TIRED and DEPRESSION. On 20 Dec 2012, the patient experienced ADRENAL GLANDS LOW. On 23 Dec 2012, the AGITATION, SADNESS, CRYING, BLACKING OUT, THROWING UP, SUICIDAL, TIRED and DEPRESSION resolved. In December 2012, the HIGH TESTOSTERONE LEVEL resolved. In Oct 2012, the patient started ANDROGEL 1.62% two pumps daily. The patient later found out that his co-workers noticed an immediate increase in his agitation level. In Nov 2012, the patient reported that he lost his temper (something he denied ever doing before) and got into a fight with an acquaintance. The patient reported these changes to his physician who decreased his ANDROGEL to alternating two pumps with one pump every other day in response to high testosterone levels. Then all of a sudden in Dec, the patient became sad and depressed. The patient reported crying for three weeks. The patient would become very tired and black out. The patient also began throwing up. The week before Christmas, the patient reported being suicidal. The physician reported his adrenal glands were low and stopped the ANDROGEL on 20 Dec 2012. All the symptoms resolved three days after stopping the ANDROGEL. The patient was taking ANDOVER 1.62, and the patient reported that it had to stop due to extreme agitation and depression, which resulted in an intervention of upper staffing at his place of work and counseling. The patient reported that the conclusionwas the ANDROJEL 1.62. The patient was a man that always was a very passive person, and these were symptoms that were not him. The patient was also blacking out and throwing up for no reason. The patient reported that it caused his adrenal glands to go haywire. One the patient stopped the gel, the problems stopped within three days. The patient reported that this was very serious for him, his health and life. The patient had never in his life had suicide thoughts, but he reported that with this, it was terrible.

The patient's past medications include:
UNKNOWN TESTOSTERONE SHOT for LOW TESTOSTERONE LEVEL (2012 - 2012)
ALEVE

Relevant Medical History:

PITUITARY TUMOR (Started July 2012)
NON-SMOKER
NON DRINKER
DRUG ALLERGY ALEVE

***Age in Years displays a mid-value where the Age Unit in the report is in DECADE**

Disease/Surgical Procedure	Start Date	End Date	Continuing?	Comment
Pituitary tumour	Jul-2012			
Abstains from alcohol				
Drug hypersensitivity				
Non-tobacco user				

Medical History Product(s)	Start Date	End Date	Indication(s)	MedDRA Preferred Term(s)
UNKNOWN TESTOSTERONE SHOT	2012	2012	Blood testosterone decreased	
ALEVE				

Relevant Laboratory Data:

Test Date	Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail Y/N
01-Nov-2012	Testosterone	High				N
20-Dec-2012	Lab test	Adrenal glands low				N

Concomitant Products:

#	Product Name	Dose/Frequency	Route	Dosage Text	Indication(s)	Start Date	End Date	Interval 1st Dose to Event

Reporter Source:

Study Report:	Study Name:	Study Type:	Sponsor Study:	Protocol	IND #:
No					

Literature Text:

Country of Event: USA **Sender MFR:** ABBOTT

***Age in Years displays a mid-value where the Age Unit in the report is in DECADE**

FDA - Adverse Event Reporting System (FAERS)

Batch Printing Report for Cases

Reporter Name:	In confidence	**Reporter Type:**	
Reporter Org.:		**Reporter Email:**	
Reporter Street:		**Reporter Phone:**	
Reporter City:		**Reporter State:**	
Reporter Zip:		**Reporter Country:**	UNITED STATES
Health Prof.:		**Sent To:**	
Occupation:	CONSUMER OR OTHER NON HEALTH PROFESSIONAL	**Identity Disclosed:**	

***Age in Years displays a mid-value where the Age Unit in the report is in DECADE**

FDA - Adverse Event Reporting System (FAERS)

Batch Printing Report for Cases

Case Information:

Case Id: 9130115 **Version:** 1 **Case Type:** PERIODIC **eSub:** Yes **HP:** **Country:** USA **Outcome(s):**

FDA Rcvd. Date: 28-Feb-2013 **Init FDA Rcvd. Date:** 28-Feb-2013 **Mfr Rcvd. Date:** 06-Feb-2013 **Application Type:** NDA **Application #:** 022309

Mfr. Control #: US-ABBOTT-13P-163-1046622-00

Patient Information:

Patient ID: UNKNOWN **Age:** **Age in Years:** **Sex:** Male **Weight:** **DoB:**

Suspect Products:

#	Product Name	Dose/Frequency	Route	Dosage Text	Indication(s)	Start Date	End Date	Interval 1st Dose to Event	ReC	DeC
1	ANDROGEL 1.62%	/		1 pump daily	Blood testosterone decreased	Jan-2013	Feb-2013		NA	No

#	Product Name	Lot#	Exp Date	NDC #	Labeler	OTC
1	ANDROGEL 1.62%	unknown				

Event Information:

MedDRA © PreferredTerm	Start Date	End Date	Outcomes	Highlighted Terms	ReC
Suicidal Ideation			NOT RECOVERED/ NOT RESOLVED	N	NA

Event/Problem Narrative:

Spontaneous report from the USA by a physician of a male with an event of non-serious SUICIDAL THOUGHTS with ANDROGEL 1.62% (TESTOSTERONE). There was no reported medical history.

On an unknown date, the patient experienced SUICIDAL THOUGHTS. The physician noted that the patient was prescribed CRESTOR the same time he was prescribed ANDROGEL. The physician mentioned that the patient had been on CRESTOR in the past and did not experience this event. The physician decided to discontinue both medications.

Relevant Medical History:

Not reported.

Disease/Surgical Procedure	Start Date	End Date	Continuing?	Comment

***Age in Years displays a mid-value where the Age Unit in the report is in DECADE**

FDA - Adverse Event Reporting System (FAERS)

Batch Printing Report for Cases

Medical History Product(s)	Start Date	End Date	Indication(s)	MedDRA Preferred Term(s)

Relevant Laboratory Data:

Test Date	Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail Y/N

Concomitant Products:

#	Product Name	Dose/Frequency	Route	Dosage Text	Indication(s)	Start Date	End Date	Interval 1st Dose to Event
1	CRESTOR	/			Product used for unknown indication	Jan-2013	Feb-2013	

Reporter Source:

Study Report:	Study Name:	Study Type:	Sponsor Study:	Protocol	IND #:
No					

Literature Text:

Country of Event: USA

Sender MFR: ABBOTT

Reporter Name: (b) (6)

Reporter Org.:

Reporter Street:

Reporter City:

Reporter Zip:

Health Prof.:

Occupation: PHYSICIAN

Reporter Type:

Reporter Email:

Reporter Phone:

Reporter State: (b) (6)

Reporter Country: UNITED STATES

Sent To:

Identity Disclosed:

***Age in Years displays a mid-value where the Age Unit in the report is in DECADE**

FDA - Adverse Event Reporting System (FAERS)

Batch Printing Report for Cases

Case Information:

Case Id: 9158659 **Version:** 1 **Case Type:** 15-DAY **eSub:** Yes **HP:** **Country:** USA **Outcome(s):** OT,

FDA Rcvd. Date: 12-Mar-2013 **Init FDA Rcvd. Date:** 12-Mar-2013 **Mfr Rcvd. Date:** 01-Mar-2013 **Application Type:** NDA **Application #:** 022504

Mfr. Control #: US-ELI_LILLY_AND_COMPANY-US201303001018

Patient Information:

Patient ID: UNK **Age:** 35 YR **Age in Years:** 35 YR **Sex:** Male **Weight:** **DoB:**

Suspect Products:

#	Product Name	Dose/Frequency	Route	Dosage Text	Indication(s)	Start Date	End Date	Interval 1st Dose to Event	ReC	DeC
1	AXIRON	60 MG/		60 mg, UNK	Blood testosterone decreased				NA	NA

#	Product Name	Lot#	Exp Date	NDC #	Labeler	OTC
1	AXIRON	1470582			ELI LILLY AND CO	

Event Information:

MedDRA © PreferredTerm	Start Date	End Date	Outcomes	Highlighted Terms	ReC
Anxiety			UNKNOWN	N	NA
Suicidal Ideation			UNKNOWN	N	NA

Event/Problem Narrative:

This Spontaneous case, reported by a physician via a sales representative, concerns a 35 year old male patient of unknown ethnicity.

No medical history or concomitant medications were reported.

The patient received testosterone solution (Axiron) 60 mg via disposable applicator for treatment of low testosterone beginning on an unknown date. On an unknown date, an unknown time to onset, the patient experienced anxiety and suicidal thoughts whilst taking testosterone solution (events considered to be medically significant by the reporting physician). The patient stated the testosterone solution caused him major anxiety and feelings of wanting to commit suicide whilst taking the medication. The patient brought the testosterone solution back to the physicians office and told the physician he no longer wanted to take the medication. The physician discontinued the testosterone solution and told the patient if he was still having the suicidal thoughts he may need to take alprazolam. No laboratory data or corrective treatments were reported. Outcome of the events was not reported.

***Age in Years displays a mid-value where the Age Unit in the report is in DECADE**

The physician stated that he believed the patient would have experienced these events on any testosterone replacement treatment and stated the events were related to the testosterone solution.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?	Comment

Medical History Product(s)	Start Date	End Date	Indication(s)	MedDRA Preferred Term(s)

Relevant Laboratory Data:

Test Date	Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail Y/N

Concomitant Products:

#	Product Name	Dose/Frequency	Route	Dosage Text	Indication(s)	Start Date	End Date	Interval 1st Dose to Event

Reporter Source:

Study Report:	Study Name:	Study Type:	Sponsor Study:	Protocol	IND #:
No					

Literature Text:

Country of Event: USA **Sender MFR:** ELI LILLY AND CO

***Age in Years displays a mid-value where the Age Unit in the report is in DECADE**

FDA - Adverse Event Reporting System (FAERS)

Batch Printing Report for Cases

Reporter Name: (b) (6)
Reporter Org.:
Reporter Street:
Reporter City:
Reporter Zip:
Health Prof.:
Occupation: CONSUMER OR OTHER NON HEALTH PROFESSIONAL

Reporter Type:
Reporter Email:
Reporter Phone:
Reporter State:
Reporter Country: UNITED STATES
Sent To:
Identity Disclosed:

Reporter Name: (b) (6)
Reporter Org.:
Reporter Street:
Reporter City:
Reporter Zip:
Health Prof.:
Occupation: PHYSICIAN

Reporter Type:
Reporter Email:
Reporter Phone:
Reporter State: (b) (6)
Reporter Country: UNITED STATES
Sent To:
Identity Disclosed:

***Age in Years displays a mid-value where the Age Unit in the report is in DECADE**

FDA - Adverse Event Reporting System (FAERS)

Batch Printing Report for Cases

Case Information:

Case Id: 9163244 **Version:** 1 **Case Type:** 15-DAY **eSub:** Yes **HP:** **Country:** FRA **Outcome(s):** OT

FDA Rcvd. Date: 14-Mar-2013 **Init FDA Rcvd. Date:** 14-Mar-2013 **Mfr Rcvd. Date:** 12-Mar-2013 **Application Type:** NDA **Application #:** 017533

Mfr. Control #: FR-ROCHE-1201576

Patient Information:

Patient ID: UNKNOWN **Age:** **Age in Years:** **Sex:** Male **Weight:** **DoB:**

Suspect Products:

#	Product Name	Dose/Frequency	Route	Dosage Text	Indication(s)	Start Date	End Date	Interval 1st Dose to Event	ReC	DeC
1	ANDROGEL	100 MG/QD	PO		Libido disorder	25-Sep-2008	25-Sep-2008	1 Day	NA	Yes
2	NEURONTIN	800 MG/QID	PO		Depression		26-Sep-2008		NA	Yes
3	RIVOTRIL	4 MG/QD	PO		Depression		26-Sep-2008		NA	Yes
4	SERESTA	100 MG/QD	PO		Depression		26-Sep-2008		NA	Yes

#	Product Name	Lot#	Exp Date	NDC #	Labeler	OTC
1	ANDROGEL					
2	NEURONTIN					
3	RIVOTRIL					
4	SERESTA					

Event Information:

MedDRA © PreferredTerm	Start Date	End Date	Outcomes	Highlighted Terms	ReC
Aggression	26-Sep-2008		RECOVERED/ RESOLVED	Y	NA
Anterograde Amnesia	26-Sep-2008		RECOVERED/ RESOLVED	Y	NA
Confusional State	26-Sep-2008		RECOVERED/ RESOLVED	Y	NA
Incorrect Dose Administered					NA
Suicide Attempt					NA

***Age in Years displays a mid-value where the Age Unit in the report is in DECADE**

MedDRA © PreferredTerm	Start Date	End Date	Outcomes	Highlighted Terms	ReC
Vasodilatation					NA

Event/Problem Narrative:

Initial Information for this Spontaneous case, AER number 1201576, was received on 12/Mar/2013 from a physician via AFSSAPS (Agence Francaise de Securite Sanitaire des Produits de Sante) and concerns a Male patient of an unknown age who was treated with CLONAZEPAM, Rivotril, TESTOSTERONE, ANDROGEL, GABAPENTIN, NEURONTIN (ARGENTINA), OXAZEPAM, SERESTA for DEPRESSIVE STATE.

No medical history was reported. Concurrent conditions included DEPRESSION.
Concomitant medications included ALPROSTADIL, HYDROXYZINE HYDROCHLORIDE, PARACETAMOL.

On an unspecified date, the patient started therapy with Oral CLONAZEPAM at a dose of 4 mg, every day, Oral GABAPENTIN, at a dose of 800mg, 4 times a day,
Oral OXAZEPAM, at a dose of 100mg, every day. On 25/Sep/2008, he received Oral TESTOSTERONE, at a dose of 100mg, every day. After the intake of TESTOSTERONE, ALPROSTADIL and Viagra there was occurrence of vasodilatation of the face with marked cerebral stimulation, euphorisant for 2 to 3 hours.
(b) (6) the patient woke up in a confuso-oniric state with cerebral retardation and anterograde amnesia. The patient had a fit of violence and stabbed her wife with a knife. He committed a suicide attempt in swallowing 272 tablets of his daily treatment. No precise medication could be suspected, 4 medications had an identical intrinsic imputability score of I4 (CLONAZEPAM, OXAZEPAM, TESTOSTERONE, GABAPENTIN). It was not possible to clearly differentiate the reason of the act, that medically or pharmacologically. On (b) (6) therapy with CLONAZEPAM, TESTOSTERONE, GABAPENTIN, OXAZEPAM was stopped. The events ANTEROGRADE AMNESIA, MENTAL CONFUSION, AGGRESSIVENESS were resolved. Treatment with TESTOSTERONE, GABAPENTIN, OXAZEPAM and CLONAZEPAM was not reintroduced.

The reporter assesed events ANTEROGRADE AMNESIA, MENTAL CONFUSION, AGGRESSIVENESS as medically significant.
According to the Health Authorities, there was a causal relationship between the events anterograde amnesia, mental confusion, aggressiveness and the products TESTOSTERONE, GABAPENTIN, OXAZEPAM, CLONAZEPAM.
According to the Health Authorities, french imputability for TESTOSTERONE, GABAPENTIN, OXAZEPAM, CLONAZEPAM was chronology 1 (C1) semiology 3 (S3) imputability 2 (I2).

no further information was provided.

Relevant Medical History:

FDA - Adverse Event Reporting System (FAERS)

Batch Printing Report for Cases

Disease/Surgical Procedure	Start Date	End Date	Continuing?	Comment
Depression				

Medical History Product(s)	Start Date	End Date	Indication(s)	MedDRA Preferred Term(s)

Relevant Laboratory Data:

Test Date	Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail Y/N

Concomitant Products:

#	Product Name	Dose/Frequency	Route	Dosage Text	Indication(s)	Start Date	End Date	Interval 1st Dose to Event
1	ATARAX (FRANCE)	200 MG/QD	PO		Anxiety		26-Sep-2008	
2	PARACETAMOL	1 G/TID	PO		Pain		26-Sep-2008	
3	MUSE	/QD	URH		Erectile dysfunction	25-Sep-2008	25-Sep-2008	

Reporter Source:

Study Report:	Study Name:	Study Type:	Sponsor Study:	Protocol	IND #:
No					

Literature Text:

Country of Event: FRA **Sender MFR:** ROCHE

***Age in Years displays a mid-value where the Age Unit in the report is in DECADE**

FDA - Adverse Event Reporting System (FAERS)

Batch Printing Report for Cases

Reporter Name:	reporter known to authority	**Reporter Type:**	
Reporter Org.:		**Reporter Email:**	
Reporter Street:		**Reporter Phone:**	
Reporter City:		**Reporter State:**	
Reporter Zip:		**Reporter Country:**	FRANCE
Health Prof.:		**Sent To:**	
Occupation:	PHYSICIAN	**Identity Disclosed:**	

***Age in Years displays a mid-value where the Age Unit in the report is in DECADE**

FDA - Adverse Event Reporting System (FAERS)

Batch Printing Report for Cases

Case Information:

Case Id: 9241510 **Version:** 2 **Case Type:** 15-DAY **eSub:** Yes **HP:** **Country:** USA **Outcome(s):** HO,OT

FDA Rcvd. Date: 03-Jul-2013 **Init FDA Rcvd. Date:** 19-Apr-2013 **Mfr Rcvd. Date:** 01-Jul-2013 **Application Type:** NDA **Application #:** 021463

Mfr. Control #: US-ENDO PHARMACEUTICALS INC.-FORT20130111

Patient Information:

Patient ID: **Age:** 29 YR **Age in Years:** 29 YR **Sex:** Male **Weight:** **DoB:**

Suspect Products:

#	Product Name	Dose/Frequency	Route	Dosage Text	Indication(s)	Start Date	End Date	Interval 1st Dose to Event	ReC	DeC
1	FORTESTA	10 MG/	TOP	10 MG	Blood testosterone decreased				NA	Yes
2	PREDNISONE TABLETS	/	PO	60 MG, 50 MG, 40 MG, ETC. TAPERING DOSE	Dermatitis allergic				NA	Yes

#	Product Name	Lot#	Exp Date	NDC #	Labeler	OTC
1	FORTESTA				ENDO	
2	PREDNISONE TABLETS					

Event Information:

MedDRA © PreferredTerm	Start Date	End Date	Outcomes	Highlighted Terms	ReC
Delirium			RECOVERED/ RESOLVED	N	NA
Potentiating Drug Interaction			RECOVERED/ RESOLVED	N	NA
Substance-Induced Psychotic Disorder			RECOVERED/ RESOLVED	N	NA
Suicide Attempt			RECOVERED/ RESOLVED	N	NA

Event/Problem Narrative:

Initial Notification (11-APR-2013):

A report was received from a physician concerning a 29-year-old Caucasian male patient who began using Fortesta gel for low testosterone. Other suspect medication included prednisone (manufacturer unknown) 60 mg, 50 mg, 40 mg, etc. tapered dose for an allergic skin reaction.

***Age in Years displays a mid-value where the Age Unit in the report is in DECADE**

The patient was concurrently experiencing unspecified emotional issues. The patient had used Androderm (testosterone transdermal system) within 30 days of the events.

The physician stated that the patient attempted suicide and experienced loss of orientation / no recollection of the suicide attempt while using Fortesta gel and prednisone. The patient previously used Androderm for ten days and experienced an allergic skin reaction to the patch. The Androderm patch was discontinued and Fortesta gel was started. Two to three days after Fortesta was started, the patient was prescribed a prednisone taper (60 mg, 50 mg, 40 mg, etc.) by a physician assistant for the allergic skin rash. Three days after that, the patient attempted suicide by slashing his wrists with a box cutter and he lost orientation for twelve hours. The physician stated that the patient remembered taking a bath and the next thing he remembered was waking up in the hospital. The physician stated that the patient had no recollection of the suicide attempt. Fortesta and prednisone were discontinued and the patient recovered.

The mental health providers at the local hospital and the main hospital where the patient was treated attributed the event to steroid psychosis. The reporting physician thought that the event may have been due to a combination of factors, including emotional issues in the patient's personal life and Fortesta gel and prednisone therapies; he questioned whether testosterone replacement therapy could change the way that steroids like prednisone are metabolized, essentially making the dose of the prednisone higher than it otherwise would be.

The company physician considered the events of suicide attempt and loss of orientation / no recollection of suicide attempt to be serious due to hospitalization, and the possible potentiating drug interaction between Fortesta and prednisone to be serious due to medical importance.

This report was linked to PRED20130019.

Follow up received from the physician on (01-JUL-2013):

Concomitant medications included Medrol (methylprednisolone) dose pack.

The physician stated that the consumer experienced acute delirium which resulted in confusion and attempted suicide by cutting the wrists with a box cutter. The consumer was treated in the emergency room, inpatient and outpatient mental health. The physician was unsure if Fortesta gel/prednisone tablets caused the event.

Therapy with Fortesta gel was discontinued. The event was resolved.

The company physician considered the event of acute delirium to be serious due to hospitalization, and the event steroid psychosis to be serious due to medical importance.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?	Comment
Blood testosterone decreased				
Dermatitis allergic				TO ANDRODERM
Emotional disorder				

Medical History Product(s)	Start Date	End Date	Indication(s)	MedDRA Preferred Term(s)

Relevant Laboratory Data:

Test Date	Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail Y/N

Concomitant Products:

#	Product Name	Dose/Frequency	Route	Dosage Text	Indication(s)	Start Date	End Date	Interval 1st Dose to Event
1	ANDRODERM	/	TDER	UNK	Blood testosterone decreased			
2	MEDROL	/	UNK	UNK	Product used for unknown indication			

Reporter Source:

Study Report:	Study Name:	Study Type:	Sponsor Study:	Protocol	IND #:
No					

Literature Text:

Country of Event: USA **Sender MFR:** ENDO

***Age in Years displays a mid-value where the Age Unit in the report is in DECADE**

FDA - Adverse Event Reporting System (FAERS)

Batch Printing Report for Cases

Reporter Name:	(b) (6)	**Reporter Type:**	
Reporter Org.:		**Reporter Email:**	
Reporter Street:		**Reporter Phone:**	
Reporter City:		**Reporter State:**	(b) (6)
Reporter Zip:		**Reporter Country:**	UNITED STATES
Health Prof.:		**Sent To:**	
Occupation:	PHYSICIAN	**Identity Disclosed:**	

***Age in Years displays a mid-value where the Age Unit in the report is in DECADE**

FDA - Adverse Event Reporting System (FAERS)

Batch Printing Report for Cases

Case Information:

Case Id: 9292935 **Version:** 1 **Case Type:** 15-DAY **eSub:** Yes **HP:** **Country:** USA **Outcome(s):** OT,

FDA Rcvd. Date: 16-May-2013 **Init FDA Rcvd. Date:** 16-May-2013 **Mfr Rcvd. Date:** 13-May-2013 **Application Type:** NDA **Application #:** 021015

Mfr. Control #: US-ABBOTT-13P-163-1088871-00

Patient Information:

Patient ID: (b) (6) **Age:** 52.(b) (6) YR **Age in Years:** 52.(b) (6) YR **Sex:** Male **Weight:** 86.71 KG **DoB:** (b) (6)

Suspect Products:

#	Product Name	Dose/Frequency	Route	Dosage Text	Indication(s)	Start Date	End Date	Interval 1st Dose to Event	ReC	DeC
1	ANDROGEL	3.75 G/QD	TOP	3 pumps Gel	Blood testosterone decreased	Apr-2013	Apr-2013	1 Month	NA	Yes
2	ANDROGEL	2.5 G/QD	TOP	2 pumps		11-May-2013	13-May-2013	1 Month	NA	Yes
3	ANDROGEL	5 G/QD	TOP	4 pumps		Apr-2013	11-May-2013	1 Month	NA	Yes

#	Product Name	Lot#	Exp Date	NDC #	Labeler	OTC
1	ANDROGEL	71317				
2	ANDROGEL	71317				
3	ANDROGEL	71317				

Event Information:

MedDRA © PreferredTerm	Start Date	End Date	Outcomes	Highlighted Terms	ReC
Anxiety	29-Apr-2013		RECOVERING/ RESOLVING	N	NA
Nervousness	29-Apr-2013		RECOVERING/ RESOLVING	N	NA
Suicidal Ideation	01-May-2013		NOT RECOVERED/ NOT RESOLVED	N	NA
Weight Decreased	06-May-2013		NOT RECOVERED/ NOT RESOLVED	N	NA
Depression			UNKNOWN	N	NA
Hot Flush			UNKNOWN	N	NA

***Age in Years displays a mid-value where the Age Unit in the report is in DECADE**

Event/Problem Narrative:

Spontaneous report from the USA by a consumer of a 52 year old male with events of SUICIDAL THOUGHTS and non-serious ANXIETY, DEPRESSION, HOT FLASHES, NERVOUSNESS and LOST WEIGHT with ANDROGEL (TESTOSTERONE).

On unknown dates, the patient experienced DEPRESSION and HOT FLASHES. On 29 Apr 2013, the patient experienced ANXIETY and NERVOUSNESS. In May 2013, the patient experienced SUICIDAL THOUGHTS. On 06 May 2013, the patient experienced LOST WEIGHT. Since 29 Apr 2013, the patient experienced anxiety and nervousness after taking ANDROGEL. In May 2013, a few days ago, the patient experienced suicidal thoughts, described as making a plan to kill himself. Since stopping ANDROGEL, the patient no longer has that plan. Since 06 May 2013, about one week ago, the patient experienced weight loss of six pounds. On 13 May 2013, the patient discontinued ANDROGEL, and called the prescriber's office to inform them of the events and discontinuation of the medication.

The patient's pastmedications include:
CIPRO for UNKNOWN INDICATION
SULFA for UNKNOWN INDICATION

Change History

Amendment to data received on 13 May 2013 with changes to narrative description.
No new medical information was received. Version created only to amend the narrative in which it was stated that the lot information was not available. (Lot information was reported).

Relevant Medical History:

NONSMOKER
ABSTAINS FROM ALCOHOL
BIPOLAR DISEASE/DISORDER
DRUG ALLERGY CIPRO
DRUG ALLERGY CIPRO was manifested by Aggrivated bipolar disorder.
AGGRIVATED BIPOLAR DISORDER
DRUG ALLERGY SULFA
DRUG ALLERGY SULFA was manifested by Eyes turn red.
EYES TURN RED

Disease/Surgical Procedure	Start Date	End Date	Continuing?	Comment
Abstains from alcohol				

***Age in Years displays a mid-value where the Age Unit in the report is in DECADE**

Bipolar disorder

Drug hypersensitivity

Non-tobacco user

Ocular hyperaemia

Medical History Product(s)	Start Date	End Date	Indication(s)	MedDRA Preferred Term(s)
CIPRO			Product used for unknown indication	
SULFA			Product used for unknown indication	

Relevant Laboratory Data:

Test Date	Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail Y/N

Concomitant Products:

#	Product Name	Dose/Frequency	Route	Dosage Text	Indication(s)	Start Date	End Date	Interval 1st Dose to Event
1	LEVOTHYROXINE (GENERIC)	/			Thyroid disorder			
2	LITHIUM	/			Bipolar disorder			
3	ZOLOFT	/			Product used for unknown indication			
4	NEXIUM	/			Product used for unknown indication			

Reporter Source:

Study Report:	Study Name:	Study Type:	Sponsor Study:	Protocol	IND #:
No					

Literature Text:

Country of Event: USA **Sender MFR:** ABBOTT

***Age in Years displays a mid-value where the Age Unit in the report is in DECADE**

FDA - Adverse Event Reporting System (FAERS)

Batch Printing Report for Cases

Reporter Name:	In Confidence	**Reporter Type:**	
Reporter Org.:		**Reporter Email:**	
Reporter Street:		**Reporter Phone:**	
Reporter City:		**Reporter State:**	
Reporter Zip:		**Reporter Country:**	UNITED STATES
Health Prof.:		**Sent To:**	
Occupation:	CONSUMER OR OTHER NON HEALTH PROFESSIONAL	**Identity Disclosed:**	

***Age in Years displays a mid-value where the Age Unit in the report is in DECADE**

FDA - Adverse Event Reporting System (FAERS)

Batch Printing Report for Cases

Case Information:

Case Id: 9410523 **Version:** 1 **Case Type:** 15-DAY **eSub:** Yes **HP:** **Country:** DNK **Outcome(s):** HO,LT,

FDA Rcvd. Date: 19-Jul-2013 **Init FDA Rcvd. Date:** 19-Jul-2013 **Mfr Rcvd. Date:** 24-Jun-2013 **Application Type:** NDA **Application #:** 021015

Mfr. Control #: DK-ABBOTT-13P-044-1122561-00

Patient Information:

Patient ID: (b) (6) **Age:** 38.(b) (6) YR **Age in Years:** 38 (b) (6) YR **Sex:** Male **Weight:** KG **DoB:** (b) (6)

Suspect Products:

#	Product Name	Dose/Frequency	Route	Dosage Text	Indication(s)	Start Date	End Date	Interval 1st Dose to Event	ReC	DeC
1	TESTOGEL	/			Klinefelter's syndrome			288 Day	NA	Yes
2	TESTOGEL	/		Reduced dose to half	Osteoporosis prophylaxis	26-Jan-2010	08-Apr-2010	288 Day	NA	Yes
3	TESTOGEL	/			Osteopenia			288 Day	NA	Yes
4	TESTOGEL	50 MG/QD	TDER		Blood testosterone decreased	15-Jun-2009		288 Day	NA	Yes

#	Product Name	Lot#	Exp Date	NDC #	Labeler	OTC
1	TESTOGEL	UNKNOWN				
2	TESTOGEL	UNKNOWN				
3	TESTOGEL	UNKNOWN				
4	TESTOGEL	UNKNOWN				

Event Information:

MedDRA © PreferredTerm	Start Date	End Date	Outcomes	Highlighted Terms	ReC
Suicide Attempt	(b) (6)		RECOVERED/ RESOLVED	N	NA
Anger			RECOVERING/ RESOLVING	N	NA
Anxiety			RECOVERING/ RESOLVING	N	NA
Depression			RECOVERING/ RESOLVING	N	NA

***Age in Years displays a mid-value where the Age Unit in the report is in DECADE**

Event/Problem Narrative:

Case received on 18 Jul 2013 from Besins; reference number 2013-1635-SPO.

This case was reported by a physician via Danish Medicines Agency and concerns a 38 year old male patient who experienced serious events increasingly depressed after 1-2 months start with Testogel (Depression), attempted suicide (Suicide attempt), quick-tempered (Anger) and anxious (Anxiety) whilst using Testogel (Testosterone).

The medical history of the patient included low testosterone, decrease in bone volume (osteopenia) and Klinefelter's syndrome.

The patients did not receive any concomitant medication at the time of onset of adverse events.

On 15 Jun 2009, the patient began treatment with Testogel at 50mg daily via transdermal route topically for Klinefelter's syndrome associated low testosterone and osteopenia and to prevent osteoporosis later in life. On 26 Jan 2010, the dose of Testogel was reduced to half. The total duration of Testogel therapy was reported as 297 days.

On unknown dates, the patient experienced increasingly depressed after 1-2 months start with Testogel, attempted suicide, quick-tempered and anxious. The patient's wife contacted the hospital by telephone on 20 Jan 2010 and stated that the patient during treatment with Testogel was quick-tempered, depressed, and anxious. The patient planned a consultation on 26 Jan 2010. At the consultation on 26 Jan 2010 it was decided to reduce the dose of Testogel because of the patient's psychological symptoms. The patient was informed to contact his physician if this did not help immediately, as it could be depression or other mental strain. Despite treatment with antidepressant citalopram (taken since an unknown date), he attempted suicide on (b) (6) (b) (6) and was hospitalized for 1 day. It was believed that Testogel could be the cause of the patient's depression. Citalopram dosage was increased. The patient was discharged on (b) (6) Testogel treatment was stopped on (b) (6) (b) (6)

The patient had sought compensationbecause he believed that he had suffered an injury in the treatment with Testogel. The patient wrote in his review that after initiation of treatment with Testogel he became depressed and tried to commit suicide. The patient also wrote that he still had it bad, and that he had a hard time to fit his work and function in daily life. (b) (6) (b) (6) estimated that the patient had not suffered a physical injury as a result of treatment with Testogel. (b) (6) puts the decision emphasized that it was clear from records note from the (b) (6) that the patient was hospitalized after a suicide attempt because of depression, and that it was believed that Testogel could be the cause of depression. Psychological damage triggered by a drug was not covered by the Act. The (b) (6) (b) (6) believed that it was proper to prescribe Testogel to the patient the 15 Jun 2009 because of the patient's disease Klinefelter's syndrome with decreased male hormone and consequent decrease in bone quantity. It was also correct to reduce the dose of Testogel on 26 Jan 2010, as the patient had psychological symptoms associated with treatment. When blood tests showed a good result of treatment with Testogel, it was necessary to continue treatment. Testogel was stopped after patient's suicide attempt, which also follows experienced specialist standard.

The patient's relevant laboratory test at the time of the events included:
On an unknown date in Jan 2010, blood test results show satisfactory effects on testosterone levels.

On (b) (6) the treatment with Testogel was discontinued.

The outcome of the events increasingly depressed after 1-2 months start with Testogel, quick-tempered and anxious was recovering/resolving while the outcome for the event attempted suicide was recovered/resolved.

Additional information has been requested.

The causal relationship was reported as possible by the reporter between Testogel and the event increasingly depressed after 1-2 months start with Testogel while causality was not reported for the events attempted suicide, quick-tempered and anxious.

The company considered that the information was insufficient to assess the causality between Testogel and the events increasingly depressed after 1-2 months start with Testogel, attempted suicide, quick-tempered and anxious.

Date received by Besins Healthcare: 24 Jun 2013.

Relevant Medical History:

Concurrent Disease:
Osteopenia (??/??/??) (Continuing: Unknown): decrease in bone volume (osteopenia)
Testosterone low (??/??/??) (Continuing: Yes): Reduced male hormone (testosterone)
Klinefelter's syndrome (??/??/??) (Continuing: Yes)

Disease/Surgical Procedure	Start Date	End Date	Continuing?	Comment
Blood testosterone decreased				
Klinefelter's syndrome				
Osteopenia			UNKNOWN	

Medical History Product(s)	Start Date	End Date	Indication(s)	MedDRA Preferred Term(s)

Relevant Laboratory Data:

Test Date	Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail Y/N
01-Jan-2010	Testosterone	satisfactory effects on				N

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Test Date	Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail Y/N
		testosterone levels				

Concomitant Products:

#	Product Name	Dose/Frequency	Route	Dosage Text	Indication(s)	Start Date	End Date	Interval 1st Dose to Event

Reporter Source:

Study Report:	Study Name:	Study Type:	Sponsor Study:	Protocol	IND #:
No					

Literature Text:

Country of Event: DNK **Sender MFR:** ABBOTT

Reporter Name: Unknown
Reporter Org.:
Reporter Street:
Reporter City:
Reporter Zip:
Health Prof.:
Occupation: PHYSICIAN

Reporter Type:
Reporter Email:
Reporter Phone:
Reporter State:
Reporter Country: DENMARK
Sent To:
Identity Disclosed:

***Age in Years displays a mid-value where the Age Unit in the report is in DECADE**

FDA - Adverse Event Reporting System (FAERS)

Batch Printing Report for Cases

Case Information:

Case Id: 9479150 **Version:** 1 **Case Type:** 15-DAY **eSub:** Yes **HP:** **Country:** USA **Outcome(s):** OT,

FDA Rcvd. Date: 27-Aug-2013 **Init FDA Rcvd. Date:** 27-Aug-2013 **Mfr Rcvd. Date:** 21-Aug-2013 **Application Type:** NDA **Application #:** 022309

Mfr. Control #: US-ABBOTT-13P-163-1136347-00

Patient Information:

Patient ID: (b) (6) **Age:** **Age in Years:** **Sex:** Male **Weight:** 108.05 KG **DoB:** (b) (6)

Suspect Products:

#	Product Name	Dose/Frequency	Route	Dosage Text	Indication(s)	Start Date	End Date	Interval 1st Dose to Event	ReC	DeC
1	ANDROGEL	/QD	TOP	2 pumps Daily		2013	2013	0 Day	NA	NA
2	ANDROGEL	/QD	TOP	3 pumps Daily				0 Day	NA	NA
3	ANDROGEL	/QD	TOP	1 pump Daily	Blood testosterone decreased	Jan-2013	2013	0 Day	NA	NA

#	Product Name	Lot#	Exp Date	NDC #	Labeler	OTC
1	ANDROGEL	Unknown				
2	ANDROGEL	Unknown				
3	ANDROGEL	Unknown				

Event Information:

MedDRA © PreferredTerm	Start Date	End Date	Outcomes	Highlighted Terms	ReC
Depressed Mood	01-Jan-2013		NOT RECOVERED/ NOT RESOLVED	N	NA
Depression	01-Jan-2013		NOT RECOVERED/ NOT RESOLVED	N	NA
Suicidal Ideation	01-Jan-2013		NOT RECOVERED/ NOT RESOLVED	N	NA
Mood Swings			NOT RECOVERED/ NOT RESOLVED	N	NA

***Age in Years displays a mid-value where the Age Unit in the report is in DECADE**

Event/Problem Narrative:

Solicited report from the USA by a consumer of a 61 year old male with events of SUICIDAL THOUGHTS and non-serious MOOD SWINGS, SADNESS and DEPRESSION with ANDROGEL (TESTOSTERONE).

On an unknown date, the patient experienced MOOD SWINGS. In 2013, the patient experienced SUICIDAL THOUGHTS, SADNESS and DEPRESSION. Since the patient's ANDROGEL dose was increased to three pumps in March or April of this year, 2013, the patient has had severe mood swings. They come and go. The mood swings have included suicidal thoughts with a plan. The patient is currently not having the suicidal thoughts. The patient has also been very sad and depressed with thoughts of having nothing to live for. Last week the patient had his Testosterone level checked and he is awaiting the results. The patient has been directed to contact his physician to attend to his symptoms. The patient declined to provide his doctor's information and declined to have the physician contacted.

Relevant Laboratory & Other Diagnostic Tests

August 2013 Testosterone level: Pending

Relevant Medical History:

No family history of depression.

NO KNOWN ALLERGIES

NON-SMOKER
ALCOHOL USE: 2-3 BEERS A WEEK

Disease/Surgical Procedure	Start Date	End Date	Continuing?	Comment
Alcohol use				
Non-tobacco user				

Medical History Product(s)	Start Date	End Date	Indication(s)	MedDRA Preferred Term(s)

Relevant Laboratory Data:

Test Date	Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail Y/N
01-Aug-2013	Testosterone	Pending				N

***Age in Years displays a mid-value where the Age Unit in the report is in DECADE**

Concomitant Products:

#	Product Name	Dose/Frequency	Route	Dosage Text	Indication(s)	Start Date	End Date	Interval 1st Dose to Event
1	L-THYROXINE	/			Hypothyroidism			
2	SAW PALMETO	/			Vitamin supplementation			
3	ASPIRIN	/			Product used for unknown indication			
4	FISH OIL	/			Vitamin supplementation			
5	MULTIVITAMIN	/			Vitamin supplementation			

Reporter Source:

Study Report:	Study Name:	Study Type:	Sponsor Study:	Protocol	IND #:
No				FACILITATED COLLECT	

Literature Text:

Country of Event: USA **Sender MFR:** ABBOTT

Reporter Name:
Reporter Org.:
Reporter Street:
Reporter City:
Reporter Zip:
Health Prof.:
Occupation: CONSUMER OR OTHER NON HEALTH PROFESSIONAL

Reporter Type:
Reporter Email:
Reporter Phone:
Reporter State:
Reporter Country: UNKNOWN
Sent To:
Identity Disclosed:

***Age in Years displays a mid-value where the Age Unit in the report is in DECADE**

FDA - Adverse Event Reporting System (FAERS)

Batch Printing Report for Cases

Reporter Name:	In Confidence	**Reporter Type:**	
Reporter Org.:		**Reporter Email:**	
Reporter Street:		**Reporter Phone:**	
Reporter City:		**Reporter State:**	
Reporter Zip:		**Reporter Country:**	UNITED STATES
Health Prof.:		**Sent To:**	
Occupation:	CONSUMER OR OTHER NON HEALTH PROFESSIONAL	**Identity Disclosed:**	

***Age in Years displays a mid-value where the Age Unit in the report is in DECADE**

FDA - Adverse Event Reporting System (FAERS)

Batch Printing Report for Cases

Case Information:

Case Id: 9721702 **Version:** 4 **Case Type:** PERIODIC **eSub:** Yes **HP:** **Country:** USA **Outcome(s):**

FDA Rcvd. Date: 29-Apr-2014 **Init FDA Rcvd. Date:** 01-Dec-2013 **Mfr Rcvd. Date:** 04-Mar-2014 **Application Type:** NDA **Application #:** 022309

Mfr. Control #: US-ABBVIE-13P-163-1153267-00

Patient Information:

Patient ID: (b) (6) **Age:** 35. (b) (6) YR **Age in Years:** 35. (b) (6) YR **Sex:** Male **Weight:** 58.11 KG **DoB:** (b) (6)

Suspect Products:

#	Product Name	Dose/Frequency	Route	Dosage Text	Indication(s)	Start Date	End Date	Interval 1st Dose to Event	ReC	DeC
1	ANDROGEL 1.62%	40.5 MG/QD	TOP	Two pums	Blood testosterone decreased	15-Sep-2013	18-Sep-2013	0 Day	NA	Yes

#	Product Name	Lot#	Exp Date	NDC #	Labeler	OTC
1	ANDROGEL 1.62%	90424				

Event Information:

MedDRA © PreferredTerm	Start Date	End Date	Outcomes	Highlighted Terms	ReC
Acne	15-Sep-2013		NOT RECOVERED/ NOT RESOLVED	N	NA
Asthenia	15-Sep-2013		NOT RECOVERED/ NOT RESOLVED	N	NA
Chills	15-Sep-2013	18-Sep-2013	RECOVERED/ RESOLVED	N	NA
Dizziness	15-Sep-2013		NOT RECOVERED/ NOT RESOLVED	N	NA
Hyperhidrosis	15-Sep-2013	18-Sep-2013	RECOVERED/ RESOLVED	N	NA
Nausea	15-Sep-2013	18-Sep-2013	RECOVERED/ RESOLVED	N	NA
Paranoia	15-Sep-2013		NOT RECOVERED/ NOT RESOLVED	N	NA
Suicidal Ideation	15-Sep-2013		NOT RECOVERED/ NOT RESOLVED	N	NA

Event/Problem Narrative:

Spontaneous report from the USA by a health professional of a 35 year old male with events of non-serious NIGHT CHILLS, NAUSEA, TEETH CHATTERING, SWEATING, DIZZINESS, FACE BROKEN OUT, PRESUICIDAL THOUGHTS, PARANOIA and LACK OF ENERGY with ANDROGEL 1.62% (TESTOSTERONE).

On 15 Sep 2013, the patient experienced NIGHT CHILLS, NAUSEA, TEETH CHATTERING, SWEATING, DIZZINESS, FACE

***Age in Years displays a mid-value where the Age Unit in the report is in DECADE**

BROKEN OUT, PRESUICIDAL THOUGHTS, PARANOIA and LACK OF ENERGY. On 18 Sep 2013, the NIGHT CHILLS, NAUSEA, TEETH CHATTERING and SWEATING resolved. On 27 Sep 2013, the patient reported pre-suicidal thoughts and paranoia. The patient stated had he had seen a nurse practitioner one week ago regarding these thoughts. The patient also stated that the nurse practitioner had wanted to prescribe an ANTIDEPRESSANT for the patient, but he declined. The patient stated that the healthcare practitioner told him that the adverse events might have been related to his body not being accustomed to the increase in testosterone. The patient was advised to seek mental health services promptly. The doctor's office wasn't aware of the presuicidal thoughts and paranoia since patient never mentioned it to them. He was taken off ANDROGEL and switched to TESTIM. The patient said they used ANDROGEL for three days then becamw sweaty and chills so stopped. No treatment per physicians office. Unknow lot and expiration date. Per physician's office the patient was taking ANDROGEL from 15 Sep 2013 to 18 Sep 2013.

Relevant Laboratory & Other Diagnostic Tests
---
27 Aug 2013 Testosterone Level: 289
Baseline

Change History

On 29 Jan 2014, received updates to patient demographics, medical history, event information, reporter opinion of causality, suspect drug information and narrative description.

Amendment to data received on 04 Mar 2014 with changes to event information, reporter opinion of causality, narrative description and medical history.
No new medical information was added. Adverse event chills remove due to ducplicate.

Relevant Medical History:
NO KNOWN ALLERGIES

NON-SMOKER
DRINKER: TWO DRINKS OF WINE PER DAY
FATIGUE

Disease/Surgical Procedure	Start Date	End Date	Continuing?	Comment
Alcohol use				
Fatigue				
Non-tobacco user				

FDA - Adverse Event Reporting System (FAERS)

Batch Printing Report for Cases

Medical History Product(s)	Start Date	End Date	Indication(s)	MedDRA Preferred Term(s)

Relevant Laboratory Data:

Test Date	Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail Y/N
27-Aug-2013	Testosterone	289	BASELINE			N

Concomitant Products:

#	Product Name	Dose/Frequency	Route	Dosage Text	Indication(s)	Start Date	End Date	Interval 1st Dose to Event
1	FINASTERIDE	5 MG/QD			Alopecia			

Reporter Source:

Study Report:	Study Name:	Study Type:	Sponsor Study:	Protocol	IND #:
No					

Literature Text:

Country of Event: USA **Sender MFR:** ABBVIE

Reporter Name: (b) (6)
Reporter Org.:
Reporter Street:
Reporter City:
Reporter Zip:

Reporter Type:
Reporter Email:
Reporter Phone:
Reporter State: (b) (6)
Reporter Country: UNITED STATES

Health Prof.:
Occupation:

Sent To:
Identity Disclosed:

***Age in Years displays a mid-value where the Age Unit in the report is in DECADE**

FDA - Adverse Event Reporting System (FAERS)

Batch Printing Report for Cases

Case Information:

Case Id: 10040156 **Version:** 1 **Case Type:** 15-DAY **eSub:** Yes **HP:** **Country:** USA **Outcome(s):** OT,

FDA Rcvd. Date: 26-Mar-2014 **Init FDA Rcvd. Date:** 26-Mar-2014 **Mfr Rcvd. Date:** 18-Mar-2014 **Application Type:** NDA **Application #:** 022309

Mfr. Control #: US-ABBVIE-14P-163-1213912-00

Patient Information:

Patient ID: (b) (6) **Age:** **Age in Years:** **Sex:** Male **Weight:** 88.53 KG **DoB:** (b) (6)

Suspect Products:

#	Product Name	Dose/Frequency	Route	Dosage Text	Indication(s)	Start Date	End Date	Interval 1st Dose to Event	ReC	DeC
1	ANDROGEL	/QD	TOP	2 PUMPS DAILY		2013		2 Year	NA	NA
2	ANDROGEL	/QD	TOP	1 PUMP DAILY	Product used for unknown indication	2012	2013	2 Year	NA	NA

#	Product Name	Lot#	Exp Date	NDC #	Labeler	OTC
1	ANDROGEL	90500				
2	ANDROGEL	90500				

Event Information:

MedDRA © PreferredTerm	Start Date	End Date	Outcomes	Highlighted Terms	ReC
Blood Testosterone Decreased	01-Jan-2012		UNKNOWN	N	NA
Anxiety	01-Feb-2014		NOT RECOVERED/ NOT RESOLVED	N	NA
Depressed Mood	01-Feb-2014		NOT RECOVERED/ NOT RESOLVED	N	NA
Depression	01-Feb-2014		NOT RECOVERED/ NOT RESOLVED	N	NA
Hostility	01-Mar-2014		NOT RECOVERED/ NOT RESOLVED	N	NA
Suicidal Ideation	01-Mar-2014		NOT RECOVERED/ NOT RESOLVED	N	NA
Incorrect Dose Administered			UNKNOWN	N	NA

***Age in Years displays a mid-value where the Age Unit in the report is in DECADE**

Event/Problem Narrative:

Solicited report from the USA by a physician of a 50 year old male with events of SUICIDAL THOUGHTS and non-serious DEPRESSED, ANXIOUS, FEELING SAD, HOSTILE, LOW TESTOSTERONE LEVELS and PHYSICIAN INCREASED DOSE TO 3 PUMPS DAILY BUT DECIDED TO TAKE 2 PUMPS DAILY with ANDROGEL (TESTOSTERONE). The patient had a relevant medical history of ANXIETY.

On an unknown date, the patient experienced PHYSICIAN INCREASED DOSE TO 3 PUMPS DAILY BUT DECIDED TO TAKE 2 PUMPS DAILY. The patient started ANDROGEL two years ago on an unknown date. The patient was originally prescribed one pump daily. The patient went for a blood test about nine months after starting ANDROGEL and his testosterone levels were low. The physician increased his dose to three pumps daily but the patient decided to only do two pumps daily. In 2012, the patient experienced LOW TESTOSTERONE LEVELS. In February 2014, the patient experienced DEPRESSED, ANXIOUS and FEELING SAD. Recently he had been feeling sad, anxious, hostile and depressed. The patient had suicidal thoughts. The patient had not notified his physician. It was reported that the patient had no history of depression, lung, liver, or kidney disease. In March 2014, the patient experienced SUICIDAL THOUGHTS and HOSTILE. The physician spoke with the patient and felt that the symptoms that the patient was experiencing were not related to Androgel. He encouraged the patient to come in for an appointment. No further information was provided.

Relevant Laboratory & Other Diagnostic Tests

2012 SERUM TESTOSTERONE LEVEL: Low

Relevant Medical History:

NO KNOWN ALLERGIES

HIGH CHOLESTEROL
ANXIETY
NON-SMOKER
DRINKER: RARELY ON AN OCCASION

Disease/Surgical Procedure	Start Date	End Date	Continuing?	Comment
Alcohol use				
Anxiety				
Blood cholesterol increased				
Non-tobacco user				

***Age in Years displays a mid-value where the Age Unit in the report is in DECADE**

FDA - Adverse Event Reporting System (FAERS)

Batch Printing Report for Cases

Medical History Product(s)	Start Date	End Date	Indication(s)	MedDRA Preferred Term(s)

Relevant Laboratory Data:

Test Date	Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail Y/N
01-Jan-2012	Serum testosterone	Low				N

Concomitant Products:

#	Product Name	Dose/Frequency	Route	Dosage Text	Indication(s)	Start Date	End Date	Interval 1st Dose to Event
1	ZYRTEC	/			Product used for unknown indication			
2	LIPITOR	/			Product used for unknown indication			
3	FISH OIL	/			Product used for unknown indication			
4	MULTIVITAMIN	/			Product used for unknown indication			
5	VITAMIN D	/			Product used for unknown indication			

Reporter Source:

Study Report:	Study Name:	Study Type:	Sponsor Study:	Protocol	IND #:
No				FACILITATED COLLECT	

Literature Text:

Country of Event: USA **Sender MFR:** ABBVIE

***Age in Years displays a mid-value where the Age Unit in the report is in DECADE**

FDA - Adverse Event Reporting System (FAERS)

Batch Printing Report for Cases

Reporter Name:	(b) (6)	**Reporter Type:**	
Reporter Org.:		**Reporter Email:**	
Reporter Street:		**Reporter Phone:**	
Reporter City:		**Reporter State:**	(b) (6)
Reporter Zip:		**Reporter Country:**	UNITED STATES
Health Prof.:		**Sent To:**	
Occupation:	PHYSICIAN	**Identity Disclosed:**	

Reporter Name:		**Reporter Type:**	
Reporter Org.:		**Reporter Email:**	
Reporter Street:		**Reporter Phone:**	
Reporter City:		**Reporter State:**	
Reporter Zip:		**Reporter Country:**	UNKNOWN
Health Prof.:		**Sent To:**	
Occupation:	PHYSICIAN	**Identity Disclosed:**	

***Age in Years displays a mid-value where the Age Unit in the report is in DECADE**

FDA - Adverse Event Reporting System (FAERS)

Batch Printing Report for Cases

Case Information:

Case Id: 10399181 **Version:** 1 **Case Type:** 15-DAY **eSub:** Yes **HP:** **Country:** USA **Outcome(s):** OT,

FDA Rcvd. Date: 21-Aug-2014 **Init FDA Rcvd. Date:** 21-Aug-2014 **Mfr Rcvd. Date:** 16-Aug-2014 **Application Type:** NDA **Application #:** 022309

Mfr. Control #: US-ABBVIE-14P-163-1273643-00

Patient Information:

Patient ID: (b) (6) **Age:** 51 YR **Age in Years:** 51 YR **Sex:** Male **Weight:** **DoB:**

Suspect Products:

#	Product Name	Dose/Frequency	Route	Dosage Text	Indication(s)	Start Date	End Date	Interval 1st Dose to Event	ReC	DeC
1	ANDROGEL	/	TOP		Drug use for unknown indication				NA	NA
2	SYNTHROID	/			Drug use for unknown indication	1976			NA	NA

#	Product Name	Lot#	Exp Date	NDC #	Labeler	OTC
1	ANDROGEL	unknown				
2	SYNTHROID	unknown				

Event Information:

MedDRA © PreferredTerm	Start Date	End Date	Outcomes	Highlighted Terms	ReC
Alopecia			UNKNOWN	N	NA
Asthenia			UNKNOWN	N	NA
Depressed Mood			UNKNOWN	N	NA
Depression			UNKNOWN	N	NA
Emotional Distress			UNKNOWN	N	NA
Fatigue			UNKNOWN	N	NA
Suicidal Ideation			UNKNOWN	N	NA

***Age in Years displays a mid-value where the Age Unit in the report is in DECADE**

Event/Problem Narrative:

Spontaneous report from the USA by a consumer of a 51 year old male with events of SUICIDAL THOUGHTS and non-serious DEPRESSION, SADNESS, FEELING WEAKER, FATIGUE, HAIR LOSS and FRANTIC with ANDROGEL (TESTOSTERONE) and SYNTHROID (LEVOTHYROXINE).

On unknown dates, the patient experienced SUICIDAL THOUGHTS, DEPRESSION, SADNESS, FEELING WEAKER, FATIGUE, HAIR LOSS and FRANTIC. He reported that since he has been off his Androgel he has felt depressed, sad and had suicidal thoughts. In additions to him being off his Androgel he is also off his Synthroid and he experienced fatigue, weakness, and hair loss. His physician was aware. Primary reporter does not have the lot number information, because the Primary reporter no longer had the product.

Causality for ANDROGEL(TESTOSTERONE)

The reporter's statement of causality for the events of SUICIDAL THOUGHTS, DEPRESSION, SADNESS and FRANTIC was not provided. The reporter stated that there is no reasonable possibility that the events of FEELING WEAKER, FATIGUE and HAIR LOSS are related to ANDROGEL(TESTOSTERONE).

Causality for SYNTHROID(LEVOTHYROXINE)

The reporter stated that there is no reasonable possibility that the events of SUICIDAL THOUGHTS, DEPRESSION and SADNESS are related to SYNTHROID(LEVOTHYROXINE). The reporter stated that there is a reasonable possibility that the events of FEELING WEAKER, FATIGUE and HAIR LOSS are related to SYNTHROID(LEVOTHYROXINE). The reporter's statement of causality for the event of FRANTIC was not provided.

Relevant Medical History:

The patient reported the following: "When I went to my endrocronoligst about 6 years ago, he told me that there was a disease preventing ALL my hormone producing glands from working, and he had never seen that before! Obviously I was scared and terrified to die a slow death. I am 51 years old and my testosterone level should be at a minimum of 325-450, after my test, mine was at 20. My kidneys were shutting down and I had pitting edema all through my legs and body. Your medicine saved my life! BUT, since my health was bad, my company decided to fire me after 28 years of faithful and above average work and work ethics."

ADDISON'S DISEASE
KIDNEYS SHUTTING DOWN
PITTING EDEMA
HORMONE GLANDS NOT WORKING
CHEMICAL EXPOSURE

Disease/Surgical Procedure	Start Date	End Date	Continuing?	Comment
Addison's disease				
Chemical exposure				

Hormone level abnormal

Kidney failure

Pitting edema

Medical History Product(s)	Start Date	End Date	Indication(s)	MedDRA Preferred Term(s)

Relevant Laboratory Data:

Test Date	Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail Y/N
01-Jan-2008	Serum testosterone	20	NG/DL			N

Concomitant Products:

#	Product Name	Dose/Frequency	Route	Dosage Text	Indication(s)	Start Date	End Date	Interval 1st Dose to Event
1	UNKNOWN STEROIDS	/			Drug use for unknown indication			

Reporter Source:

Study Report:	Study Name:	Study Type:	Sponsor Study:	Protocol	IND #:
No					

Literature Text:

Country of Event: USA **Sender MFR:** ABBVIE

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FDA - Adverse Event Reporting System (FAERS)

Batch Printing Report for Cases

Reporter Name:	In confidence	**Reporter Type:**	
Reporter Org.:		**Reporter Email:**	
Reporter Street:		**Reporter Phone:**	
Reporter City:		**Reporter State:**	
Reporter Zip:		**Reporter Country:**	UNITED STATES
Health Prof.:		**Sent To:**	
Occupation:	CONSUMER OR OTHER NON HEALTH PROFESSIONAL	**Identity Disclosed:**	

***Age in Years displays a mid-value where the Age Unit in the report is in DECADE**

FDA - Adverse Event Reporting System (FAERS)

Batch Printing Report for Cases

Case Information:

Case Id: 10497771 **Version:** 1 **Case Type:** 15-DAY **eSub:** Yes **HP:** **Country:** USA **Outcome(s):** OT,

FDA Rcvd. Date: 06-Oct-2014 **Init FDA Rcvd. Date:** 06-Oct-2014 **Mfr Rcvd. Date:** 30-Sep-2014 **Application Type:** ANDA **Application #:** 085635

Mfr. Control #: US-PFIZER INC-2014271832

Patient Information:

Patient ID: PRIVACY **Age:** **Age in Years:** **Sex:** Male **Weight:** **DoB:**

Suspect Products:

#	Product Name	Dose/Frequency	Route	Dosage Text	Indication(s)	Start Date	End Date	Interval 1st Dose to Event	ReC	DeC
1	Depo-Testosterone	/		UNK			Aug-2014		NA	NA

#	Product Name	Lot#	Exp Date	NDC #	Labeler	OTC
1	Depo-Testosterone				PFIZER	

Event Information:

MedDRA © PreferredTerm	Start Date	End Date	Outcomes	Highlighted Terms	ReC
Depressed Mood			UNKNOWN		NA
Irritability			UNKNOWN		NA
Suicidal Ideation			UNKNOWN		NA
Weight Increased			UNKNOWN		NA

Event/Problem Narrative:

This is a spontaneous report from Non-Clinical Study Program "Pfizer RXPathways" received by a contactable consumer. A male patient of an unspecified age and ethnicity started to receive testosterone cipionate (DEPO-TESTOSTERONE), at unknown dose and frequency and for an unspecified indication. Relevant medical history included disability from an unknown date. Concomitant medications were unknown. It was reported that the patient was feeling irritable, gaining weight, feeling low and almost suicidal after he stopped taking testosterone cipionate because he no longer had his medication as he ran out of it in Aug2014 (he could not afford it). The outcome of the events was unknown.

Relevant Medical History:

***Age in Years displays a mid-value where the Age Unit in the report is in DECADE**

FDA - Adverse Event Reporting System (FAERS)

Batch Printing Report for Cases

Disease/Surgical Procedure	Start Date	End Date	Continuing?	Comment
Disability				

Medical History Product(s)	Start Date	End Date	Indication(s)	MedDRA Preferred Term(s)

Relevant Laboratory Data:

Test Date	Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail Y/N

Concomitant Products:

#	Product Name	Dose/Frequency	Route	Dosage Text	Indication(s)	Start Date	End Date	Interval 1st Dose to Event

Reporter Source:

Study Report:	Study Name:	Study Type:	Sponsor Study:	Protocol	IND #:
No					

Literature Text:

Country of Event: USA **Sender MFR:** PFIZER

Reporter Name: PRIVACY
Reporter Org.:
Reporter Street:
Reporter City:
Reporter Zip:
Health Prof.:
Occupation: CONSUMER OR OTHER NON HEALTH PROFESSIONAL

Reporter Type:
Reporter Email:
Reporter Phone:
Reporter State:
Reporter Country: UNITED STATES
Sent To:
Identity Disclosed:

***Age in Years displays a mid-value where the Age Unit in the report is in DECADE**

FDA - Adverse Event Reporting System (FAERS)

Batch Printing Report for Cases

Case Information:

Case Id: 10507806 **Version:** 1 **Case Type:** 15-DAY **eSub:** Yes **HP:** **Country:** USA **Outcome(s):** OT,

FDA Rcvd. Date: 09-Oct-2014 **Init FDA Rcvd. Date:** 09-Oct-2014 **Mfr Rcvd. Date:** 02-Oct-2014 **Application Type:** NDA **Application #:** 021015

Mfr. Control #: US-ABBVIE-14P-163-1291127-00

Patient Information:

Patient ID: (b) (6) **Age:** **Age in Years:** **Sex:** Male **Weight:** **DoB:** (b) (6)

Suspect Products:

#	Product Name	Dose/Frequency	Route	Dosage Text	Indication(s)	Start Date	End Date	Interval 1st Dose to Event	ReC	DeC
1	ANDROGEL	/	TOP	Two 5 gram packet daily	Drug use for unknown indication				NA	Unk

#	Product Name	Lot#	Exp Date	NDC #	Labeler	OTC
1	ANDROGEL	unknown				

Event Information:

MedDRA © PreferredTerm	Start Date	End Date	Outcomes	Highlighted Terms	ReC
Suicidal Ideation			NOT RECOVERED/ NOT RESOLVED	N	NA

Event/Problem Narrative:

Spontaneous report from the USA by a consumer of a male with an event of SUICIDAL IDEATION with ANDROGEL (TESTOSTERONE). The patient had a relevant medical history of ANXIETY and DEPRESSION.

On an unknown date, the patient experienced SUICIDAL IDEATION. The patient recently was not approved for coverage with the Patient assistance program for his ANDROGEL. The patient stated that if he was without his ANDROGEL he would be suicidal. The patient gave no further information. The primary reporter does not have the lot number information, because the primary reporter declined to report the lot number.

The patient's past medications include:
DILALUDID for UNKNOWN INDICATION

Causality for ANDROGEL(TESTOSTERONE)

The reporter stated that there is a reasonable possibility that the event of SUICIDAL IDEATION is related to

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ANDROGEL(TESTOSTERONE).

Relevant Medical History:

HIGH BLOOD PRESSURE
HIGH CHOLESTEROL
ANXIETY
DEPRESSION
ALLERGY INDUCE ASTHMA
DRUG ALLERGY DILAUDID

Disease/Surgical Procedure	Start Date	End Date	Continuing?	Comment
Allergic asthma				
Anxiety				
Blood pressure high				
Depression				
Drug allergy				
High cholesterol				

Medical History Product(s)	Start Date	End Date	Indication(s)	MedDRA Preferred Term(s)
DILAUDID			Drug use for unknown indication	

Relevant Laboratory Data:

Test Date	Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail Y/N

Concomitant Products:

#	Product Name	Dose/Frequency	Route	Dosage Text	Indication(s)	Start Date	End Date	Interval 1st Dose to Event
1	MONTELUKAST	/			Drug use for unknown indication			
2	BUPROPION	/			Drug use for unknown indication			

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	Product Name	Dose/Frequency	Route	Dosage Text	Indication(s)	Start Date	End Date	Interval 1st Dose to Event
3	CLONAZEPAM	/			Drug use for unknown indication			
4	AZELASTINE	/			Drug use for unknown indication			
5	NITROFURANTOIN	/			Drug use for unknown indication			
6	DOXAZOSIN	/			Drug use for unknown indication			
7	SIMVASTATIN	/			Drug use for unknown indication			
8	CARVEDILOL	/			Drug use for unknown indication			
9	OMEPRAZOLE	/			Drug use for unknown indication			
10	FLUTICASONE	/			Drug use for unknown indication			
11	LISINOPRIL	/			Drug use for unknown indication			

Reporter Source:

Study Report:	Study Name:	Study Type:	Sponsor Study:	Protocol	IND #:
No					

Literature Text:

Country of Event: USA **Sender MFR:** ABBVIE

***Age in Years displays a mid-value where the Age Unit in the report is in DECADE**

FDA - Adverse Event Reporting System (FAERS)

Batch Printing Report for Cases

Reporter Name:	In Confidence	**Reporter Type:**	
Reporter Org.:		**Reporter Email:**	
Reporter Street:		**Reporter Phone:**	
Reporter City:		**Reporter State:**	
Reporter Zip:		**Reporter Country:**	UNITED STATES
Health Prof.:		**Sent To:**	
Occupation:	CONSUMER OR OTHER NON HEALTH PROFESSIONAL	**Identity Disclosed:**	

***Age in Years displays a mid-value where the Age Unit in the report is in DECADE**

FDA - Adverse Event Reporting System (FAERS)

Batch Printing Report for Cases

Case Information:

Case Id: 10545194 **Version:** 1 **Case Type:** 15-DAY **eSub:** Yes **HP:** **Country:** USA **Outcome(s):** OT,

FDA Rcvd. Date: 27-Oct-2014 **Init FDA Rcvd. Date:** 27-Oct-2014 **Mfr Rcvd. Date:** 15-Oct-2014 **Application Type:** NDA **Application #:** 022504

Mfr. Control #: US-ELI_LILLY_AND_COMPANY-US201410006180

Patient Information:

Patient ID: UNK **Age:** **Age in Years:** **Sex:** Male **Weight:** **DoB:**

Suspect Products:

#	Product Name	Dose/Frequency	Route	Dosage Text	Indication(s)	Start Date	End Date	Interval 1st Dose to Event	ReC	DeC
1	Axiron	60 MG/QD	UNK	60 mg, qd	Hypogonadism	30-Sep-2014	14-Oct-2014	1 Day	Unk	NA

#	Product Name	Lot#	Exp Date	NDC #	Labeler	OTC
1	Axiron				ELI LILLY AND CO	

Event Information:

MedDRA © PreferredTerm	Start Date	End Date	Outcomes	Highlighted Terms	ReC
Depression	30-Sep-2014		UNKNOWN	N	NA
Suicidal Ideation	30-Sep-2014		UNKNOWN	N	NA

Event/Problem Narrative:

This spontaneous case was reported by a physician via a sales representative and concerns a Caucasian male in his 30s.

Medical history was not provided. He was not on any concomitant medications.

Patient started testosterone solution two percent (Axiron) 60 mg daily, via disposable pump and applicator on 30Sep2014 for treatment of hypogonadism. Route not provided. On 30Sep2014, the day that he started testosterone therapy, (conflicting information was also reported as after being on testosterone therapy for two weeks), he complained of being really depressed and had not felt like leaving the house. He was also having suicidal thoughts. The events of depression and suicidal thoughts were considered medically significant by the company. Information regarding corrective treatment was not provided. The physician had the patient discontinue the testosterone solution on 14Oct2014 and referred him to a psychiatrist. Event outcomes were unknown.

The reporting physician did not relate the events to the testosterone solution.

***Age in Years displays a mid-value where the Age Unit in the report is in DECADE**

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?	Comment

Medical History Product(s)	Start Date	End Date	Indication(s)	MedDRA Preferred Term(s)

Relevant Laboratory Data:

Test Date	Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail Y/N

Concomitant Products:

#	Product Name	Dose/Frequency	Route	Dosage Text	Indication(s)	Start Date	End Date	Interval 1st Dose to Event

Reporter Source:

Study Report:	Study Name:	Study Type:	Sponsor Study:	Protocol	IND #:
No					

Literature Text:

Country of Event: USA **Sender MFR:** ELI LILLY AND CO

***Age in Years displays a mid-value where the Age Unit in the report is in DECADE**

FDA - Adverse Event Reporting System (FAERS)

Batch Printing Report for Cases

Reporter Name:	(b) (6)	**Reporter Type:**	
Reporter Org.:		**Reporter Email:**	
Reporter Street:		**Reporter Phone:**	
Reporter City:		**Reporter State:**	(b) (6)
Reporter Zip:		**Reporter Country:**	UNITED STATES
Health Prof.:		**Sent To:**	
Occupation:	PHYSICIAN	**Identity Disclosed:**	

Reporter Name:	(b) (6)	**Reporter Type:**	
Reporter Org.:		**Reporter Email:**	
Reporter Street:	(b) (6)	**Reporter Phone:**	
Reporter City:		**Reporter State:**	
Reporter Zip:		**Reporter Country:**	UNITED STATES
Health Prof.:		**Sent To:**	
Occupation:	CONSUMER OR OTHER NON HEALTH PROFESSIONAL	**Identity Disclosed:**	

***Age in Years displays a mid-value where the Age Unit in the report is in DECADE**

FDA - Adverse Event Reporting System (FAERS)

Batch Printing Report for Cases

Case Information:

Case Id: 10555750 **Version:** 2 **Case Type:** 15-DAY **eSub:** Yes **HP:** **Country:** CAN **Outcome(s):** OT,

FDA Rcvd. Date: 24-Nov-2014 **Init FDA Rcvd. Date:** 30-Oct-2014 **Mfr Rcvd. Date:** 12-Nov-2014 **Application Type:** NDA **Application #:** 021015

Mfr. Control #: CA-ABBVIE-14P-028-1302179-00

Patient Information:

Patient ID: (b) (6) **Age:** 63. (b) (6) YR **Age in Years:** 63. (b) (6) YR **Sex:** Male **Weight:** **DoB:** (b) (6)

Suspect Products:

#	Product Name	Dose/Frequency	Route	Dosage Text	Indication(s)	Start Date	End Date	Interval 1st Dose to Event	ReC	DeC
1	ANDROGEL	5 G/QD	TOP		Serum testosterone decreased	15-Sep-2014	07-Oct-2014		NA	Yes
2	ANDROGEL	/			Energy decreased				NA	Yes
3	ANDROGEL	/			Libido decreased				NA	Yes

#	Product Name	Lot#	Exp Date	NDC #	Labeler	OTC
1	ANDROGEL	UNKNOWN				
2	ANDROGEL	UNKNOWN				
3	ANDROGEL	UNKNOWN				

Event Information:

MedDRA © PreferredTerm	Start Date	End Date	Outcomes	Highlighted Terms	ReC
Depression	01-Sep-2014	01-Oct-2014	RECOVERED/ RESOLVED	N	NA
Suicidal Ideation	15-Sep-2014	22-Oct-2014	RECOVERED/ RESOLVED	N	NA

Event/Problem Narrative:

This case was received from ABBOTT on 21 NOV 2014 (Ref. number CA-ABBOTT-14X-028-1195412-00) Spontaneous report from CANADA by a physician of a 63 year old male with events of SUICIDAL IDEATION and DEPRESSION WORSENED/EXACERBATION OF DEPRESSION with ANDROGEL (TESTOSTERONE). This case was received from Physician via company representative. The patient had a relevant medical history of DECREASED ENERGY, DECREASED LIBIDO, SLEEP APNEA, WEIGHT GAIN, DEPRESSION and TYPE 2 DIABETES MELLITUS.

***Age in Years displays a mid-value where the Age Unit in the report is in DECADE**

On an unknown date, the patient started treatment with ANDROGEL (TESTOSTERONE). Concomitant medications were not reported. The patient's depression worsened and he became suicidal. In September 2014, the patient experienced DEPRESSION WORSENED/EXACERBATION OF DEPRESSION. On 15 Sep 2014, the patient experienced SUICIDAL IDEATION. On an unknown date, treatment with the suspect drug ANDROGEL (TESTOSTERONE) was discontinued and patient felt much better.
The reporter causality for the events SUICIDALIDEATION and DEPRESSION WORSENED was not provided.

This case was serious (other medically important).

This case was reported as non-serious; however it was upgraded to serious by Abbott after internal medical case review due to Abbotts List of Adverse Event/Reaction Terms to be considered always SERIOUS where the event SUICIDAL IDEATION is listed.

Follow up information was received on 12 Nov 2014 from physician.

The patient demographic details were updated. The physician specified that in Jul 2014 patient had weight gain, sleep apnea, type 2 Diabetes Mellitus (for years), decreased energy and decreased libido. Blood work showed very low testosterone level. They decided to start ANDROGEL (TESTOSTERONE) for a trial period. The patient started ANDROGEL (TESTOSTERONE) on 15 Sep 2014 at 5 gram once daily topically (lot number and expiration date unknown) for DECREASED SERUM TESTOSTERONE, ENERGY & LIBIDO, but within two weeks he was feeling very depressed with suicidal ideation. In September 2014, the patient experienced DEPRESSION WORSENED/EXACERBATION OF DEPRESSION. On 15 Sep 2014, the patient experienced SUICIDAL IDEATION. Concomitant medications included Metformin (oral, 500 mg thrice a day) for Type 2 diabetes and Effexor (oral, unit dose 37.5mg) for depression. He stopped the ANDROGEL (TESTOSTERONE) on 07 Oct 2014 and the depression started to clear. He did not see the physician until 22 Oct 2014 at what point he was feeling much better. The physician reported that depression and suicidal ideation settled within two weeks of stopping ANDROGEL (TESTOSTERONE).

No hospitalization or treatment needed. Final diagnosis was exacerbation of depression secondary to testosterone treatment. No laboratory or diagnostic tests performed. On 22 Oct 2014, the SUICIDAL IDEATION resolved. In October 2014, the DEPRESSION WORSENED/EXACERBATION OF DEPRESSION resolved. The reporter's causality for the events Suicidal ideation and Depression worsened/Exacerbation of depression with ANDROGEL (TESTOSTERONE) was probable.

Depression worsened/Exacerbation of depression was reported non serious, however it was upgraded to serious by Abbott after internal medical case review due to Abbotts List of Adverse Event/Reaction Terms to be considered always SERIOUS where the event Depression (diagnosed by specialist and treated) is listed.

Change History

On 12 Nov 2014, received updates to patient demographics, medical history, event information, reporter opinion of causality, suspect drug information, concomitant drug information and narrative description. The serious event of "SUICIDAL IDEATION" was added. The event of "SUICIDAL IDEATION" was amended to "DEPRESSION WORSENED/EXACERBATION OF DEPRESSION".

Relevant Medical History:

No laboratory or diagnostic tests performed.

NO KNOWN ALLERGIES

DECREASED ENERGY (Started July 2014)
DECREASED LIBIDO (Started July 2014)
SLEEP APNEA (Started July 2014)
WEIGHT GAIN (Started July 2014)
DEPRESSION
TYPE 2 DIABETES MELLITUS
NON TOBACCO USER
ABSTAINS FROM ALCOHOL

Disease/Surgical Procedure	Start Date	End Date	Continuing?	Comment
Energy decreased	Jul-2014			
Libido decreased	Jul-2014			
Sleep apnea	Jul-2014			
Weight gain	Jul-2014			
Abstains from alcohol				
Depression				
Non-smoker				
Type 2 diabetes mellitus				

Medical History Product(s)	Start Date	End Date	Indication(s)	MedDRA Preferred Term(s)

Relevant Laboratory Data:

Test Date	Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail Y/N

Concomitant Products:

#	Product Name	Dose/Frequency	Route	Dosage Text	Indication(s)	Start Date	End Date	Interval 1st Dose to Event
1	METFORMIN	500 MG/TID	PO		Type 2 diabetes mellitus			
2	EFFEXOR	37.5 MG/	PO		Depression			

Reporter Source:

Study Report:	Study Name:	Study Type:	Sponsor Study:	Protocol	IND #:
No					

Literature Text:

Country of Event: CAN **Sender MFR:** ABBVIE

Reporter Name: In Confidence
Reporter Org.:
Reporter Street:
Reporter City:
Reporter Zip:
Health Prof.:
Occupation: PHYSICIAN

Reporter Type:
Reporter Email:
Reporter Phone:
Reporter State:
Reporter Country: CANADA
Sent To:
Identity Disclosed:

***Age in Years displays a mid-value where the Age Unit in the report is in DECADE**

FDA - Adverse Event Reporting System (FAERS)

Batch Printing Report for Cases

Case Information:

Case Id: 10557923 **Version:** 1 **Case Type:** 15-DAY **eSub:** Yes **HP:** **Country:** USA **Outcome(s):** DE,

FDA Rcvd. Date: 31-Oct-2014 **Init FDA Rcvd. Date:** 31-Oct-2014 **Mfr Rcvd. Date:** 17-Oct-2014 **Application Type:** ANDA **Application #:** 086030

Mfr. Control #: US-WATSON-2014-23073

Patient Information:

Patient ID: (b) (6) **Age:** 47. (b) (6) YR **Age in Years:** 47. (b) (6) YR **Sex:** Male **Weight:** 82 KG **DoB:** (b) (6)

Suspect Products:

#	Product Name	Dose/Frequency	Route	Dosage Text	Indication(s)	Start Date	End Date	Interval 1st Dose to Event	ReC	DeC
1	Testosterone Cypionate (Watson Laboratories)	1 ML/	IM	200 mg/ml 1 ml every 3 days	Blood testosterone decreased		15-Apr-2014		NA	NA

#	Product Name	Lot#	Exp Date	NDC #	Labeler	OTC
1	Testosterone Cypionate (Watson Laboratories)	Unknown			WATSON	

Event Information:

MedDRA © PreferredTerm	Start Date	End Date	Outcomes	Highlighted Terms	ReC
Anxiety	01-Dec-2013		FATAL		NA
Depression	01-Dec-2013		FATAL		NA
Completed Suicide	(b) (6)		FATAL		NA

Event/Problem Narrative:

Date of initial report: 17-OCT-2014 00:00:00

This initial report was received from a wife of a 47 years male patient (Patient Initials (b) (6)) who committed a Suicide on (b) (6) (b) (6) and was experiencing from Depression and Anxiety since DEC-2013 after using Testosterone Cypionate 200mg/ml 1 ml intramuscular injection every three days for low testosterone starting from unknown period of time. Reporter provided the NDC 0591-3223-79.

Patient's medical history includes Low testosterone and Bipolar disorder. Patient's concomitant medications included Unspecified Insulin unknown dose, Progesterone 50/75 mg cream, Liothyronine 25 mg three times a day orally, Alprazolam 1 mg, Paroxetine 25 mg, Dextroamphetamine salt 20 mg, Avodart 0.5 mg, Cialis 10 mg and Lamotrigine 150 mg for unknown indication from unknown period of time.

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Reported outcome for the events Depression and Anxiety was fatal. It was not reported if autopsy was performed. No other information was provided.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?	Comment
Bipolar disorder				
Blood testosterone decreased				

Medical History Product(s)	Start Date	End Date	Indication(s)	MedDRA Preferred Term(s)

Relevant Laboratory Data:

Test Date	Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail Y/N

Concomitant Products:

#	Product Name	Dose/Frequency	Route	Dosage Text	Indication(s)	Start Date	End Date	Interval 1st Dose to Event
1	PROGESTERONE	/	UNK	50/75 mg	Product used for unknown indication			
2	DEXTROAMPHETAMINE /00016601/	20 MG/		20 mg, UNK	Product used for unknown indication			
3	ALPRAZOLAM	1 MG/	UNK	1 mg, UNK	Product used for unknown indication			
4	CIALIS	10 MG/	UNK	10 mg, unknown	Product used for unknown indication			
5	INSULIN	/	UNK		Product used for unknown indication			
6	AVODART	.5 MG/	UNK	0.5 mg, UNK	Product used for unknown indication			
7	LIOTHYRONINE	/TID	PO	25 mcg, tid	Product used for unknown indication			

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	Product Name	Dose/Frequency	Route	Dosage Text	Indication(s)	Start Date	End Date	Interval 1st Dose to Event
8	PAROXETINE ER	25 MG/	UNK	25 mg, UNK	Product used for unknown indication			
9	LAMOTRIGINE	150 MG/	UNK	150 mg, unknown	Product used for unknown indication			

Reporter Source:

Study Report:	Study Name:	Study Type:	Sponsor Study:	Protocol	IND #:
No					

Literature Text:

Country of Event: USA **Sender MFR:** WATSON

Reporter Name: (b) (6)
Reporter Org.:
Reporter Street:
Reporter City:
Reporter Zip:

Reporter Type:
Reporter Email:
Reporter Phone:
Reporter State: (b) (6)
Reporter Country: UNITED STATES

Health Prof.:
Occupation: CONSUMER OR OTHER NON HEALTH PROFESSIONAL

Sent To:
Identity Disclosed:

***Age in Years displays a mid-value where the Age Unit in the report is in DECADE**

FDA - Adverse Event Reporting System (FAERS)

Batch Printing Report for Cases

Case Information:

Case Id: 10996878 **Version:** 1 **Case Type:** 15-DAY **eSub:** Yes **HP:** **Country:** CAN **Outcome(s):** HO,OT,

FDA Rcvd. Date: 08-Apr-2015 **Init FDA Rcvd. Date:** 08-Apr-2015 **Mfr Rcvd. Date:** 30-Mar-2015 **Application Type:** NDA **Application #:** 021121

Mfr. Control #: CA-JNJFOC-20150400972

Patient Information:

Patient ID: Private **Age:** 14 YR **Age in Years:** 14 YR **Sex:** Male **Weight:** KG **DoB:**

Suspect Products:

#	Product Name	Dose/Frequency	Route	Dosage Text	Indication(s)	Start Date	End Date	Interval 1st Dose to Event	ReC	DeC
1	CONCERTA	54 MG/QD	PO		Attention deficit/hyperactivity disorder				Unk	Unk
2	TESTOSTERONE	/	IM		Growth retardation				NA	Unk
3	TESTOSTERONE	/	IM		Delayed puberty				NA	Unk

#	Product Name	Lot#	Exp Date	NDC #	Labeler	OTC
1	CONCERTA					
2	TESTOSTERONE					
3	TESTOSTERONE					

Event Information:

MedDRA © PreferredTerm	Start Date	End Date	Outcomes	Highlighted Terms	ReC
Depression			UNKNOWN	Y	NA
Suicide Attempt			UNKNOWN	Y	NA

Event/Problem Narrative:

This spontaneous report was received from other health professional, via a regulatory authority (Janssen Inc., Canada - 000366210), and concerns a 14-year-old male patient from Canada: Local case ID: JAOCAN2015008551.

The patient's height was 153 centimeters and weight was 80 pounds. The patient's concurrent condition included attention deficit/hyperactivity disorder (sub-type unspecified), growth retardation and delayed puberty. The patient was treated with

***Age in Years displays a mid-value where the Age Unit in the report is in DECADE**

OROS methylphenidate hydrochloride (sustained release tablets, oral) 54 mg once a day, initiated on an unspecified date for attention deficit/hyperactivity disorder. Non-company suspect drug included testosterone (unspecified formulation, intramuscular) at an unspecified dose, once a month, initiated on an unspecified date for growth retardation and delayed puberty. Concomitant medications were not reported. On an unspecified date, the patient experienced depression and had a suicide attempt. Action taken with OROS methylphenidate hydrochloride and testosterone was not reported. The patient's outcome was not reported for the events depression and suicide attempt at the time of this report.

This report was serious (hospitalization, medically significant).

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?	Comment
Attention deficit/hyperactivity disorder				ADHD (sub-type unspecified)
Delayed puberty			UNKNOWN	
Growth retardation			UNKNOWN	

Medical History Product(s)	Start Date	End Date	Indication(s)	MedDRA Preferred Term(s)

Relevant Laboratory Data:

Test Date	Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail Y/N

Concomitant Products:

#	Product Name	Dose/Frequency	Route	Dosage Text	Indication(s)	Start Date	End Date	Interval 1st Dose to Event

Reporter Source:

Study Report:	Study Name:	Study Type:	Sponsor Study:	Protocol	IND #:
No					

***Age in Years displays a mid-value where the Age Unit in the report is in DECADE**

Literature Text:

Country of Event: CAN

Sender MFR: JANSSEN

Reporter Name: Private Private Private

Reporter Org.:

Reporter Street: Private

Reporter City: Private

Reporter Zip: Private

Health Prof.:

Occupation:

Reporter Type:

Reporter Email:

Reporter Phone:

Reporter State:

Reporter Country: CANADA

Sent To:

Identity Disclosed:

***Age in Years displays a mid-value where the Age Unit in the report is in DECADE**

FDA - Adverse Event Reporting System (FAERS)

Batch Printing Report for Cases

Case Information:

Case Id: 11083034 **Version:** 1 **Case Type:** PERIODIC **eSub:** Yes **HP:** **Country:** USA **Outcome(s):**

FDA Rcvd. Date: 01-May-2015 **Init FDA Rcvd. Date:** 01-May-2015 **Mfr Rcvd. Date:** 18-Nov-2014 **Application Type:** NDA **Application #:** 022309

Mfr. Control #: US-ABBVIE-14P-163-1309900-00

Patient Information:

Patient ID: (b) (6) **Age:** 70 YR **Age in Years:** 70 YR **Sex:** Male **Weight:** KG **DoB:**

Suspect Products:

#	Product Name	Dose/Frequency	Route	Dosage Text	Indication(s)	Start Date	End Date	Interval 1st Dose to Event	ReC	DeC
1	ANDROGEL	/	UNK			2012	2014		NA	Yes
2	ANDROGEL	/	UNK	4 pumps	Testosterone low	2012			NA	Yes
3	ANDROGEL	/	UNK			2012	2014		NA	Yes
4	ANDROGEL	/	UNK		Testosterone low	2010	2012		NA	Yes

#	Product Name	Lot#	Exp Date	NDC #	Labeler	OTC
1	ANDROGEL	unknown				
2	ANDROGEL	unknown				
3	ANDROGEL	unknown				
4	ANDROGEL	unknown				

Event Information:

MedDRA © PreferredTerm	Start Date	End Date	Outcomes	Highlighted Terms	ReC
Asthenia	01-Jan-2012	01-Jan-2012	RECOVERED/ RESOLVED	N	NA
Blood Glucose Increased	01-Jan-2012	01-Jan-2012	RECOVERED/ RESOLVED	N	NA
Blood Testosterone Decreased	01-Jan-2012	01-Jan-2012	RECOVERED/ RESOLVED	N	NA
Depression	01-Jan-2012	01-Jan-2012	RECOVERED/ RESOLVED	N	NA
Drug Ineffective	01-Jan-2012	01-Jan-2012	RECOVERED/ RESOLVED	N	NA

***Age in Years displays a mid-value where the Age Unit in the report is in DECADE**

MedDRA © PreferredTerm	Start Date	End Date	Outcomes	Highlighted Terms	ReC
Suicidal Ideation	01-Jan-2012		UNKNOWN	N	NA

Event/Problem Narrative:

Spontaneous report from the USA by a consumer of a 70 year old male with events of non-serious SUICIDAL IDEATION, MEDICATION DIDN'T WORK WELL, ELEVATED FASTING BLOOD SUGARS, ENERGY LEVEL LOW, DEPRESSED and TESTOSTERONE LEVEL LOW with ANDROGEL (TESTOSTERONE) and ANDROGEL (TESTOSTERONE).

In 2012, the patient experienced SUICIDAL IDEATION, MEDICATION DIDN'T WORK WELL, ELEVATED FASTING BLOOD SUGARS, ENERGY LEVEL LOW, DEPRESSED and TESTOSTERONE LEVEL LOW. The reporter stated with the patient was on ANDROGEL 1.62% he reported that the medication didn't work well, he had elevated fasting blood sugars, low energy level, he was depressed and wanted to kill himself but made no attempt and his testosterone level was low. The reporter did not have any dates or test results available. The reporter stated that after the patient came off of the ANDROGEL 1.62% his testosterone level had come up and the reported events resolved. The primary reporter had to get off the phone and was unable to provide further information. The primary reporter does not have the lot number information because: it was not available from the patient. The Primary reporter did not have alcohol, tobacco, medical history, allergy or list of concomitant medications available. In 2012, the MEDICATION DIDN'T WORK WELL, ELEVATED FASTING BLOOD SUGARS, ENERGY LEVEL LOW, DEPRESSED and TESTOSTERONE LEVEL LOW resolved.

Causality for ANDROGEL(TESTOSTERONE)

The reporter stated that there is a reasonable possibility that the events of SUICIDAL IDEATION, MEDICATION DIDN'T WORK WELL, ELEVATED FASTING BLOOD SUGARS, ENERGY LEVEL LOW, DEPRESSED and TESTOSTERONE LEVEL LOW are related to ANDROGEL(TESTOSTERONE).

Causality for ANDROGEL(TESTOSTERONE)

The reporter stated that there is a reasonable possibility that the events of SUICIDAL IDEATION, MEDICATION DIDN'T WORK WELL, ELEVATED FASTING BLOOD SUGARS, ENERGY LEVEL LOW, DEPRESSED and TESTOSTERONE LEVEL LOW are related to ANDROGEL(TESTOSTERONE). The reporter's statement of causality for the events of SUICIDAL IDEATION, MEDICATION DIDN'T WORK WELL, ELEVATED FASTING BLOOD SUGARS, ENERGY LEVEL LOW, DEPRESSED and TESTOSTERONE LEVEL LOW was not provided.

Relevant Laboratory & Other Diagnostic Tests

2012 fasting blood sugars: upper 100-200

Change History

On 16 Dec 2014, received updates to event information, reporter opinion of causality, suspect drug information, concomitant drug information and narrative description.

Relevant Medical History:
DEPRESSION
DIABETES

Disease/Surgical Procedure	Start Date	End Date	Continuing?	Comment
Depression				
Diabetes				

Medical History Product(s)	Start Date	End Date	Indication(s)	MedDRA Preferred Term(s)

Relevant Laboratory Data:

Test Date	Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail Y/N
01-Jan-2012	Fasting blood glucose	upper 100-200				N

Concomitant Products:

#	Product Name	Dose/Frequency	Route	Dosage Text	Indication(s)	Start Date	End Date	Interval 1st Dose to Event
1	INSULIN	/	UNK		Drug use for unknown indication			

Reporter Source:

Study Report:	Study Name:	Study Type:	Sponsor Study:	Protocol	IND #:
No					

Literature Text:

Country of Event: USA **Sender MFR:** ABBVIE

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FDA - Adverse Event Reporting System (FAERS)

Batch Printing Report for Cases

Reporter Name:	In Confidence	**Reporter Type:**	
Reporter Org.:		**Reporter Email:**	
Reporter Street:		**Reporter Phone:**	
Reporter City:		**Reporter State:**	
Reporter Zip:		**Reporter Country:**	UNITED STATES
Health Prof.:		**Sent To:**	
Occupation:	CONSUMER OR OTHER NON HEALTH PROFESSIONAL	**Identity Disclosed:**	

***Age in Years displays a mid-value where the Age Unit in the report is in DECADE**

FDA - Adverse Event Reporting System (FAERS)

Batch Printing Report for Cases

Case Information:

Case Id: 11130269 **Version:** 2 **Case Type:** 15-DAY **eSub:** Yes **HP:** **Country:** USA **Outcome(s):** HO,OT,

FDA Rcvd. Date: 13-Aug-2015 **Init FDA Rcvd. Date:** 22-May-2015 **Mfr Rcvd. Date:** 05-Aug-2015 **Application Type:** NDA **Application #:** 022309

Mfr. Control #: US-ABBVIE-15P-163-1393742-00

Patient Information:

Patient ID: (b) (6) **Age:** **Age in Years:** **Sex:** Male **Weight:** 83.99 KG **DoB:**

Suspect Products:

#	Product Name	Dose/Frequency	Route	Dosage Text	Indication(s)	Start Date	End Date	Interval 1st Dose to Event	ReC	DeC
1	ANDROGEL	/QD	TOP		Androgen replacement therapy	18-Oct-2012	Mar-2013	407 Day	NA	NA
2	DEPO-TESTOSTERONE	/	IM		Androgen replacement therapy	Mar-2012	Aug-2012		NA	NA

#	Product Name	Lot#	Exp Date	NDC #	Labeler	OTC
1	ANDROGEL	UNKNOWN				
2	DEPO-TESTOSTERONE	G00497,OBXU3,O3XTP,OBYWA,0B0AX,F215				

Event Information:

MedDRA © PreferredTerm	Start Date	End Date	Outcomes	Highlighted Terms	ReC
Ischaemic Stroke	(b) (6)		UNKNOWN	N	NA
Weight Decreased	27-Feb-2013		UNKNOWN	N	NA
Affective Disorder	11-Mar-2013		UNKNOWN	N	NA
Anxiety Disorder	11-Mar-2013		UNKNOWN	N	NA
Decreased Appetite	06-May-2013		UNKNOWN	N	NA
Depression	06-May-2013		UNKNOWN	N	NA
Suicidal Behaviour	29-Nov-2013		UNKNOWN	N	NA
Constipation	(b) (6)		UNKNOWN	N	NA
Haematuria	(b) (6)		UNKNOWN	N	NA

***Age in Years displays a mid-value where the Age Unit in the report is in DECADE**

MedDRA © PreferredTerm	Start Date	End Date	Outcomes	Highlighted Terms	ReC
Partner Stress	(b) (6)		UNKNOWN	N	NA
Personality Disorder	(b) (6)		UNKNOWN	N	NA
Antisocial Personality Disorder	(b) (6)		UNKNOWN	N	NA

Event/Problem Narrative:

Spontaneous report from the USA by a lawyer of a male with events of SUICIDAL BEHAVIOR, RECURRENT RIGHT ISCHEMIC STROKE WITH WORSENING LEFT ARM HEMIPARESIS, ANTISOCIAL PERSONALITY DISORDER and CLUSTER B PERSONALITY DISORDER and non-serious PARTNER RELATIONAL PROBLEMS, FRANK HEMATURIA, CONSTIPATION, DEPRESSION, ANOREXIA, MOOD DISORDER, ANXIETY DISORDER and LOSS OF WEIGHT with ANDROGEL (TESTOSTERONE).

On 04 Nov 2012, the patient experienced RECURRENT RIGHT ISCHEMIC STROKE WITH WORSENING LEFT ARM HEMIPARESIS. The patient suffered two strokes while on testosterone therapy. The first stroke was on (b) (6) while taking DEPO-TESTOSTERONE (TESTOSTERONE CIPIONATE). In (b) (6) the patient went to the emergency room because of weakness in his hand and arm. He was diagnosed with a right MCA ischemic CVA. He was hospitalized for treatment and rehabilitation for 30 days. On 18 Oct 2012, the patient began ANDROGEL (TESTOSTERONE). The second stroke occurred on (b) (6) and he was hospitalized for approximately six days. He lost the use of his left hand and arm. He had to use a wheelchair then a walker for a period of time after his stroke. His legs are getting weaker and he will eventually need a wheelchair all the time. On 27 Feb 2013, the patient experienced LOSS OF WEIGHT. On 11 Mar 2013, the patient experienced MOOD DISORDER and ANXIETY DISORDER. On 06 May 2013, the patient experienced DEPRESSION and ANOREXIA. On 29 Nov 2013, the patient experienced SUICIDAL BEHAVIOR. The patient was hospitalized from (b) (6) (b) (6) until (b) (6) for suicidal behavior. On (b) (6) the patient experienced CLUSTER B PERSONALITY DISORDER, PARTNER RELATIONAL PROBLEMS, FRANK HEMATURIA and CONSTIPATION. On (b) (6) the patient experienced ANTISOCIAL PERSONALITY DISORDER. No further information is available. DEPO-TESTOSTERONE (TESTOSTERONE CIPIONATE) was also considered suspect.

Discharge summary from hospitalization from (b) (6) until (b) (6) ADMISSION DX: Recurrent right side ischemic stroke. DISCHARGE DX: RECURRENT RIGHT ISCHEMIC STROKE WITH WORSENING LEFT ARM HEMIPARESIS. HOSPITALIZATION COURSE: Pt was transferred from other hospital on (b) (6) after admission on (b) (6) due to right ischemic stroke. 1. RIGHT ISCHEMIC STROKE: second within 3 months; evaluated by neurology who recommended Cardiology eval, Aggrenox bid, PT/OT, DVT prophylaxis, Ace inhibitor, statin; will cont. on aggrenox, PT/OT consulted and following; Neck CTA showed right carotid stenosis of just 40%. I discussed this finding over the phone with a vascular surgeon, who recommended no surgery at this point continue with medical treatment. Another physician, also from vascular surgery, re-evaluate this pt on (b) (6) who also agrees to continue with medical therapy and no endardectomy at this moment; pt was evaluated by physical therapy and occupational therapy; consulted PMR for inpt rehab but he was not

accepted; ordered home OT/PT 3 times a week for one month - needs f/up with PCP in 2 weeks. 2. DEPRESSION: pt was evaluated by psychiatry. They recommended continuing on sertraline 100mg po q daily and follow up in psychology clinic. HX OF HTN: his BP had been on the low side; on lisinopril 2.5mg po q daily. DVT PROPHY: on lovenox.

Discharge Summary for hospitalization from (b) (6) until (b) (6): DIAGNOSTIC IMPRESSION: DSM 5 criteria 1- Mood NOS (with high likelihood of either true suicide attempt v manipulative attempt v lesser possibility BZD abuse) 2- marital/family conflict (marriage previously noted irreparable; The patient claims it is "good", except conflict over porn and no sex) 3- r/o BZD abuse 4- ASPD by exam and hx, primary dx? (also noted to be unreliable reporter, NOT felt d/t cognitive concerns). SIGNIFICANT FINDINGS WHICH NEED FOLLOW-UP CARE: mood- this admission predominantly d/t chronic conflict with wife; recommend o/p SWer work with the patient to obtain separate housing to lessen his mood complaints. Sertraline increased for mood, temazepam replaced with Mirtazepine for sleep (PLEASE avoid controlled substance rx'ing given the known h/o polysubstance abuse). Prazosin started for off label nightmare reduction. Please monitor for surreptitious substance abuse with truly random UDS, GGT's. No outside rx's per pharm database check. Neurology consult felt no new cognitive decline, no significant changes rec by them, but monitor for further future cognitive decline, esp if substance abuse recurs. Medical- including pain. Recommend against opiate pain meds stronger than tramadol, caution about overuse risk/serotonin syndrome should be reinforced. The patient has had some low BP readings prior to Prazosin; pls continue to monitor this issue.
Initial psychiatry admit note: CHIEF COMPLAINT: "I didn't try to kill myself; it was simply by mistake I took too many sleeping pills". HISTORY OF PRESENTING PROBLEM: 56 MHM, 20%sc for back, with past MH dx's of anxiety, depression, adjustment d/o, admitted on B52 transfer from area hospital for OD. Transfer paperwork indicated '26' temazepam sleeping pills ingested in possible suicide attempt. However, in the interview today, the patient continues to deny emphatically any suicidal attempt or significant mood disruption. The patient states that unbeknownst to him his previous 15 mg (7.5mg x2) temazepam was increased to 30 mg, and that he mistakenly took 60 mg instead of his usual 15 mg the evening prior to admission. He says that he became very sedated, threw up, then went to bed, but threw out the rest of the bottle in the toilet b/c he didnt like the way it made him feel. When his wife found him next to an empty pill bottle, she tried to wake him, then she called (EMS) and he woke up in hospital, apparently with some time spent on a vent (basically again calling into question veracity of reporting; 60mg temazepam highly unlikely to have this type of result on a nightly BZD user). The patient says he cannot account for why '26' pills were listed on transfer paperwork, did give me permission to speak with his wife to obtain collateral info. On further inquiry, the patient denied any significant stressors, even denied prior MH contacts. Then said Sertraline begun after consult s/p CVA 9/2012 was from PCP, AGAIN later said, when reminded of contradictory info noting psychiatry and psychology f/u, that he had in fact seen both providers on a few occasions. (This was not felt representative of a cognitive limitation, i.e., memory decline 2nd CVA). Basically, it was my impression that primary stressor in this event was marital conflict (noted in chart) which he admitted includes "porn addiction" (doesnt meet criteria) that upsets his wife; some impression that she may have threatened or implied marriage would end and the patient either had true suicide intent, possible manipulation to keep marriage together, or that there may have been frank BZD abuse unrelated to marital conflict or suicide attempt. This will need to be d/w his wife. On inquiry, the patient says he has not had sex with his wife in at least 3 years, because his wife had a hysterectomy, she doesn't want to have sex, but he does. The patient denies he has any substance

abuse hx other than brief experimenting in the '70's. Says he has never been told he has ever abused or misused his controlled meds, says he hasnt gotten any non-VA controlled Rx in years. Despite his h/o mood disturbance with psych consult, marital/family conflict, he has never had a UDS since enrollment in our system in 2008, (not yet clear to me what results, if any, from prior hosp. will check). The patient feels that the only cognitive or mental health problem after the stroke, at this time, is he forgot his entire childhood (yet he has recently endorsed recent sudden recovered memory at last psychiatry appointment: He was raped as a teenager by a gang of truckers); this does not appear to be consistent with actual significant post stroke memory/cognitive issues however. PAST PSYCHIATRIC HISTORY: Record reflects 6/2010 depression care mgmt. consult in context of mood r/t sexual dysfxn, patient declined. Otherwise lists 1st MH contact in life was 9/2012 Psychiatry consult s/p CVA. His last MH contact was 10/28/13 CBOC psychiatry, noted below. The patient denies ANY h/o suicidality/violence/impulse control in his life.
Per 6/13/13 CBOC psychiatry interview: The patient reported that he has been taking only sertraline and not mirtazapine. Reported that mirtazapine was too sedating, and found that he was sleeping until the following afternoon. Currently he is sleeping approx. 10 hrs at HS without medication. Reported that his appetite has improved and that he is gaining weight. Reported having more energy. Continues to have marital conflict. When asked about hallucinations, the pt. described various encounters with UFOs which were reportedly witnessed by his friends and written about in the local newspaper in the 1970s and another time while in the military, whereby he reportedly had to sign a statement that he would not talk about it for 10 years. Pt. also reported incidents whereby a foreign object was found under his skin that could not be identified and having a scar on his abdomen of unknown origin.
Hospital course: The patient was admitted to psychiatry for mood stabilization and safety evaluation, possible substance withdrawal with detox protocol in place. He did not display any dangerous or potentially self-injurious behaviors during his stay with us, was generally compliant with medications and any routine, although he did report several perceived slights and grievances that were felt to be representative of Axis II characterological concerns. No clear evidence of any withdrawal concerns. No evidence of psychosis or bipolarity. However, sertraline was increased to 150 mg daily, no benefits yet clearly noted. Mirtazapine was restarted for sleep purposes to replace temazepam, the patient claims no benefit, although he seems to be trying to get prior temazepam back instead. It appeared very clear that the main issue involved in this admission was the patients ongoing conflicts with his wife as opposed to stand alone mood disorder. Originally, the wife was unwilling to have him return home, then unexpectedly agreed to have him return home with the understanding he would modulate his behaviors. The patient reluctantly agreed to return home as he did not have the money to move out on his own at this time. He did seem to gain insight into the fact that his situation at home was highly unlikely to change, and that decision to move out on his own is quite likely the correct decision. Social worker had spoken with his wife, and she related a very egregious pattern of conduct including visiting porn websites, actually bringing other women until the home for sex and then having some of her expenses personal items vanish. She related he has a long history of manipulation, threatening, cruelty, other maladaptive behaviors not related to substance abuse or a mood decompensation. Neurology consult was placed to see if his memory complaints were consistent with post stroke and/or requiring any new treatments; neurology felt there was no need for any current change and plan, and that cognition was not significantly affected by previous stroke. On the morning of discharge, he reported his mood was stable enough for discharge, although he still feels that his situation at home is unresolved. He still feels it would be at least a couple of weeks until he would have enough money to live on his own, and that is the long term plan for him at this

time. He doesn't think that mirtazapine has been especially helpful for sleep, although in the past he claimed it made him sleep far too much. I again emphasized to him that he should not be on temazepam or any other benzodiazepines given his history, and reminded him to avoid substances to prevent mood decompensation.

The patient's past medications include:
TD-ADULT for UNKNOWN INDICATION (29 Sep 2008 - 29 Sep 2008)

Causality for ANDROGEL(TESTOSTERONE)

The reporter's statement of causality for the events of SUICIDAL BEHAVIOR, RECURRENT RIGHT ISCHEMIC STROKE WITH WORSENING LEFT ARM HEMIPARESIS, ANTISOCIAL PERSONALITY DISORDER, CLUSTER B PERSONALITY DISORDER, PARTNER RELATIONAL PROBLEMS, FRANK HEMATURIA, CONSTIPATION, DEPRESSION, ANOREXIA, MOOD DISORDER, ANXIETY DISORDER and LOSS OF WEIGHT was not provided.

Relevant Laboratory & Other Diagnostic Tests
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27 Feb 2013 Abdominal obstructive series:
Abdominal obstructive series (27 Feb 2013): No pulmonary consolidation. Unremarkable bowel gas pattern. No radiographic evidence of complete or high-grade small bowel obstruction. Very early or low grade bowel obstruction, gastrointestinal tract pathology and parenchymal pathology cannot be excluded on plain radiograph. If clinically indicated, more sensitive evaluation can made with CT abdomen and pelvis. Question splenomegaly. More definitive evaluation can made with CT abdomen and pelvis or abdominal ultrasound.
26 Mar 2014 Chest PA and Lat X-Ray:
Chest PA& Lat (26 Mar 2014): 1. No CT evidence of acute intracranial pathology. No significant change from prior study. 2. Stable bilateral cerebral atrophy with chronic microvascular ischemic like white matter changes. Old infarctions in the right temporoparietal lobes and right lenticular nucleus of the basal ganglia with encephalomalacia and ex vacuole dilatation of the anterior horn of the right lateral ventricle. If there is concern about recurrent or extension of an old infarction MRI with diffusion weighted imaging would be indicated.
27 Dec 2012 Chest X-ray:
Chest X-ray (27 Dec 2012): Two thin curvilinear densities overlying the lateral edge of the left lung apex. These are most likely superimposed densities from the left scapula appears; however, a pneumothorax cannot be entirelyexcluded. Repeat chest radiograph including a PA view with the left scapula not superimposed over the left lung and lordotic view.
18 Mar 2013 CT ABD/PELVIS:
18 Mar 2013 (CT ABD/PEL): 1. Long segment of mild mucosal thickening seen in the sigmoid colon and possibly the rectum. Very mild inflammation also noted in the adjacent mesentery. In a patient with left lower quadrant pain findings are concerning for diverticulitis. Recommend clinical and CT follow up to resolution as well correlation with endoscopy as indicated. 2. Bladder wall thickening which may be the result of bladder outlet obstruction in this patient with mild prostatomegaly.

24 Sep 2012 CT Head:
CT Head: (24 Sep 2012): 1. No CT evidence of acute intracranial pathology. 2. Minimal bilateral cerebral atrophy with chronic microvascular ischemic like white matter changes. 3. Low-attenuation foci in the right parietal and right basal ganglia regions consistent with infarction likely remote. No edema or hemorrhage is seen.
18 Mar 2013 CT Head:
18 Mar 2013: CT Head: 1. Findings consistent with ischemic small vessel disease and atrophy. 2. Previous lacunar infarcts in the posterior limb of both internal capsules. 3. Interval increase in the low density deficit in the right lenticular nucleus compared to previous exam of 24 Sep 2012. No other significant intracranial abnormality identified. Diffusion weighted MR exam may be helpful for further evaluation, if clinically indicated. (b) (6)
25 Jun 2013 CT Head:
CT Head (25 Jun 2013): Encephalomalacia change in the right frontoparietal lobe associated with ex vacuo dilatation of the right lateral ventricle. This is unchanged from March 2013. This focus has significantly decreased in density since September 2012. Chronic infarcts with encephalomalacia change in the peripheral right parieto-occipital region and peripheral right temporal region. Cerebral atrophy.
26 Mar 2014 CT Head:
CT Head/brain (26 Mar 2014): 1. No CT evidence of acute intracranial pathology. No significant change from prior study. 2. Stable bilateral cerebral atrophy with chronic microvascular ischemic like white matter changes. Old infarctions in the right temporoparietal lobes and right lenticular nucleus of the basal ganglia with encephalomalacia and ex vacuole dilatation of the anterior horn of the right lateral ventricle. If there is concern about recurrent or extension of an old infarction MRI with diffusion weighted imaging would be indicated.
(b) (6) CT head:
CT Head/Brain w/o contrast ((b) (6)): No definite acute intracranial findings. No interval changes.
18 Mar 2013 CT left upper extremity:
CT left upper extremity (18 Mar 2013): Humerus left x-ray (18 Apr 2013): Healing fracture of the proximal humerus with no significant change in alignment. Multiple small lytic lesions suspected.
(b) (6) CTA Angiography:
CTA Angiography: (14 Nov 2012): Mild stenosis proximal right internal carotid artery (0-40%)Hypoplastic A1 segment of the left anterior cerebral artery. Sinusitis as described. No interval change in the right parietal and basal ganglia infarcts described on the previous CT scan of 24 Sep 2012.
07 Mar 2013 Hand Left x-ray:
X-ray Hand left: (07 Mar 2013): Inferior subluxation of the left humerus in relation to the glenoid fossa of mild to moderate degree. No prior left shoulder radiograph available for comparison. The inferior subluxation of the left humerus may be chronic for the patient.
04 Apr 2014 MRI Brain:
MRI Brain (04 Apr 2014): 1. No visible acute radiographic abnormality. No restriction is seen with diffusion-weighted imaging. 2. Redemonstration of ventriculomegaly. 3. Chronic brain changes in the right basal ganglia, right temporal lobe and right parietal lobe, consistent with sequela of old strokes. 4. Chronic white matter changes.

18 Apr 2013 X-ray Left Humerus:
Humerus left x-ray (18 Apr 2013): Healing fracture of the proximal humerus with no significant change in alignment. Multiple small lytic lesions suspected.
07 Mar 2013 x-ray shoulder left:
X-ray Left shoulder: (07 Mar 2013): Severe osteopenia of the left shoulder, making osseous detail suboptimal. Question fracture of the left humeral neck. More definitive evaluation can be made with CT or MRI of the left shoulder.
Inferior subluxation of the left humerus in relation to the glenoid fossa of mild to moderate degree. No prior left shoulder radiograph available for comparison. The inferior subluxation of the left humerus may be chronic for the patient.

Change History

On 05 Aug 2015, received updates to patient demographics, medical history, event information, reporter opinion of causality, suspect drug information, concomitant drug information, past drug information, laboratory/diagnostic procedures and narrative description. The serious events of "SUICIDAL BEHAVIOR", "RECURRENT RIGHT ISCHEMIC STROKE WITH WORSENING LEFT ARM HEMIPARESIS", "ANTISOCIAL PERSONALITY DISORDER" and "CLUSTER B PERSONALITY DISORDER" were added.

Relevant Medical History:

BROKEN BACK (Started 1975)
CHRONIC LOW BACK PAIN (Started 29 Sep 2008)
HYPERCHOLESTEROLEMIA (Started 29 Sep 2008)
IMPOTENCE OF ORGANIC ORIGIN (Started 29 Sep 2008)
CHEST PAIN (Started 15 Jan 2009)
ESSENTIAL HYPERTENSION (Started 03 Mar 2009)
GERD (Started 03 Mar 2009)
COLONIC DIVERTICULOSIS (Started 07 Apr 2010)
HIATAL HERNIA (Started 07 Apr 2010)
INTERNAL HEMORRHOIDS (Started 07 Apr 2010)
WRIST SPRAIN (Started 04 Jun 2010)
FEVER (Started 30 Jul 2010)
PRESSURE ULCER, BUTTOCK (Started 01 Oct 2010)
CELLULITIS (Started 22 Oct 2010)
DISRUPTION OF EXTERNAL OPERATION (SURGICAL) WOUND (Started 22 Oct 2010)
INSECT BITE (Started 02 Jun 2011)
DIARRHEA (Started 18 Aug 2011)
VITAMIN B12 DEFICIENCY (Started 10 Nov 2011)
ADJUSTMENT DISORDER WITH MIXED ANXIETY AND DEPRESSED MOOD (Started 14 Mar 2012)
HYPOGONADISM MALE (Started 14 Mar 2012)
FALL (Started August 2012)
RIGHT CAROTID STENOSIS (Started August 2012)
SUBACUTE RIGHT MCA ISCHEMIC CVA W/ RESIDUAL LUE/LLE PARESIS (Started (b) (6))
HOSPITALIZATION (b) (6) - (b) (6))
REHABILITATION (b) (6) - 28 Sep 2012)

***Age in Years displays a mid-value where the Age Unit in the report is in DECADE**

Disease/Surgical Procedure	Start Date	End Date	Continuing?	Comment
Spinal fracture	1975			
Hypercholesterolemia	29-Sep-2008			
Impotence of organic origin	29-Sep-2008			
Low back pain	29-Sep-2008			
Chest pain	15-Jan-2009			
Essential hypertension	03-Mar-2009			
GERD	03-Mar-2009			
Colonic diverticulosis	07-Apr-2010			
Hiatal hernia	07-Apr-2010			
Internal hemorrhoids	07-Apr-2010			
Wrist sprain	04-Jun-2010			
Fever	30-Jul-2010			
Pressure sore	01-Oct-2010			
Cellulitis	22-Oct-2010			
Postoperative wound complication	22-Oct-2010			
Insect bite NOS	02-Jun-2011			
Diarrhea	18-Aug-2011			
Vitamin B12 deficiency	10-Nov-2011			
Adjustment disorder with mixed anxiety and depressed mood	14-Mar-2012			
Hypogonadism male	14-Mar-2012			
Carotid artery stenosis	Aug-2012			

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Fall	Aug-2012	
Hemiparesis (left)	(b) (6)	
Ischemic stroke	(b) (6)	
Hospitalization	(b) (6)	(b) (6)
Rehabilitation therapy	(b) (6)	28-Sep-2012

Medical History Product(s)	Start Date	End Date	Indication(s)	MedDRA Preferred Term(s)
TD (ADULT)	29-Sep-2008	29-Sep-2008	Drug use for unknown indication	

Relevant Laboratory Data:

Test Date	Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail Y/N
13-Jul-2011	Tuberculin test	Negative (0 mm)				N
(b) (6)	Albumin	3.4				N
(b) (6)	Platelet count	232				N
(b) (6)	Alanine aminotransferase	25				N
(b) (6)	Protein total	6.9				N
(b) (6)	Hemoglobin	15.7				N
(b) (6)	MCH	28.2				N
(b) (6)	WBC	8.4				N
(b) (6)	Bilirubin total	0				N
(b) (6)	Aspartate aminotransferase	20				N
(b) (6)	MCHC	34.0				N
(b) (6)	Hematocrit	46.2				N
(b) (6)	RBC count	5.57				N
(b) (6)	Alkaline phosphatase	73				N

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Test Date	Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail Y/N
(b) (6)	MCV	82.9				N
(b) (6)	Carbon dioxide	32				N
(b) (6)	Glucose	103				N
(b) (6)	Creatinine	1.06				N
(b) (6)	Calcium	9.2				N
(b) (6)	Glomerular filtration rate	>=60				N
(b) (6)	Blood urea nitrogen	19				N
(b) (6)	Potassium	4.7				N
(b) (6)	Chloride	100				N
(b) (6)	Sodium	140				N
(b) (6)	Anion gap	8				N
24-Sep-2012	Computerised tomogram head	See narrative				N
(b) (6)	CT angiography	See narrative				N
27-Dec-2012	Chest X-ray	see narrative				N
27-Feb-2013	Abdominal X-ray	See Narrative				N
07-Mar-2013	Upper limb X-ray	see narrative.				N
07-Mar-2013	Upper limb X-ray	see narrative				N
18-Mar-2013	CT scan	See narrative				N
18-Mar-2013	Computerized tomogram abdomen	see narrative				N
18-Mar-2013	Computerised tomogram head	see narrative				N
18-Apr-2013	Upper limb X-ray	see narrative				N
25-Jun-2013	Computerised tomogram head	See Narrative				N

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Test Date	Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail Y/N
(b) (6)	Computerised tomogram head	See narrative				N
26-Mar-2014	Chest X-ray	See Narrative				N
26-Mar-2014	Computerised tomogram head	See Narrative				N
04-Apr-2014	MRI brain	see narrative				N

Concomitant Products:

#	Product Name	Dose/Frequency	Route	Dosage Text	Indication(s)	Start Date	End Date	Interval 1st Dose to Event
1	MIRTAZAPINE	15 MG/QD	PO	QHS	Difficulty sleeping	16-Dec-2013	17-Dec-2014	
2	NAPROXEN	/	PO	1 TAB BID PRN	Pain	11-Jul-2011		
3	NAPROXEN	/			Inflammation			
4	SERTRALINE HCL	100 MG/QD	PO	1 tab	Mood disorder NOS	2013	2014	
5	TRAMADOL HCL	/	PO	1 tab TID as needed	Pain	14-Nov-2013		
6	PEG 400 0.4%/PROP GLYCOL 0.3% OPH SOLN	1 GTT/	OPH	QID PRN	Drug use for unknown indication	16-Sep-2013	17-Sep-2014	
7	TEMAZEPAM	15 MG/	PO	QHS PRN		18-Oct-2013	20-Apr-2014	
8	TEMAZEPAM	7.5 MG/	PO	QHS PRN		25-Jun-2013	12-Sep-2013	
9	AGGRENOX	1 DF/BID	PO	25/200MG BID	Thrombosis prophylaxis	21-Nov-2012		
10	TEMAZEPAM	1 DF/	PO	1 CAP QHS PRN	Difficulty sleeping	30-Oct-2013	02-May-2014	
11	TEMAZEPAM	15 MG/	PO	QHS PRN		11-Jul-2011	19-Aug-2012	
12	RANITIDINE HCL	300 MG/QD	PO		Gastric disorder	27-Sep-2012	26-Dec-2012	
13	PNEUMOCOCCAL VACCINE	/			Drug use for unknown indication	30-Oct-2013	30-Oct-2013	
14	CYANOCOBALAMIN	/			Drug use for unknown indication			
15	MIRTAZAPINE	7.5 MG/QD	PO	1/2 tab	Mood disorder NOS	30-Apr-2013	01-May-2014	

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	Product Name	Dose/Frequency	Route	Dosage Text	Indication(s)	Start Date	End Date	Interval 1st Dose to Event
16	METHOCARBAMOL	/	PO	1 TAB BID PRN	Muscle relaxant therapy	2011		
17	ATORVASTATIN CALCIUM	80 MG/QD	PO	QHS	Cholesterol	2013	2014	
18	DTAP IPV	/			Drug use for unknown indication	27-Feb-2014	27-Feb-2014	
19	NITROGLYCERIN	/			CHEST PAIN			
20	TRAZODONE HCL	100 MG/QD	PO	QHS (May take 50mg if to sedated)	Mood disorder NOS	2013		
21	TRAZODONE HCL	/			Difficulty sleeping			
22	PRAZOSIN HCL	2 MG/QD	PO	QHS	Nightmare disorder	2013		
23	MIRTAZAPINE	22.5 MG/QD	PO	1/2 tab	Anxiety	03-Feb-2014	05-Mar-2015	
24	AGGRENOX	/			Cerebrovascular accident prophylaxis			
25	LISINOPRIL	2.5 MG/QD	PO	QHS	BLOOD PRESSURE	18-Oct-2012	2013	
26	GABAPENTIN	100 MG/TID	PO		Pain	2013		
27	TEMAZEPAM	1 DF/	PO	1 CAP QHS PRN		21-Nov-2012	28-Jun-2013	
28	METOPROLOL TARTRATE	25 MG/BID	PO		Cardiac disorder	15-Mar-2011	11-Jul-2012	
29	FLUOXETINE HCL	40 MG/QD	PO		Mood disorder NOS	2013		
30	OMEPRAZOLE	40 MG/QD	PO	2 caps QAM BEFORE BREAKFAST	Gastric disorder	2013		
31	TEMAZEPAM	15 MG/	PO	QHS PRN		07-Mar-2013	07-Sep-2013	
32	CLOPIDOGREL BISULFATE	1 DF/QD	PO		Thrombosis prophylaxis	18-Oct-2012	2013	
33	ROSUVASTATIN CALCIUM	20 MG/QD	PO	1.2 tab QHS	Cholesterol	12-Jul-2011	12-Jul-2012	
34	METOPROLOL TARTRATE	/			BLOOD PRESSURE			
35	MULTIVITAMIN	1 DF/QD	PO		Drug use for unknown indication			

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	Product Name	Dose/Frequency	Route	Dosage Text	Indication(s)	Start Date	End Date	Interval 1st Dose to Event
36	ASPIRIN	/			Anticoagulant therapy	2012		

Reporter Source:

Study Report:	Study Name:	Study Type:	Sponsor Study:	Protocol	IND #:
No					

Literature Text:

Country of Event: USA **Sender MFR:** ABBVIE

Reporter Name: (b) (6)
Reporter Org.:
Reporter Street:
Reporter City:
Reporter Zip:

Reporter Type:
Reporter Email:
Reporter Phone:
Reporter State: (b) (6)
Reporter Country: UNITED STATES

Health Prof.:
Occupation:

Sent To:
Identity Disclosed:

***Age in Years displays a mid-value where the Age Unit in the report is in DECADE**

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Case Information:

Case Id: 11459348 **Version:** 2 **Case Type:** 15-DAY **eSub:** Yes **HP:** **Country:** USA **Outcome(s):** DS,HO,OT,

FDA Rcvd. Date: 13-Jan-2016 **Init FDA Rcvd. Date:** 04-Sep-2015 **Mfr Rcvd. Date:** 08-Jan-2016 **Application Type:** ANDA **Application #:** 085635

Mfr. Control #: US-PFIZER INC-2015296391

Patient Information:

Patient ID: PRIVACY **Age:** 42 YR **Age in Years:** 42 YR **Sex:** Male **Weight:** **DoB:**

Suspect Products:

#	Product Name	Dose/Frequency	Route	Dosage Text	Indication(s)	Start Date	End Date	Interval 1st Dose to Event	ReC	DeC
1	ANDROGEL	/		UNK (12 samples received)	Hormone replacement therapy	2009	2009		NA	Unk
2	ANDROGEL	/			Libido decreased				NA	Unk
3	ANDROGEL	/QD		UNK, 1x/day (every morning)	Energy decreased	25-Aug-2009	23-Oct-2009		NA	Unk
4	ANDROGEL	/			Erectile dysfunction				NA	Unk
5	Depo-Testosterone	/QD		UNK, 1x/day	Hormone replacement therapy	24-Oct-2009	19-Jul-2014		NA	Unk
6	Depo-Testosterone	/			Libido decreased				NA	Unk
7	Depo-Testosterone	/			Energy decreased				NA	Unk
8	Depo-Testosterone	/			Erectile dysfunction				NA	Unk

#	Product Name	Lot#	Exp Date	NDC #	Labeler	OTC
1	ANDROGEL					
2	ANDROGEL					
3	ANDROGEL					
4	ANDROGEL					
5	Depo-Testosterone				PFIZER	
6	Depo-Testosterone				PFIZER	

***Age in Years displays a mid-value where the Age Unit in the report is in DECADE**

FDA - Adverse Event Reporting System (FAERS)

Batch Printing Report for Cases

#	Product Name	Dose/Frequency	Route	Dosage Text	Indication(s)	Start Date	End Date	Interval 1st Dose to Event	ReC	DeC
#	Product Name	Lot#	Exp Date		NDC #	Labeler			OTC	
7	Depo-Testosterone					PFIZER				
8	Depo-Testosterone					PFIZER				

Event Information:

MedDRA © PreferredTerm	Start Date	End Date	Outcomes	Highlighted Terms	ReC
Thrombophlebitis	(b) (6)		UNKNOWN		NA
Deep Vein Thrombosis	01-Jan-2013		UNKNOWN		NA
Pulmonary Embolism	(b) (6)		UNKNOWN		NA
Loss Of Personal Independence In Daily Activities			NOT RECOVERED/ NOT RESOLVED		NA
Post Thrombotic Syndrome			UNKNOWN		NA
Suicidal Ideation			UNKNOWN		NA

Event/Problem Narrative:

This is a spontaneous report from a contactable attorney by way of Master Short Form Complaint. A male patient of an unknown age and ethnicity was prescribed and took testosterone cipionate (DEPO-TESTOSTERONE) and testosterone (ANDROGEL) from Aug2009 to Jul2014 as a testosterone replacement therapy (TRT). The dose, frequency and route of administration were unknown. The relevant medical history, concomitant medication and past drug history were unknown. The patient was diagnosed with pulmonary embolism on (b) (6) and deep vein thrombosis on (b) (6) The relevant lab data was unknown. The action taken with the suspect products in response to the events pulmonary embolism and deep vein thrombosis was unknown. The therapeutic measures taken were unknown. At the time of the report, the clinical outcome of the events pulmonary embolism and deep vein thrombosis was unknown.

Follow-up (08Jan2016): This contactable attorney reported by way of Plaintiff Fact Sheet. This 42-year-old, male patient was prescribed and took testosterone cipionate (DEPO-TESTOSTERONE) injection once a day from 24Oct2009 to 19Jul2014 and testosterone (ANDROGEL) gel applied every morning from 25Aug2009 to 23Oct2009 for low energy, low libido and erectile dysfunction. It was reported that the patient also received testosterone gel 12 samples in 2009. The relevant medical history included low energy, low libido and erectile dysfunction (treated with testosterone replacement therapy (TRT)) on an unknown date, hypothyroid (treated with thyroid (ARMOUR THYROID) and levothyroxine (SYNTHROID)) since an unknown date, androgen deficiency or hypogonadism in 2009 and factor V leiden (blood clotting disorder) in 2012. His social history included alcohol use approximately 1 to 2 drinks per month and caffeinated beverages (hot tea or lightly sweetened ice tea) use approximately one drink per day (five years prior to TRT) since an unknown date. His family history included hypertension

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(father) on an unknown date. His concomitant medications included thyroid (ARMOUR THYROID) and levothyroxine (SYNTHROID) since 2005 for hypothyroid. On an unknown date, he had constant pain, burning, post thrombotic syndrome and suicidal ideation. On an unknown date, he was no longer be active and complete daily activities and was reported that, this condition was continuing. In (b) (6) he had pain and swelling and was diagnosed with thrombophlebitis. On (b) (6), he experienced shortness of breath, chest and back pain and was diagnosed with pulmonary embolism (PE). In 2013, he had blood clots or thrombosis and deep vein thrombosis (DVT). On (b) (6) he again experienced severe left leg pain and swelling and was diagnosed with chronic and acute DVT in left leg. He was hospitalized in (b) (6) for thrombophlebitis and from (b) (6) tc(b) (6) for PE. He was also hospitalized in (b) (6) for DVT, from (b) (6) to (b) (6) for DVT and blood clot, in 2014 for blood clot, in (b) (6) for DVT, in (b) (6) DVT and clotted stents and in (b) (6) for DVT. He applied social security disability claim in 2014 for chronic DVT. He underwent left leg venogram and vena cavagram for which the results were unknown during the time period of (b) (6) to 04Mar2014. He underwent venograms for which the results were unknown in (b) (6) and in (b) (6). He underwent venograms five times in (b) (6) for which the results were unknown. He was treated with warfarin (COUMADIN) from 2011 to 2012 and underwent unknown surgeries in (b) (6) for thrombophlebitis. He was on anticoagulation treatment since 27Sep2013 for PE. In (b) (6) he underwent inferior vena cava (IVC) filter placement and treated with anti coagulants for blood clots or thrombosis and DVT. He underwent percutaneous thrombectomy and thrombolysis during the time period of (b) (6) to (b) (6) for DVT. He was treated with apixaban (ELIQUIS) from unknown date in 2015 to Jul2015 and warfarin (COUMADIN) since Jul2015 for chronic clots. During hospitalization in (b) (6) he underwent angioplasty with stent placement for DVT. During hospitalization in (b) (6) he underwent stents placement for DVT. He underwent angioplasty and was treated with heparin drip in (b) (6) for DVT. At the time of the report, the clinical outcome of the events thrombophlebitis, suicidal ideation and post thrombotic syndrome was unknown and the event no longer be active and complete daily activities was not recovered.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?	Comment
Androgen deficiency	2009		UNKNOWN	
Hypogonadism male	2009		UNKNOWN	
Factor V Leiden mutation	2012		UNKNOWN	
Alcohol use				approximately 1 to 2 drinks per month (five years prior to TRT)
Caffeine consumption				hot tea or lightly sweetened ice tea use, approximately one drink per day (five years prior to TRT)
Energy decreased				treated with TRT

Erectile dysfunction	treated with TRT
Family history of cardiovascular disorder	hypertension (father)
Hypothyroidism	treated with thyroid (ARMOUR THYROID) and levothyroxine (SYNTHROID)
Libido decreased	treated with TRT

Medical History Product(s)	Start Date	End Date	Indication(s)	MedDRA Preferred Term(s)

Relevant Laboratory Data:

Test Date	Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail Y/N
01-Jan-2014	Venogram	unknown				N
(b) (6)	Venogram	unknown				N
(b) (6)	Venogram	unknown				N
(b) (6)	Venogram	unknown				N

Concomitant Products:

#	Product Name	Dose/Frequency	Route	Dosage Text	Indication(s)	Start Date	End Date	Interval 1st Dose to Event
1	ARMOUR THYROID	/		UNK	Hypothyroidism	2005		
2	SYNTHROID	/		UNK	Hypothyroidism	2005		

Reporter Source:

Study Report:	Study Name:	Study Type:	Sponsor Study:	Protocol	IND #:
No					

Literature Text:

Country of Event: USA **Sender MFR:** PFIZER

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FDA - Adverse Event Reporting System (FAERS)

Batch Printing Report for Cases

Reporter Name:	(b) (6)	**Reporter Type:**	
Reporter Org.:		**Reporter Email:**	
Reporter Street:		**Reporter Phone:**	
Reporter City:		**Reporter State:**	(b) (6)
Reporter Zip:		**Reporter Country:**	UNITED STATES
Health Prof.:		**Sent To:**	
Occupation:		**Identity Disclosed:**	

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FDA - Adverse Event Reporting System (FAERS)

Batch Printing Report for Cases

Case Information:

Case Id: 11579501 **Version:** 2 **Case Type:** 15-DAY **eSub:** Yes **HP:** **Country:** USA **Outcome(s):** DS,

FDA Rcvd. Date: 01-Oct-2015 **Init FDA Rcvd. Date:** 30-Sep-2015 **Mfr Rcvd. Date:** 24-Sep-2015 **Application Type:** NDA **Application #:** 021015

Mfr. Control #: US-ABBVIE-15P-163-1472247-00

Patient Information:

Patient ID: (b) (6) **Age:** **Age in Years:** **Sex:** Male **Weight:** **DoB:**

Suspect Products:

#	Product Name	Dose/Frequency	Route	Dosage Text	Indication(s)	Start Date	End Date	Interval 1st Dose to Event	ReC	DeC
1	ANDROGEL	/	TOP		Drug use for unknown indication				NA	Unk

#	Product Name	Lot#	Exp Date	NDC #	Labeler	OTC
1	ANDROGEL	Unknown				

Event Information:

MedDRA © PreferredTerm	Start Date	End Date	Outcomes	Highlighted Terms	ReC
Crying			UNKNOWN	N	NA
Drug Ineffective			UNKNOWN	N	NA
Suicidal Ideation			UNKNOWN	N	NA

Event/Problem Narrative:

Spontaneous report from the USA by a consumer of a male with events of SUICIDAL CRYING EXPERIENCE and non-serious PRODUCT NOT WORKING with ANDROGEL (TESTOSTERONE). There was no reported medical history.

On unknown dates, the patient experienced SUICIDAL CRYING EXPERIENCE and PRODUCT NOT WORKING. The patient stated that his experience with TESTOSTERONE was the worst ever. The primary reporter had not provided the lot number and expiration date. No further information was available.

Causality for ANDROGEL(TESTOSTERONE)

The reporter's statement of causality for the events of SUICIDAL CRYING EXPERIENCE unknown onset, SUICIDAL CRYING EXPERIENCE unknown onset and PRODUCT NOT WORKING was not provided.

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Relevant Medical History:

Not reported.

Disease/Surgical Procedure	Start Date	End Date	Continuing?	Comment

Medical History Product(s)	Start Date	End Date	Indication(s)	MedDRA Preferred Term(s)

Relevant Laboratory Data:

Test Date	Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail Y/N

Concomitant Products:

#	Product Name	Dose/Frequency	Route	Dosage Text	Indication(s)	Start Date	End Date	Interval 1st Dose to Event

Reporter Source:

Study Report:	Study Name:	Study Type:	Sponsor Study:	Protocol	IND #:
No					

Literature Text:

Country of Event: USA **Sender MFR:** ABBVIE

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FDA - Adverse Event Reporting System (FAERS)

Batch Printing Report for Cases

Reporter Name:	In Confidence	**Reporter Type:**	
Reporter Org.:		**Reporter Email:**	
Reporter Street:		**Reporter Phone:**	
Reporter City:		**Reporter State:**	
Reporter Zip:		**Reporter Country:**	UNITED STATES
Health Prof.:		**Sent To:**	
Occupation:	CONSUMER OR OTHER NON HEALTH PROFESSIONAL	**Identity Disclosed:**	

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FDA - Adverse Event Reporting System (FAERS)

Batch Printing Report for Cases

Case Information:

Case Id: 11655713 **Version:** 1 **Case Type:** 15-DAY **eSub:** Yes **HP:** **Country:** CAN **Outcome(s):** LT,

FDA Rcvd. Date: 23-Oct-2015 **Init FDA Rcvd. Date:** 23-Oct-2015 **Mfr Rcvd. Date:** 20-Oct-2015 **Application Type:** NDA **Application #:** 021015

Mfr. Control #: CA-ABBVIE-15P-028-1487040-00

Patient Information:

Patient ID: UNKNOWN **Age:** 52 YR **Age in Years:** 52 YR **Sex:** Male **Weight:** KG **DoB:**

Suspect Products:

#	Product Name	Dose/Frequency	Route	Dosage Text	Indication(s)	Start Date	End Date	Interval 1st Dose to Event	ReC	DeC
1	ANDROGEL	/QD	TOP		Andropause				NA	Unk

#	Product Name	Lot#	Exp Date	NDC #	Labeler	OTC
1	ANDROGEL	UNKNOWN				

Event Information:

MedDRA © PreferredTerm	Start Date	End Date	Outcomes	Highlighted Terms	ReC
Aggression			RECOVERED/ RESOLVED	N	NA
Depression			RECOVERED/ RESOLVED	N	NA
Impatience			RECOVERED/ RESOLVED	N	NA
Suicidal Ideation			RECOVERED/ RESOLVED	N	NA
Violence-Related Symptom			RECOVERED/ RESOLVED	N	NA

Event/Problem Narrative:

This case was received from ABBOTT on 23 OCT 2015 (Ref. number CA-ABBOTT-15X-028-1233380-00)

Case was received at Abbott on 20 Oct 2015 from Health Authority (Canada Vigilance), reference number 000653415.

Spontaneous report from CANADA by a pharmacist of a 52 year old male with events of SUICIDAL IDEATION, AGGRESSION, IMPATIENCE, VIOLENCE-RELATED SYMPTOM and DEPRESSION with ANDROGEL (TESTOSTERONE). There was no reported medical history.

The patient's past medications were not reported. On unknown date, patient started therapy with ANDROGEL

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(TESTOSTERONE) gel topically 10 gm once a day (form strength, batch number and expiry date unknown) for andropause. The concomitant drugs included fluvoxamine, lamotrigine, lorazepam and quetiapine. On unknown dates, the patient experienced SUICIDAL IDEATION, AGGRESSION, IMPATIENCE, VIOLENCE-RELATED SYMPTOM and DEPRESSION. The action taken with ANDROGEL (TESTOSTERONE) was unknown. On unknown dates, SUICIDAL IDEATION, AGGRESSION, IMPATIENCE, VIOLENCE-RELATED SYMPTOM and DEPRESSION resolved.

This case was serious due to life threatening.

The reporter causality for AGGRESSION, DEPRESSION, IMPATIENCE, SUICIDAL IDEATION and VIOLENCE-RELATED SYMPTOM with use of ANDROGEL (TESTOSTERONE) was not reported.

The above narrative was created by Abbott Laboratories. Health Authority did not provide case narrative.

No additional information will be available since the case was reported by Health Authority (Canada Vigilance).

Relevant Medical History:

Not reported.

Disease/Surgical Procedure	Start Date	End Date	Continuing?	Comment

Medical History Product(s)	Start Date	End Date	Indication(s)	MedDRA Preferred Term(s)

Relevant Laboratory Data:

Test Date	Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail Y/N

Concomitant Products:

#	Product Name	Dose/Frequency	Route	Dosage Text	Indication(s)	Start Date	End Date	Interval 1st Dose to Event
1	QUETIAPINE	/	UNK		Drug use for unknown indication			
2	LORAZEPAM	/	UNK		Drug use for unknown indication			
3	FLUVOXAMINE	/	UNK		Drug use for unknown indication			
4	LAMOTRIGINE	/	UNK		Drug use for unknown indication			

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Reporter Source:

Study Report:	Study Name:	Study Type:	Sponsor Study:	Protocol	IND #:
No					

Literature Text:

Country of Event: CAN **Sender MFR:** ABBVIE

Reporter Name: Anonymous
Reporter Org.:
Reporter Street:
Reporter City:
Reporter Zip:
Health Prof.:
Occupation:

Reporter Type:
Reporter Email:
Reporter Phone:
Reporter State:
Reporter Country: CANADA
Sent To:
Identity Disclosed:

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FDA - Adverse Event Reporting System (FAERS)

Batch Printing Report for Cases

Case Information:

Case Id: 12045382 **Version:** 3 **Case Type:** 15-DAY **eSub:** Yes **HP:** **Country:** USA **Outcome(s):** DE,HO,OT,

FDA Rcvd. Date: 17-Apr-2017 **Init FDA Rcvd. Date:** 08-Feb-2016 **Mfr Rcvd. Date:** 10-Apr-2017 **Application Type:** NDA **Application #:** 022504

Mfr. Control #: US-ELI_LILLY_AND_COMPANY-US201602001192

Patient Information:

Patient ID: (b) (6) **Age:** 53. (b) (6) YR **Age in Years:** 53 (b) (6) YR **Sex:** Male **Weight:** 99.77 KG **DoB:** (b) (6)

Suspect Products:

#	Product Name	Dose/Frequency	Route	Dosage Text	Indication(s)	Start Date	End Date	Interval 1st Dose to Event	ReC	DeC
1	ANDROGEL	2 DF/QD	UNK	2 DF, qd	Blood testosterone decreased	Apr-2012			NA	Unk
2	ANDROGEL	4 DF/QD	UNK	4 DF, qd	Blood testosterone decreased		Mar-2013		NA	Unk
3	Axiron	120 MG/QD	UNK	120 mg, qd	Blood testosterone decreased	15-Aug-2012	Sep-2012	747 Day	Unk	Unk
4	TESTOSTERONE /00103103/	200 MG/	IM	200 mg, every 2 weeks	Blood testosterone decreased	Oct-2011	Mar-2012		NA	Unk

#	Product Name	Lot#	Exp Date	NDC #	Labeler	OTC
1	ANDROGEL					
2	ANDROGEL					
3	Axiron				ELI LILLY AND CO	
4	TESTOSTERONE /00103103/					

Event Information:

MedDRA © PreferredTerm	Start Date	End Date	Outcomes	Highlighted Terms	ReC
Cerebrovascular Accident	(b) (6)		UNKNOWN	N	NA
Cerebrovascular Accident	(b) (6)		UNKNOWN	N	NA
Completed Suicide	(b) (6)	(b) (6)	FATAL	N	NA
Suicidal Ideation			UNKNOWN	N	NA

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Event/Problem Narrative:

This spontaneous legal case, reported by an attorney, with additional information from an attorney in the form of medical records and plaintiff fact sheet via the legal department, concerns a 53 year old Caucasian male patient.

Medical history included depression, anxiety, bipolar disorder, hypertension, angina, coronary artery disease (CAD), heart attack (MI), angioplasty (2003 and 2012), arteriosclerosis with unspecified surgeries (2003 and 2012),high cholesterol, dyslipidemia, arthritis, osteoarthritis, cervical C4 C5 spinal stenosis/neck problems, Hepatitis C (secondary to intravenous drug abuse) treated with interferon, benign prostatic hyperplasia (BPH), Type 2 diabetes mellitus, gastrooesophageal reflux disease (GERD), fibromyalgia, chest pain secondary to costochondritis, androgen deficiency or hypogonadism, tobacco use, alcohol use, and caffeine consumption. Family medical history included diabetes and cardiovascular disorders (mother, father, brother: chest pain, abnormal heart-beat, arteriosclerosis, cardiovascular disease, congenital heart condition, congestive heart failure or cardiomyopathy, CAD, MI and HTN). Concomitant medications were not provided.

The patient received testosterone 2% solution (Axiron) via disposable applicator, 120 mg (2 pumps to each axilla) daily as testosterone replacement therapy (TRT), beginning in Aug2012 through Sep2012. As additional TRT he also received testosterone 1.62% (AndroGel) initially at one pump to each arm daily beginning in 2011and then increased on an unknown date to two pumps to each arm daily for low testosterone; conflicting information reported approximate dates of therapy as Apr2012 through Mar2013. Additionally the patient received testosterone cipionate 200mg intramuscular (IM) injection every two weeks for low testosterone beginning in Oct2011 through Mar2012. The total period of time the patient received TRT was reported as Oct2011 throughMar2013. On approximately (b) (6), an unknown period of time after starting testosterone 2% solution, he experienced a stroke which was considered to be serious by the company. On (b) (6) the patient experienced an acute cerebrovascular accident (CVA) requiring hospitalization. The dates of hospitalization were reported as (b) (6) (b) (6) The patient presented with neck pain radiating into his arm, right facial numbness, headache and slurred speech. Computed tomography (CT) of the brain revealed no acute abnormalities; however his magnetic resonance imaging (MRI) of the brain revealed multiple subacute embolic infarcts to the left cerebral hemisphere. Magnetic resonance angiogram (MRA) of the carotid arteries revealed 80% high-grade stenosis at the distal cavernous segment of the left internal carotid artery. Echocardiogram revealed mild concentric left ventricular hypertrophy, ventricular wall and IVS wall thickness are mildly increased and mild thickening/calcification of the anterior and posterior mitral leaflets. His symptoms improved over the course of his stay. His speech was still slightly slow at the time of discharge on (b) (6) Discharge medications included clopidogrel bisulfate, docusate sodium and sennoside a+b, nicotine patch, hydrocodone bitartrate and paracetamol, and alprazolam. On (b) (6) he had a successful angioplasty of the cavernous portion of the left internal carotid artery. The patient experienced multiple left hemispheric transient ischemic attacks (TIA) including (b) (6) and (b) (6) The TIAs were considered medically significant. Treatment medications included clopidogrel bisulfate and acetylsalicylic acid. On (b) (6) his CT of the brain showed no acute abnormalities, but there were scattered areas of decreased attenuation in the deep periventricular white matter, probable small vessel ischemic changes. On (b) (6) in the emergency room, the patient stated he had thought about hanging himself (suicidal ideation) and has attempted suicide before in the past (details not provided). On (b) (6) the patient committed suicide by hanging himself. Cause of death was completed suicide. An autopsy was not performed. Information regarding additional diagnostic testing, corrective treatments and the remaining event

outcomes was not provided. The TRT was discontinued in (b) (6) Information was not provided regarding which TRT was taken at the time of the events and the reason for discontinuation of each TRT was not provided. Additionally, according to the reporting attorney the TRT had an unspecified design defect.

The physician reporter did not provide an opinion of relatedness. The consumer and attorney reporters felt the events were related to testosterone 2% solution as well as the additional testosterone replacement therapy.

Follow-up will not be pursued since follow-up on any filed case regarding Axiron is not permissible.

Update 05May2016: Additional information was received from an attorney in the form of medical records and plaintiff fact sheet via the legal department on 02May2016. Added serious events (acute CVA and suicidal ideation), causality, consumer and physician reporters, patient middle initial, date of birth, race, height, weight, medical history, family medical history, suspect drug (testosterone cipionate), treatment medication, date of death, no autopsy performed, dosing regimen and frequency for Axiron and Androgel, conflicting start dates for suspect drugs added to narrative only, and testing. Updated verbatim, coding and start date of event (death due to suicide: hung himself), corresponding fields and narrative.

Update 13Apr2017: Additional information was received on 10Apr2017 from a consumer in the form of an amended plaintiff fact sheet forwarded by an attorney. Added more specific dates to medical history heart attack, arteriosclerosis, angioplasty, and hypertension. Added medical history of androgen deficiency and hypogonadism. Added statement to narrative describing more specific dates for total period of time treated with TRT. Updated start date and dates of use for testosterone 2% solution; and updated other TRT with more specific dates for duration of use. Updated the narrative and fields accordingly.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?	Comment
Angina pectoris	2003		UNKNOWN	
Arteriosclerosis	(b) (6)		UNKNOWN	2003 & 2012: unspecified surgeries
Hypertension	(b) (6)		UNKNOWN	
Myocardial infarction	(b) (6)		UNKNOWN	inferior posterior MI with thrombolytic therapy
Stent placement	(b) (6)		UNKNOWN	
Angioplasty	(b) (6)		UNKNOWN	

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Coronary artery disease	(b) (6)	UNKNOWN	2003 and 2012
Androgen deficiency	2011	UNKNOWN	
Hypogonadism	2011	UNKNOWN	
Angioplasty	2012	UNKNOWN	
Alcohol use			12 drinks per week
Anxiety			
Arthritis			
Benign prostatic hyperplasia			
Bipolar disorder			
Blood cholesterol increased			
Caffeine consumption			2 drinks per day (coffee)
Cervical spinal stenosis			C4, C5
Costochondritis			
Depression			
Drug abuser			
Dyslipidaemia			
Familial risk factor			
Familial risk factor			M,D,B:CP,abnormal HB,arteriosclerosis,CVD, congenital heart condition,CHF/CM,CAD,MI,HTN
Fibromyalgia			
Gastrooesophageal reflux disease			
Hepatitis C			secondary to IV drug abuse
Non-cardiac chest pain			

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Osteoarthritis

Tobacco user

Type 2 diabetes mellitus

Medical History Product(s)	Start Date	End Date	Indication(s)	MedDRA Preferred Term(s)
INTERFERON			Hepatitis C	No adverse event

Relevant Laboratory Data:

Test Date	Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail Y/N
(b) (6)	Nuclear magnetic resonance imaging					Y
(b) (6)	Echocardiogram					Y
(b) (6)	Brain CT					Y
(b) (6)	MRI brain					Y
(b) (6)	Brain CT					Y

Concomitant Products:

#	Product Name	Dose/Frequency	Route	Dosage Text	Indication(s)	Start Date	End Date	Interval 1st Dose to Event

Reporter Source:

Study Report:	Study Name:	Study Type:	Sponsor Study:	Protocol	IND #:
No					

Literature Text:

Country of Event: USA **Sender MFR:** ELI LILLY AND CO

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Batch Printing Report for Cases

Reporter Name: (b) (6)
Reporter Org.:
Reporter Street:
Reporter City:
Reporter Zip:
Health Prof.:
Occupation:

Reporter Type:
Reporter Email:
Reporter Phone:
Reporter State: (b) (6)
Reporter Country: UNITED STATES
Sent To:
Identity Disclosed:

Reporter Name: (b) (6)
Reporter Org.:
Reporter Street:
Reporter City:
Reporter Zip:
Health Prof.:
Occupation: PHYSICIAN

Reporter Type:
Reporter Email:
Reporter Phone:
Reporter State: (b) (6)
Reporter Country: UNITED STATES
Sent To:
Identity Disclosed:

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FDA - Adverse Event Reporting System (FAERS)

Batch Printing Report for Cases

Reporter Name:	(b) (6)	**Reporter Type:**	
Reporter Org.:		**Reporter Email:**	
Reporter Street:		**Reporter Phone:**	
Reporter City:		**Reporter State:**	(b) (6)
Reporter Zip:		**Reporter Country:**	UNITED STATES
Health Prof.:		**Sent To:**	
Occupation:	CONSUMER OR OTHER NON HEALTH PROFESSIONAL	**Identity Disclosed:**	

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FDA - Adverse Event Reporting System (FAERS)

Batch Printing Report for Cases

Case Information:

Case Id: 12089154 **Version:** 3 **Case Type:** 15-DAY **eSub:** Yes **HP:** **Country:** USA **Outcome(s):** OT,

FDA Rcvd. Date: 17-Mar-2017 **Init FDA Rcvd. Date:** 18-Feb-2016 **Mfr Rcvd. Date:** 10-Mar-2017 **Application Type:** NDA **Application #:** 021015

Mfr. Control #: US-ABBVIE-16P-163-1559493-00

Patient Information:

Patient ID: (b) (6) **Age:** **Age in Years:** **Sex:** Male **Weight:** KG **DoB:** (b) (6)

Suspect Products:

#	Product Name	Dose/Frequency	Route	Dosage Text	Indication(s)	Start Date	End Date	Interval 1st Dose to Event	ReC	DeC
1	ANDROGEL	/	TOP	12. 5mg of testostone daily			2015		NA	Yes
2	ANDROGEL	/	TOP	12. 5mg of testostone daily	Hypogonadism	2007			NA	Yes
3	TESTOSTERONE	/	UNK			2015	2016		NA	NA
4	TESTOSTERONE	/	UNK	PELLETS		2015	2015		NA	NA
5	TESTOSTERONE	/	OTH		Hypogonadism	Sep-2016			NA	NA

#	Product Name	Lot#	Exp Date	NDC #	Labeler	OTC
1	ANDROGEL	32809,NOT AVAILABLE				
2	ANDROGEL	32809,NOT AVAILABLE				
3	TESTOSTERONE	UNKNOWN,UNKNOWN,UNKNOWN				
4	TESTOSTERONE	UNKNOWN,UNKNOWN,UNKNOWN				
5	TESTOSTERONE	UNKNOWN,UNKNOWN,UNKNOWN				

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FDA - Adverse Event Reporting System (FAERS)

Batch Printing Report for Cases

Event Information:

MedDRA © PreferredTerm	Start Date	End Date	Outcomes	Highlighted Terms	ReC
Depression	01-Jan-2013	01-Jan-2013	RECOVERED/ RESOLVED	N	NA
Emotional Distress	01-Jan-2013	01-Jan-2013	RECOVERED/ RESOLVED	N	NA
Fatigue	01-Jan-2013	01-Jan-2013	RECOVERED/ RESOLVED	N	NA
Suicidal Ideation	01-Jan-2013	01-Jan-2013	RECOVERED/ RESOLVED	N	NA
Asthenia	01-Jan-2015		NOT RECOVERED/ NOT RESOLVED	N	NA
Depression	01-Jan-2015		NOT RECOVERED/ NOT RESOLVED	N	NA
Hot Flush	01-Jan-2015		NOT RECOVERED/ NOT RESOLVED	N	NA
Hyperhidrosis	01-Jan-2015		NOT RECOVERED/ NOT RESOLVED	N	NA
Withdrawal Syndrome	01-Jan-2015		NOT RECOVERED/ NOT RESOLVED	N	NA
Feeling Abnormal			NOT RECOVERED/ NOT RESOLVED	N	NA

Event/Problem Narrative:

Solicited report from the USA by a consumer of an adult male with events of SUICIDAL IDEATION, DEPRESSION WORSEN and EMOTIONAL CRASH and non-serious FATIGUE, WITHDRAWAL SYNDROME, PHYSICAL WEAKNESS, DEPRESSION, HOT FLASHES, SWEATING and BRAIN FOG with ANDROGEL (TESTOSTERONE).

On an unknown date, the patient experienced BRAIN FOG. In 2013, the patient experienced SUICIDAL IDEATION, DEPRESSION WORSEN, EMOTIONAL CRASH and FATIGUE. In 2013, the SUICIDAL IDEATION, DEPRESSION WORSEN, EMOTIONAL CRASH and FATIGUE resolved. In 2015, the patient experienced WITHDRAWAL SYNDROME, PHYSICAL WEAKNESS, DEPRESSION, HOT FLASHES and SWEATING. TESTOSTERONE was also considered suspect.

In 2013 the patient had to stop using Androgel because his insurance stopped covering it and he could not afford it. Shortly after he stopped using Androgel he experience as he stated an emotional crash, extreme fatigue where he needed to take 3 naps a day, his depression worsen and had suicidal ideation. His physician was aware. No treatment was given. He switched to another insurance that did cover Androgel. When he was able to resume his Androgel therapy his events resolved.

In 2015 the patient stopped his Androgel 1% due to cost. The patient experienced intermittently withdrawal syndrome described as physical weakness, depression worsening, hot flashes, sweating, and brain fog and his physician prescribed Testosterone pellets. After 3 months his physician switched him to the Testosterone cream for 6 months then testosterone injections which he still experiences intermittent withdrawal syndrome, physical weakness, depression worsening, hot flashes, sweating, and brain fog. The patient stated stated he started using androgel 8 years ago to gain increased energy and sense of well being. however 3 years ago he stopped taking due to not being able to afford and he had very debilitating withdrawal symptoms; weakness, hot flashes, sweating, depression and brain fog. His physician was aware andno treatment was given

.The patient was on concomitant medications but declined to provide. The patient did not give us permission to contact his physician. The patient had no further information. Primary reporter does not have the lot number information, because the packaging was discarded.

The patient's past medications include:
ANXIRON for HYPOGONADISM

Causality for ANDROGEL(TESTOSTERONE)

The reporter's causality for the event(s) of SUICIDAL IDEATION, DEPRESSION WORSEN, EMOTIONAL CRASH and FATIGUE with ANDROGEL(TESTOSTERONE) was a reasonable possibility. The reporter's causality for the event(s) of WITHDRAWAL SYNDROME, PHYSICAL WEAKNESS, DEPRESSION, HOT FLASHES, SWEATING and BRAIN FOG with ANDROGEL(TESTOSTERONE) was no reasonable possibility.

Change History

On 01 Mar 2017, received updates to patient demographics, medical history, event information, reporter opinion of causality, suspect drug information, concomitant drug information and narrative description.

On 10 Mar 2017, received updates to suspect drug information and narrative description.

Relevant Medical History:

Patient Medical History

NO KNOWN ALLERGIES
DEPRESSION
ANXIETY
NON SMOKER
DRINKS 1 GLASS OF WINE A YEAR
HIGH BLOOD PRESSURE
HIGH CHOLESTEROL
DIABETES

Disease/Surgical Procedure	Start Date	End Date	Continuing?	Comment
Anxiety				
Blood pressure high				

Depression

Diabetes

High cholesterol

Non-smoker

Social alcohol drinker

Medical History Product(s)	Start Date	End Date	Indication(s)	MedDRA Preferred Term(s)
ANXIRON			Hypogonadism	

Relevant Laboratory Data:

Test Date	Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail Y/N

Concomitant Products:

#	Product Name	Dose/Frequency	Route	Dosage Text	Indication(s)	Start Date	End Date	Interval 1st Dose to Event
1	MULTIVITAMIN	/			Drug use for unknown indication			
2	METFORMIN	/			Diabetes			
3	COD LIVER OIL	/			Drug use for unknown indication			
4	METOPROLOL	/			Blood pressure high			
5	MAGNESIUM	/			Drug use for unknown indication			
6	PRAVASTATIN	/			High cholesterol			
7	WELLBUTRIN	/			Depression			
8	VITAMIN D	/			Drug use for unknown indication			
9	CARTIA	/			Blood pressure high			
10	SERELAX	/			Depression			

***Age in Years displays a mid-value where the Age Unit in the report is in DECADE**

FDA - Adverse Event Reporting System (FAERS)

Batch Printing Report for Cases

Reporter Source:

Study Report:	Study Name:	Study Type:	Sponsor Study:	Protocol	IND #:
No	FACILITATED COLLECTION				

Literature Text:

Country of Event: USA **Sender MFR:** ABBVIE

Reporter Name:
Reporter Org.:
Reporter Street:
Reporter City:
Reporter Zip:
Health Prof.:
Occupation: CONSUMER OR OTHER NON HEALTH PROFESSIONAL

Reporter Type:
Reporter Email:
Reporter Phone:
Reporter State:
Reporter Country: UNKNOWN
Sent To:
Identity Disclosed:

Reporter Name: (b) (6)
Reporter Org.:
Reporter Street:
Reporter City:
Reporter Zip:
Health Prof.:
Occupation: CONSUMER OR OTHER NON HEALTH PROFESSIONAL

Reporter Type:
Reporter Email:
Reporter Phone:
Reporter State: (b) (6)
Reporter Country: UNITED STATES
Sent To:
Identity Disclosed:

***Age in Years displays a mid-value where the Age Unit in the report is in DECADE**

FDA - Adverse Event Reporting System (FAERS)

Batch Printing Report for Cases

Case Information:

Case Id: 12113842 **Version:** 1 **Case Type:** 15-DAY **eSub:** Yes **HP:** **Country:** USA **Outcome(s):** DE

FDA Rcvd. Date: 25-Feb-2016 **Init FDA Rcvd. Date:** 25-Feb-2016 **Mfr Rcvd. Date:** 17-Oct-2014 **Application Type:** ANDA **Application #:** 091244

Mfr. Control #: US-WEST-WARD PHARMACEUTICALS CORP.-US-H14001-16-00309

Patient Information:

Patient ID: UNKNOWN **Age:** 47. (b) (6) YR **Age in Years:** 47. (b) (6) YR **Sex:** Male **Weight:** **DoB:** (b) (6)

Suspect Products:

#	Product Name	Dose/Frequency	Route	Dosage Text	Indication(s)	Start Date	End Date	Interval 1st Dose to Event	ReC	DeC
1	TESTOSTERONE CYPIONATE INJECTION	1 ML/	IM		Testosterone low				NA	NA

#	Product Name	Lot#	Exp Date	NDC #	Labeler	OTC
1	TESTOSTERONE CYPIONATE INJECTION				HIKMA	

Event Information:

MedDRA © PreferredTerm	Start Date	End Date	Outcomes	Highlighted Terms	ReC
Mental Disorder	(b) (6)		FATAL	N	NA
Completed Suicide	(b) (6)	(b) (6)	FATAL	N	NA
Anxiety			FATAL	N	NA
Depression			FATAL	N	NA
Partner Stress					NA

Event/Problem Narrative:

Case reference number US-H14001-16-00309 is a spontaneous case report from the United States received from a consumer, the patient's wife, on 17-Oct-2014, which concerns a 47-year-old Caucasian male patient with a medical history of a little anxiety, low testosterone and bipolar disorder.

The patient?s concomitant medications included insulin, Antivert (nicotinic acid and meclozine hydrochloride), lamotrigine, Paxil (piroxicam), Xanax (alprazolam) for anxiety, an unknown mood stabiliser and unspecified thyroid medication; no further information was provided.

Approximately four years prior to reporting, the patient was taking AndroGel (testosterone) for low testosterone, but it was not

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working. One to two years before the report, the patient switched to intramuscular Testosterone Cypionate Injection (testosterone cypionate) on his request, at a dose of 1 mL every three days.

The patient?s wife reported that she felt her husband's dose was excessive and stated that the health care professional who prescribed it got arrested for dispensing narcotics.

Over the year to year and a half preceding the report, the patient developed bad depression and experienced increased anxiety. Eight months prior to the patient?s suicide, he and his wife separated. The reporter noticed more anxiety in the patient after their separation.

On (b) (6) the patient emailed his lawyer and stated he had an illness and he was going to hospital, which he did not carry out. He stated he was having a mini nervous breakdown. On (b) (6) the patient jumped off (b) (6) and committed suicide.

It was unknown if the patient's therapy with testosterone was ongoing at the time of his death.

No further information was available.

Company comment: Completed suicide, depression with fatal outcome, increased anxiety with fatal outcome and mini nervous breakdown with fatal outcome are unlisted for testosterone. The patient was on prolonged therapy with testosterone when he experienced increased anxiety and depression. In that period the patient got divorced which probably contributed to mini nervous breakdown and decision to commit suicide. However, contribution of testosterone could not be excluded and therefore causal relationship between testosterone and all mentioned events is possible.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?	Comment
Anxiety				a little
Bipolar disorder				
Testosterone low				

FDA - Adverse Event Reporting System (FAERS)

Batch Printing Report for Cases

Medical History Product(s)	Start Date	End Date	Indication(s)	MedDRA Preferred Term(s)
ANDROGEL	2010		Testosterone low	

Relevant Laboratory Data:

Test Date	Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail Y/N

Concomitant Products:

#	Product Name	Dose/Frequency	Route	Dosage Text	Indication(s)	Start Date	End Date	Interval 1st Dose to Event
1	ANTIVERT	/	UNK		Drug use for unknown indication			
2	LAMOTRIGINE	/	UNK		Drug use for unknown indication			
3	INSULIN	/	UNK		Drug use for unknown indication			
4	PAXIL	/	UNK		Drug use for unknown indication			
5	XANAX	/	UNK		Anxiety			

Reporter Source:

Study Report:	Study Name:	Study Type:	Sponsor Study:	Protocol	IND #:
No					

Literature Text:

Country of Event: USA **Sender MFR:** WESTWARD

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FDA - Adverse Event Reporting System (FAERS)

Batch Printing Report for Cases

Reporter Name:	(b) (6)	**Reporter Type:**	
Reporter Org.:		**Reporter Email:**	
Reporter Street:		**Reporter Phone:**	
Reporter City:		**Reporter State:**	
Reporter Zip:		**Reporter Country:**	UNITED STATES
Health Prof.:		**Sent To:**	
Occupation:	CONSUMER OR OTHER NON HEALTH PROFESSIONAL	**Identity Disclosed:**	

***Age in Years displays a mid-value where the Age Unit in the report is in DECADE**

FDA - Adverse Event Reporting System (FAERS)

Batch Printing Report for Cases

Case Information:

Case Id: 12125692 **Version:** 1 **Case Type:** PERIODIC **eSub:** Yes **HP:** **Country:** USA **Outcome(s):**

FDA Rcvd. Date: 29-Feb-2016 **Init FDA Rcvd. Date:** 29-Feb-2016 **Mfr Rcvd. Date:** 23-Sep-2015 **Application Type:** NDA **Application #:** 021015

Mfr. Control #: US-ABBVIE-15P-163-1472625-00

Patient Information:

Patient ID: (b) (6) **Age:** 60.(b) (6) YR **Age in Years:** 60.(b) (6) YR **Sex:** Male **Weight:** **DoB:** (b) (6)

Suspect Products:

#	Product Name	Dose/Frequency	Route	Dosage Text	Indication(s)	Start Date	End Date	Interval 1st Dose to Event	ReC	DeC
1	ANDROGEL	/QD	TOP	81 milligram		Sep-2015			NA	NA
2	ANDROGEL	/QD	TOP	2 pumps, 40.5 milligram daily	Testosterone low	Aug-2015	Sep-2015		NA	NA

#	Product Name	Lot#	Exp Date	NDC #	Labeler	OTC
1	ANDROGEL	90823				
2	ANDROGEL	90823				

Event Information:

MedDRA © PreferredTerm	Start Date	End Date	Outcomes	Highlighted Terms	ReC
Agitation	01-Sep-2015		NOT RECOVERED/ NOT RESOLVED	N	NA
Anxiety	01-Sep-2015		NOT RECOVERED/ NOT RESOLVED	N	NA
Blood Testosterone Decreased	01-Sep-2015		NOT RECOVERED/ NOT RESOLVED	N	NA
Chest Pain	01-Sep-2015	01-Sep-2015	RECOVERED/ RESOLVED	N	NA
Dyspnoea	01-Sep-2015	01-Sep-2015	RECOVERED/ RESOLVED	N	NA
Muscular Weakness	01-Sep-2015		NOT RECOVERED/ NOT RESOLVED	N	NA
Suicidal Ideation			UNKNOWN	N	NA

***Age in Years displays a mid-value where the Age Unit in the report is in DECADE**

Event/Problem Narrative:

Solicited report from the USA by a consumer of a male with events of non-serious CHEST PAIN, ANXIETY INCREASED, AGITATION INCREASED, SHORTNESS OF BREATH, TOTAL TESTOSTERONE LEVEL DECREASED, LEG WEAKNESS and WISHED HIS LIFE WOULD END with ANDROGEL (TESTOSTERONE).

On an unknown date, the patient experienced WISHED HIS LIFE WOULD END. In September 2015, the patient experienced CHEST PAIN, ANXIETY INCREASED, AGITATION INCREASED, SHORTNESS OF BREATH, TOTAL TESTOSTERONE LEVEL DECREASED and LEG WEAKNESS. In September 2015, the CHEST PAIN and SHORTNESS OF BREATH resolved. Approximately three weeks ago, the patient's ANDROGEL was increased to 81mg due to low total testosterone level. The patient had been experiencing increased anxiety and agitation that started a few days after the ANDROGEL dose was increased. The patient had an episode of shortness of breath and chest pain when he became anxious and agitated three weeks ago. The patient had been experiencing leg weakness. The patient stated to his wife that he wished his life would end so he would not have to experience anxiety and agitation. No further follow-up information is available.

The patient was treated with DICLOFENAC.

Causality for ANDROGEL(TESTOSTERONE)

The reporter's statement of causality for the events of CHEST PAIN, ANXIETY INCREASED, AGITATION INCREASED, SHORTNESS OF BREATH, TOTAL TESTOSTERONE LEVEL DECREASED, LEG WEAKNESS and WISHED HIS LIFE WOULD END was not provided.

Relevant Medical History:

NO KNOWN ALLERGIES

HYPERTENSION
ANXIETY
AGITATION
NON-SMOKER
ABSTAINS FROM ALCOHOL

Disease/Surgical Procedure	Start Date	End Date	Continuing?	Comment
Abstains from alcohol				
Agitation				
Anxiety				
Hypertension				
Non-smoker				

***Age in Years displays a mid-value where the Age Unit in the report is in DECADE**

FDA - Adverse Event Reporting System (FAERS)

Batch Printing Report for Cases

Medical History Product(s)	Start Date	End Date	Indication(s)	MedDRA Preferred Term(s)

Relevant Laboratory Data:

Test Date	Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail Y/N
01-Sep-2015	Testosterone	Low				N

Concomitant Products:

#	Product Name	Dose/Frequency	Route	Dosage Text	Indication(s)	Start Date	End Date	Interval 1st Dose to Event
1	XANAX	/	PO		Agitation			
2	PROZAC	/	PO		Anxiety			
3	LISINOPRIL	/	PO		Hypertension			
4	XANAX	/			Anxiety			

Reporter Source:

Study Report:	Study Name:	Study Type:	Sponsor Study:	Protocol	IND #:
No				FACILITATED COLLECT	

Literature Text:

Country of Event: USA **Sender MFR:** ABBVIE

***Age in Years displays a mid-value where the Age Unit in the report is in DECADE**

FDA - Adverse Event Reporting System (FAERS)

Batch Printing Report for Cases

Reporter Name:	In Confidence	**Reporter Type:**	
Reporter Org.:		**Reporter Email:**	
Reporter Street:		**Reporter Phone:**	
Reporter City:		**Reporter State:**	
Reporter Zip:		**Reporter Country:**	UNITED STATES
Health Prof.:		**Sent To:**	
Occupation:	CONSUMER OR OTHER NON HEALTH PROFESSIONAL	**Identity Disclosed:**	

Reporter Name:		**Reporter Type:**	
Reporter Org.:		**Reporter Email:**	
Reporter Street:		**Reporter Phone:**	
Reporter City:		**Reporter State:**	
Reporter Zip:		**Reporter Country:**	UNKNOWN
Health Prof.:		**Sent To:**	
Occupation:	CONSUMER OR OTHER NON HEALTH PROFESSIONAL	**Identity Disclosed:**	

***Age in Years displays a mid-value where the Age Unit in the report is in DECADE**

FDA - Adverse Event Reporting System (FAERS)

Batch Printing Report for Cases

Case Information:

Case Id: 12225860 **Version:** 1 **Case Type:** 15-DAY **eSub:** Yes **HP:** **Country:** USA **Outcome(s):** DS,HO,OT

FDA Rcvd. Date: 31-Mar-2016 **Init FDA Rcvd. Date:** 31-Mar-2016 **Mfr Rcvd. Date:** 29-Dec-2015 **Application Type:** NDA **Application #:** 009165

Mfr. Control #: US-ENDO PHARMACEUTICALS INC.-2015-005244

Patient Information:

Patient ID: (b) (6) **Age:** 45. (b) (6) YR **Age in Years:** 45. (b) (6) YR **Sex:** Male **Weight:** 77.18 KG **DoB:** (b) (6)

Suspect Products:

#	Product Name	Dose/Frequency	Route	Dosage Text	Indication(s)	Start Date	End Date	Interval 1st Dose to Event	ReC	DeC
1	ANDROGEL	/	UNK		Androgen replacement therapy	Apr-2008		7 Month	NA	NA
2	DELATESTRYL	/	UNK		Androgen replacement therapy	Mar-2002	04-Oct-2002	6 Year	NA	NA
3	DEPO TESTOSTERONE	100 MG/	IM		Androgen replacement therapy	2000		8 Year	NA	NA

#	Product Name	Lot#	Exp Date	NDC #	Labeler	OTC
1	ANDROGEL					
2	DELATESTRYL				ENDO	
3	DEPO TESTOSTERONE					

Event Information:

MedDRA © PreferredTerm	Start Date	End Date	Outcomes	Highlighted Terms	ReC
Suicide Attempt	(b) (6)		UNKNOWN	N	NA
Cardiomegaly	01-Jan-2008		NOT RECOVERED/ NOT RESOLVED	N	NA
Deep Vein Thrombosis	01-Jan-2008		UNKNOWN	N	NA
Heart Rate Irregular	01-Jan-2008		UNKNOWN	N	NA
Chronic Obstructive Pulmonary Disease	26-Mar-2008		UNKNOWN	N	NA
Acute Myocardial Infarction	(b) (6)		NOT RECOVERED/ NOT RESOLVED	N	NA
Cardiovascular Disorder	(b) (6)		NOT RECOVERED/ NOT RESOLVED	N	NA

***Age in Years displays a mid-value where the Age Unit in the report is in DECADE**

Event/Problem Narrative:

A spontaneous report was received from a legal pleading via a Company representative concerning a male patient (age not reported) who began using Delatestryl injection as prescribed and indicated for TRT (testosterone replacement therapy) in approximately March 2002 on (total daily dose not reported). Other suspect TRT included Androgel and Depo Testosterone.

According to the pleading, the patient experienced a heart attack on (b) (6) The pleading stated that the event was caused by TRT. The pleading further stated that Delatestryl's design was defective.

The patient continued TRT until approximately November 2014. The outcome of the event of heart attack was not reported.

The event of heart attack was considered serious due to medical importance.

ADDITIONAL INFORMATION WAS RECEIVED FROM AN ATTORNEY IN THE FORM OF A PFS (PLAINTIFF FACT SHEET) AND MEDICAL RECORDS ON 24-MAR-2016:

ACCORDING TO THE PFS:

A 46 year old male patient was treated with TRT from 1995 to the present. He used Depo Testosterone from 2000 to 2012 (every other week), and testosterone cypionate (every seven days) from 2012 to the present. It was unspecified what product the patient used in 1995.

Note: The PFS did not reference Delatestryl or testosterone enanthate.

It was reported that the patient experienced a heart attack in 2008, was hospitalized and underwent stent placement. The PFS further stated that the patient experienced the following in 2008: abnormal or irregular heartbeat, cardiovascular disease, enlarged heart/cardiomegaly, and deep vein thrombosis (DVT). The patient filed for disability due to heart attack in 2008.

Medical history included smoking (1 ppd for 40 years; quit 01-OCT-2015), caffeine (3 drinks per day), AIDS (1990; filed for disability in 1994), congestive heart failure or cardiomyopathy (2000; hospitalized), mental health counseling (2005-present).

The patient continued testosterone cypionate until the present.

ACCORDING TO MEDICAL RECORDS:

Pharmacy records reflect the patient was dispensed Delatestryl from 06-MAY-2002 until 04-OCT-2002. He was dispensed Depo Testosterone or testosterone cypionate on multiple occasions from 13-FEB-2002 through 2014. The patient was dispensed Androgel on 02-APR-2008.

On (b) (6) a male patient with known syphilis was found with drug overdose of temazepam, Ambien, and oxycontin, reportedly a suicide attempt. He was hospitalized with altered mental status. Home medications were noted to include testosterone 200mg, temazepam, Ambien, Rozerem; Depakote for mood swings and irritability. The patient had taken himself off Paxil. He was very agitated in the ER and was given Haldol IV and activated charcoal. Subsequently the patient was reportedly without suicidal ideation and was approved by Psychiatry for discharge on (b) (6)

Medical history included IV methamphetamine abuse, HIV, tobacco use, COPD, hypertension, syphilis, suicide attempt ((b) (6) (b) (6) hospitalized), depression, insomnia, osteoarthritis.

On (b) (6) the patient was hospitalized with COPD exacerbation. It was noted the patient had hypogonadism and was on Depo Testosterone at this time.

Hospital records reflect that a 46 year old male patient presented on (b) (6) with acute onset chest pressure, SOB, nausea after taking meth prior to intercourse. In the emergency room, the patient's EKG showed ST elevations II, III, AVF. Cath lab was activated and patient was given ASA, heparin, reopro, and metoprolol. Troponin I was 0.2 at that time. Cath result showed vasospasm of his coronary arteries and a high grade 80% lesion of his PDA which was angioplastied and stented with a bare metal stent. Patient arrived to the CCU noncompliant in nursing orders, demanding to leave and refusing medications. Risks and benefits were discussed with the patient, and with the help of his partner, medical staff were able to calm patient and have him monitored in the CCU for the day. He was transferred to telemetry the next day and did not have any events. Patient was adamant about leaving the hospital. It was recommended that he be monitored for at least 72 hours. Patient left hospital after less than 48 hours ((b) (6)). The importance of taking Plavix, aspirin, stopping IV methamphetamine and cocaine, and smoking cessation were discussed with patient. Discharge diagnosis included STEMI.

The outcome of the events of STEMI and cardiovascular disease, and enlarged heart/cardiomegaly was not recovered: PFS stated patient had an enlarged heart and continued to require monitoring of his heart condition. The outcome of the events of abnormal or irregular heartbeat, cardiovascular disease, and DVT was unspecified. The outcome of the events of suicide attempt and COPD exacerbation was not specified.

The events of STEMI and cardiovascular disease were considered serious due to hospitalization and disability or permanent damage. The events of abnormal or irregular heartbeat, enlarged heart/cardiomegaly, and DVT were considered serious due to the criterion of medical importance. The events of suicide attempt and COPD exacerbation were considered serious due to hospitalization.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?	Comment

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AIDS	1990			FILED FOR SOCIAL SECURITY DISABILITY 1994
Disability	1994			DUE TO AIDS
Cardiomyopathy	2000		UNKNOWN	
Congestive heart failure	2000		UNKNOWN	
Suicide attempt	(b) (6)		UNKNOWN	
Amphetamine abuse				
COPD				
Caffeine consumption				3 DRINKS PER DAY
Depression				
HIV positive				
Hypertension				
Insomnia			UNKNOWN	
Osteoarthritis				
Smoker		01-Oct-2015		1 PPD FOR 40 YEARS
Syphilis				

Medical History Product(s)	Start Date	End Date	Indication(s)	MedDRA Preferred Term(s)

Relevant Laboratory Data:

Test Date	Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail Y/N

Concomitant Products:

#	Product Name	Dose/Frequency	Route	Dosage Text	Indication(s)	Start Date	End Date	Interval 1st Dose to Event

***Age in Years displays a mid-value where the Age Unit in the report is in DECADE**

FDA - Adverse Event Reporting System (FAERS)

Batch Printing Report for Cases

Reporter Source:

Study Report:	Study Name:	Study Type:	Sponsor Study:	Protocol	IND #:
No					

Literature Text:

Country of Event: USA **Sender MFR:** ENDO

Reporter Name: (b) (6)
Reporter Org.:
Reporter Street:
Reporter City:
Reporter Zip:
Health Prof.:
Occupation:

Reporter Type:
Reporter Email:
Reporter Phone:
Reporter State: (b) (6)
Reporter Country: UNITED STATES
Sent To:
Identity Disclosed:

***Age in Years displays a mid-value where the Age Unit in the report is in DECADE**

FDA - Adverse Event Reporting System (FAERS)

Batch Printing Report for Cases

Case Information:

Case Id: 12323980 **Version:** 1 **Case Type:** PERIODIC **eSub:** Yes **HP:** **Country:** USA **Outcome(s):**

FDA Rcvd. Date: 02-May-2016 **Init FDA Rcvd. Date:** 02-May-2016 **Mfr Rcvd. Date:** 20-Aug-2015 **Application Type:** NDA **Application #:** 022309

Mfr. Control #: US-ABBVIE-15P-163-1449992-00

Patient Information:

Patient ID: (b) (6) **Age:** 36.(b) (6) Y **Age in Years:** 36 (b) (6) Y **Sex:** Male **Weight:** KG **DoB:** (b) (6)

Suspect Products:

#	Product Name	Dose/Frequency	Route	Dosage Text	Indication(s)	Start Date	End Date	Interval 1st Dose to Event	ReC	DeC
1	ANDROGEL 1.62%	/	TOP	2 pumps daily	Hypogonadism	05-Jun-2015	11-Jun-2015		NA	Yes

#	Product Name	Lot#	Exp Date	NDC #	Labeler	OTC
1	ANDROGEL 1.62%	unknown				

Event Information:

MedDRA © PreferredTerm	Start Date	End Date	Outcomes	Highlighted Terms	ReC
Application Site Erythema	05-Jun-2015	01-Jun-2015	RECOVERED/ RESOLVED	N	NA
Application Site Pruritus	05-Jun-2015	01-Jun-2015	RECOVERED/ RESOLVED	N	NA
Application Site Warmth	05-Jun-2015	01-Jun-2015	RECOVERED/ RESOLVED	N	NA
Suicidal Ideation	11-Jun-2015	01-Jun-2015	RECOVERED/ RESOLVED	N	NA
Hypersensitivity			RECOVERED/ RESOLVED	N	NA

Event/Problem Narrative:

Solicited report from the USA by a consumer of a 36 year old male with events of non-serious ALLERGIC REACTION, RED, RAISED, ITCHY BLOTCHES THAT WERE WARM AT APPLICATION SITE and SUICIDAL THOUGHT with ANDROGEL 1.62% (TESTOSTERONE).

On an unknown date, the patient experienced ALLERGIC REACTION. On 05 Jun 2015, the patient experienced RED, RAISED, ITCHY BLOTCHES THAT WERE WARM AT APPLICATION SITE. On 11 Jun 2015, the patient experienced SUICIDAL THOUGHT. In June 2015, the RED, RAISED, ITCHY BLOTCHES THAT WERE WARM AT APPLICATION SITE and SUICIDAL THOUGHT resolved. On an unknown date, ALLERGIC REACTION resolved. The patient developed an unknown allergic reaction while on Androgel. It was clarified by the patient's wife that the patient experienced red, raised, itchy

***Age in Years displays a mid-value where the Age Unit in the report is in DECADE**

blotches that were warm to the touch at the application site of his shoulders while on Androgel. He also experienced suicidal thoughts. His physician was aware. The patient discontinued the Androgel and no medication was prescribed for the events. All events resolved on their own. The primary reporter did no have the lot number information because the primary reporter declined to report the lot number. The reporter had no further information.

Causality for ANDROGEL 1.62%(TESTOSTERONE)

The reporter stated that there is a reasonable possibility that the events of ALLERGIC REACTION, RED, RAISED, ITCHY BLOTCHES THAT WERE WARM AT APPLICATION SITE onset 05 Jun 2015, SUICIDAL THOUGHT, RED, RAISED, ITCHY BLOTCHES THAT WERE WARM AT APPLICATION SITE onset 05 Jun 2015 and RED, RAISED, ITCHY BLOTCHES THAT WERE WARM AT APPLICATION SITE onset 05 Jun 2015 are related to ANDROGEL 1.62%(TESTOSTERONE).

Relevant Medical History:

The patient has no history of psychological, neurological, dermatological hypersensitivity, cardiovascular, liver, renal, or gastrointestinal disorders.
NO KNOWN ALLERGIES
NON SMOKER
ALCOHOL USE 1-2 BEERS PER MONTH
CPAP
DRY EYES
SLEEP APNEA

Disease/Surgical Procedure	Start Date	End Date	Continuing?	Comment
Alcohol use				
CPAP				
Dry eyes				
Non-smoker				
Sleep apnea				

Medical History Product(s)	Start Date	End Date	Indication(s)	MedDRA Preferred Term(s)

Relevant Laboratory Data:

Test Date	Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail Y/N
01-May-2015	Serum testosterone	153	NG/DL			N

***Age in Years displays a mid-value where the Age Unit in the report is in DECADE**

Concomitant Products:

#	Product Name	Dose/Frequency	Route	Dosage Text	Indication(s)	Start Date	End Date	Interval 1st Dose to Event
1	RESTASIS	/			Dry eyes			
2	TESTOSTERONE	/			Hypogonadism	Jul-2015		

Reporter Source:

Study Report:	Study Name:	Study Type:	Sponsor Study:	Protocol	IND #:
No				FACILITATED COLLECT	

Literature Text:

Country of Event: USA **Sender MFR:** ABBVIE

Reporter Name: In Confidence
Reporter Type:
Reporter Org.:
Reporter Email:
Reporter Street:
Reporter Phone:
Reporter City:
Reporter State:
Reporter Zip:
Reporter Country: UNITED STATES
Health Prof.:
Sent To:
Occupation: CONSUMER OR OTHER NON HEALTH PROFESSIONAL
Identity Disclosed:

***Age in Years displays a mid-value where the Age Unit in the report is in DECADE**

FDA - Adverse Event Reporting System (FAERS)

Batch Printing Report for Cases

Reporter Name:		**Reporter Type:**	
Reporter Org.:		**Reporter Email:**	
Reporter Street:		**Reporter Phone:**	
Reporter City:		**Reporter State:**	
Reporter Zip:		**Reporter Country:**	UNKNOWN
Health Prof.:		**Sent To:**	
Occupation:	CONSUMER OR OTHER NON HEALTH PROFESSIONAL	**Identity Disclosed:**	

***Age in Years displays a mid-value where the Age Unit in the report is in DECADE**

FDA - Adverse Event Reporting System (FAERS)

Batch Printing Report for Cases

Case Information:

Case Id: 12324544 **Version:** 1 **Case Type:** PERIODIC **eSub:** Yes **HP:** **Country:** USA **Outcome(s):**

FDA Rcvd. Date: 02-May-2016 **Init FDA Rcvd. Date:** 02-May-2016 **Mfr Rcvd. Date:** 15-Sep-2015 **Application Type:** NDA **Application #:** 022309

Mfr. Control #: US-ABBVIE-15P-163-1468048-00

Patient Information:

Patient ID: (b) (6) **Age:** **Age in Years:** **Sex:** Male **Weight:** **DoB:**

Suspect Products:

#	Product Name	Dose/Frequency	Route	Dosage Text	Indication(s)	Start Date	End Date	Interval 1st Dose to Event	ReC	DeC
1	ANDROGEL	1 PCT/	TOP		Drug use for unknown indication	2006	15-Aug-2015		NA	NA
2	ANDROGEL	1.62 PCT/	TOP		Drug use for unknown indication	2015	19-Sep-2015		NA	Yes

#	Product Name	Lot#	Exp Date	NDC #	Labeler	OTC
1	ANDROGEL	90791				
2	ANDROGEL	UNKNOWN,unknown				

Event Information:

MedDRA © PreferredTerm	Start Date	End Date	Outcomes	Highlighted Terms	ReC
Feelings Of Worthlessness	15-Aug-2015	19-Sep-2015	RECOVERED/ RESOLVED	N	NA
Headache	15-Aug-2015	19-Sep-2015	RECOVERED/ RESOLVED	N	NA
Social Avoidant Behaviour	15-Aug-2015	19-Sep-2015	RECOVERED/ RESOLVED	N	NA
Suicidal Ideation	15-Aug-2015	19-Sep-2015	RECOVERED/ RESOLVED	N	NA

Event/Problem Narrative:

Spontaneous report from the USA by a consumer of a male with events of non-serious DIDN'T WANT TO BE AROUND ANYBODY, FELT WORTHLESS, HEADACHES and SUICIDAL THOUGHTS with ANDROGEL (TESTOSTERONE) and ANDROGEL (TESTOSTERONE). There was no reported medical history.

On 15 Aug 2015, the patient experienced DIDN'T WANT TO BE AROUND ANYBODY, FELT WORTHLESS, HEADACHES and SUICIDAL THOUGHTS. On 19 Sep 2015, the DIDN'T WANT TO BE AROUND ANYBODY, FELT WORTHLESS, HEADACHES and SUICIDAL THOUGHTS resolved. The patient was on regular ANDROGEL before and did not experience

***Age in Years displays a mid-value where the Age Unit in the report is in DECADE**

the events. The patient was put on the higher concentration ANDROGEL by his physician for unknown reasons. After switching to the new concentration the patient experienced the events. The patient clarified with regards to the event of suicidal thoughts that he had no thoughts or plans to harm himself. The patient last took ANDROGEL on 19 Sep 2015 and was waiting on the Veterans Affairs clinical team to see what medication the patient will be on now. No further follow-up information is available.

Causality for ANDROGEL(TESTOSTERONE)

The reporter stated that there is a reasonable possibility that the events of DIDN'T WANT TO BE AROUND ANYBODY, FELT WORTHLESS, HEADACHES and SUICIDAL THOUGHTS are related to ANDROGEL(TESTOSTERONE).

Causality for ANDROGEL(TESTOSTERONE)

The reporter stated that there is no reasonable possibility that the events of DIDN'T WANT TO BE AROUND ANYBODY, FELT WORTHLESS, HEADACHES and SUICIDAL THOUGHTS are related to ANDROGEL(TESTOSTERONE).

Relevant Medical History:

The patient had never dealt with depression before the change in ANDROGEL concentration.

Disease/Surgical Procedure	Start Date	End Date	Continuing?	Comment

Medical History Product(s)	Start Date	End Date	Indication(s)	MedDRA Preferred Term(s)

Relevant Laboratory Data:

Test Date	Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail Y/N

Concomitant Products:

#	Product Name	Dose/Frequency	Route	Dosage Text	Indication(s)	Start Date	End Date	Interval 1st Dose to Event

Reporter Source:

Study Report:	Study Name:	Study Type:	Sponsor Study:	Protocol	IND #:
No					

***Age in Years displays a mid-value where the Age Unit in the report is in DECADE**

Literature Text:

Country of Event: USA **Sender MFR:** ABBVIE

Reporter Name: In Confidence
Reporter Type:
Reporter Org.:
Reporter Email:
Reporter Street:
Reporter Phone:
Reporter City:
Reporter State:
Reporter Zip:
Reporter Country: UNITED STATES
Health Prof.:
Sent To:
Occupation: CONSUMER OR OTHER NON HEALTH PROFESSIONAL
Identity Disclosed:

***Age in Years displays a mid-value where the Age Unit in the report is in DECADE**

FDA - Adverse Event Reporting System (FAERS)

Batch Printing Report for Cases

Case Information:

Case Id: 12386543 **Version:** 1 **Case Type:** 15-DAY **eSub:** Yes **HP:** **Country:** USA **Outcome(s):** HO

FDA Rcvd. Date: 19-May-2016 **Init FDA Rcvd. Date:** 19-May-2016 **Mfr Rcvd. Date:** 26-Feb-2016 **Application Type:** NDA **Application #:** 021454

Mfr. Control #: US-ENDO PHARMACEUTICALS INC.-2016-001479

Patient Information:

Patient ID: (b) (6) **Age:** 40.(b) (6) Y **Age in Years:** 40.(b) (6) Y **Sex:** Male **Weight:** KG **DoB:** (b) (6)

Suspect Products:

#	Product Name	Dose/Frequency	Route	Dosage Text	Indication(s)	Start Date	End Date	Interval 1st Dose to Event	ReC	DeC
1	ANDROGEL	/QD	UNK		Androgen replacement therapy	11-Dec-2011	26-Jun-2012	271 Day	NA	NA
2	TESTOSTERONE CYPIONATE	/QOW	UNK		Androgen replacement therapy	01-Jun-2011	30-Nov-2011	464 Day	NA	NA
3	Testim	/QD	TDER			12-Jun-2013	26-Feb-2014	37 Day	NA	NA
4	Testim	/QD	TDER		Androgen replacement therapy	01-Aug-2012	03-Feb-2013	37 Day	NA	NA

#	Product Name	Lot#	Exp Date	NDC #	Labeler	OTC
1	ANDROGEL					
2	TESTOSTERONE CYPIONATE					
3	Testim				AUXILIUM	
4	Testim				AUXILIUM	

Event Information:

MedDRA © PreferredTerm	Start Date	End Date	Outcomes	Highlighted Terms	ReC
Deep Vein Thrombosis	(b) (6)		UNKNOWN	N	NA
Suicide Attempt	(b) (6)		UNKNOWN	N	NA

***Age in Years displays a mid-value where the Age Unit in the report is in DECADE**

Event/Problem Narrative:

A spontaneous report was received from a legal pleading, via a Company representative, concerning a male patient (age at the time of event onset unspecified) who was prescribed and began using Testim from on or about June 2011 through on or about January 2014. The legal pleading stated that the patient was treated with another suspect drug, Androgel (testosterone), from on or about June 2011 through on or about January 2014.

The legal pleading stated that, on or about (b) (6) the patient experienced deep vein thrombosis. In addition, the legal pleading stated that because of his use of Testim the patient suffered a deep vein thrombosis. Furthermore, the legal pleading stated that Testim was defective.

Therapy with Testim was discontinued on or about January 2014. The event outcome was unspecified.

The event of deep vein thrombosis was considered serious due to the serious criterion of medical importance.

ADDITIONAL INFORMATION WAS RECEIVED FROM AN ATTORNEY IN THE FORM OF A PFS (PLAINTIFF FACT SHEET) AND MEDICAL RECORDS ON 12-MAY-2016:

ACCORDING TO THE PFS:

A male patient (67" 205 lbs) was treated with Testim daily from 01-AUG-2012 to 03-FEB-2013 and from 12-JUN-2013 to 26-FEB-2014. Other suspect TRT included testosterone cypionate bi-weekly (01-JUN-2011 to 30-NOV-2011) and Androgel daily (11-DEC-2011 to 26-JUN-2012).

It was reported that the patient experienced a deep vein thrombosis (DVT) of the left peroneal vein. The patient first became aware of the DVT when he was hospitalized for a suicide attempt ((b) (6)) and DVT was discovered during his hospital stay.

Medical history included disability due to back, neck, knee pain and mental health (approximately 2008), smoking (1982-2007; 1 ppd), snuff (1982-present, 1 can per day), caffeine (4-6 drinks per day), allergies (fluticasone: 2006-present), hypertension (2006; metoprolol: 2008-present), degenerative disc disease (2007), pain (pain management: 2007-2012), depression with anxiety (2007), syncope (ER visit, 2009), high cholesterol (atorvastatin: 2012-present), hypothyroidism (levothyroxine: 2012-present), BPH (tamsulosin: 2012-present), obstructive sleep apnea (2012), mental health treatment (psychiatrist: 2012).

Family history included coronary artery disease/heart disease and hypertension (mother).

The patient continued Testim until 03-FEB-2013. He resumed Testim therapy on 12-JUN-2013 (until 26-FEB-2014).

ACCORDING TO MEDICAL RECORDS:

Total testosterone was measured at 153 ng/dL (250-1100) on 17-APR-2012; free testosterone 36.4 pg/mL (35-155).

Records dated 28-AUG-2012 reflected patient was being slowly tapered off amitriptyline and plan was to subsequently start Viibryd. He was instructed 'ER for any suicidal or homicidal thoughts.'

Medical records reflect that a 40 year old Caucasian male was hospitalized on (b) (6) secondary to intentional suicide attempt by overdose of amitriptyline and possibly valproic acid. The patient was found unresponsive by family member after talking to a friend the evening of admission. Empty bottle of Elavil and Depakote were found next to the patient, unclear how much was taken. Patient's friend reported patient had made suicidal statements the previous week and in the past. Paramedics administered Narcan and 25 g of charcoal via NG tube. The patient was not saturating well and was intubated to protect his airway. He was put on 1:1 for agitation and any suicidal attempt. He gradually improved with no further episodes of agitation. Patient was slowly weaned off the ventilator.

While hospitalized, patient was found to have a an acute DVT of the left peroneal vein and was started on Lovenox and Coumadin. The patient was discharged on (b) (6) and signed himself in for psychiatric treatment on the same date. It was noted patient's chief complaint was 'I just did something stupid' (status post Elavil OD).

Medications at time of admission were noted to include metoprolol, Lipitor, amitriptyline, tamsulosin, cyclobenzaprine, Depakote, Synthroid, and Testim.

Medical history included major depressive disorder, anxiety disorder, insomnia, opiate abuse/dependence (Percocet, hydrocodone, methadone, MS Contin, etc., cocaine, benzodiazepines; Suboxone for narcotic abuse (for years, began 08-AUG-2007, end date unspecified), chest pain (24-SEP-2009; chest x-ray negative for cardiopulmonary abnormality), chronic pain, hypothyroidism, hyperlipidemia, BPH, hypertension, pitting edema both legs (Doppler ultrasound on 03-APR-2012 negative for DVT), obstructive sleep apnea (noted 24-JUL-2012), hypogonadism, erosive esophagitis.

The outcome of the events of DVT and intentional suicide attempt by overdose was unspecified.

The events of DVT and intentional suicide attempt by overdose were considered serious due to hospitalization.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?	Comment
Smoker	1982	2007		1 PPD

Tobacco user	1982		1 CAN PER DAY
Allergy	2006		
Hypertension	2006		
Anxiety disorder	2007		
Degenerative disc disease	2007		
Major depression	2007		
Disability	2008		DUE TO BACK, NECK, KNEE PAIN AND MENTAL HEALTH
Mental disorder	2008		
Syncope	2009		
Chest pain	24-Sep-2009	UNKNOWN	
Leg edema	03-Apr-2012	UNKNOWN	
BPH		UNKNOWN	
Caffeine consumption			4-6 DRINKS PER DAY
Chronic pain			
Cocaine abuse		UNKNOWN	
Dependence on opiates			PERCOCET, HYDROCODONE, METHADONE, MS CONTIN
Erosive esophagitis		UNKNOWN	
Family history of cardiovascular disorder			
High cholesterol			
Hypogonadism			
Hypothyroidism			
Insomnia			

***Age in Years displays a mid-value where the Age Unit in the report is in DECADE**

Obstructive sleep apnea syndrome

Medical History Product(s)	Start Date	End Date	Indication(s)	MedDRA Preferred Term(s)

Relevant Laboratory Data:

Test Date	Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail Y/N

Concomitant Products:

#	Product Name	Dose/Frequency	Route	Dosage Text	Indication(s)	Start Date	End Date	Interval 1st Dose to Event
1	LIPITOR	/	UNK		Hyperlipidemia	2012		
2	METOPROLOL	/	UNK		Hypertension	2008		
3	AMITRIPTYLINE	/	UNK		Depression			
4	TAMSULOSIN	/	UNK		BPH			
5	FLUTICASONE	/	UNK		Allergy	2006		
6	SYNTHROID	/	UNK		Hypothyroidism			
7	CYCLOBENZAPRINE	/	UNK		Drug use for unknown indication			
8	DEPAKOTE	/	UNK		Drug use for unknown indication			

Reporter Source:

Study Report:	Study Name:	Study Type:	Sponsor Study:	Protocol	IND #:
No					

Literature Text:

Country of Event: USA **Sender MFR:** ENDO

***Age in Years displays a mid-value where the Age Unit in the report is in DECADE**

FDA - Adverse Event Reporting System (FAERS)

Batch Printing Report for Cases

Reporter Name:	(b) (6)	**Reporter Type:**	
Reporter Org.:		**Reporter Email:**	
Reporter Street:		**Reporter Phone:**	
Reporter City:		**Reporter State:**	(b) (6)
Reporter Zip:		**Reporter Country:**	UNITED STATES
Health Prof.:		**Sent To:**	
Occupation:		**Identity Disclosed:**	

***Age in Years displays a mid-value where the Age Unit in the report is in DECADE**

FDA - Adverse Event Reporting System (FAERS)

Batch Printing Report for Cases

Case Information:

Case Id: 12434752 **Version:** 2 **Case Type:** 15-DAY **eSub:** Yes **HP:** **Country:** USA **Outcome(s):** DS,HO,OT

FDA Rcvd. Date: 06-Jan-2017 **Init FDA Rcvd. Date:** 03-Jun-2016 **Mfr Rcvd. Date:** 27-Dec-2016 **Application Type:** NDA **Application #:** 021454

Mfr. Control #: US-ENDO PHARMACEUTICALS INC.-2016-003589

Patient Information:

Patient ID: (b) (6) **Age:** 55.(b) (6) Y **Age in Years:** 55.(b) (6) Y **Sex:** Male **Weight:** KG **DoB:** (b) (6)

Suspect Products:

#	Product Name	Dose/Frequency	Route	Dosage Text	Indication(s)	Start Date	End Date	Interval 1st Dose to Event	ReC	DeC
1	ANDRODERM	/QD	UNK		Androgen replacement therapy	25-May-2010	16-Dec-2010	75 Day	NA	NA
2	ANDROGEL	/	UNK	1 PUMP EACH SHOULDER	Androgen replacement therapy	25-Aug-2005	01-Aug-2008	5 Year	NA	NA
3	ANDROGEL	/	UNK	1 PUMP EACH SHOULDER, FREQUENCY UNSPECIFIED		15-Oct-2013	20-May-2015	5 Year	NA	NA
4	Testim	/	TDER	1 PUMP EACH SHOULDER	Androgen replacement therapy		03-Sep-2013		NA	Unk

#	Product Name	Lot#	Exp Date	NDC #	Labeler	OTC
1	ANDRODERM					
2	ANDROGEL					
3	ANDROGEL					
4	Testim				AUXILIUM	

Event Information:

MedDRA © PreferredTerm	Start Date	End Date	Outcomes	Highlighted Terms	ReC
Cerebrovascular Accident	(b) (6)		NOT RECOVERED/ NOT RESOLVED	N	NA
Pulmonary Embolism	(b) (6)		NOT RECOVERED/ NOT RESOLVED	N	NA
Brain Injury	(b) (6)		UNKNOWN	N	NA
Suicide Attempt	(b) (6)		UNKNOWN	N	NA

***Age in Years displays a mid-value where the Age Unit in the report is in DECADE**

MedDRA Â PreferredTerm	Start Date	End Date	Outcomes	Highlighted Terms	ReC
Pulmonary Embolism	(b) (6)		NOT RECOVERED/ NOT RESOLVED	N	NA
Coronary Artery Disease	(b) (6)		UNKNOWN	N	NA
Pulmonary Infarction	(b) (6)		UNKNOWN	N	NA

Event/Problem Narrative:

INFORMATION FROM A LEGAL PLEADING (VIA A COMPANY REPRESENTATIVE) AND ADDITIONAL INFORMATION FROM AN ATTORNEY IN THE FORM OF A PFS (PLAINTIFF FACT SHEET) AND MEDICAL RECORDS WAS RECEIVED ON 26-MAY-2016, AND AN AMENDED PLEADING RECEIVED ON 31-MAY-2016:

ACCORDING TO THE LEGAL PLEADING:

A spontaneous report was received from a legal pleading via a Company representative concerning a male patient (age at the time of event onset unspecified) who began using testosterone replacement therapy (TRT) in approximately 2000. He was using Androderm (testosterone) in 2010 and then Androgel (testosterone) in 2013 and in 2015. TRT product patient used between 2000 and 2010 was not specified.

The legal pleading stated that TRT caused serious injuries and damages including but not limited to a stroke on (b) (6) while using Androderm. In approximately (b) (6) the patient experienced a pulmonary embolism (PE) while using Androgel. On (b) (6) the patient experienced another PE while using Androgel. The patient was hospitalized for treatment of his injuries. As a result of his injuries, the patient suffered economic and non-economic injuries. In addition, the pleading stated that the TRT products were defective. The legal pleading stated that at the time of his injuries, the patient did not know, nor could he have reasonably known, of the true extent of the risk of using TRT or that his use of TRT could have caused his injuries.

The patient discontinued TRT in June 2015. The outcome of the events of stroke and PE was unspecified.

The events of stroke and PE were considered serious due to hospitalization.

ACCORDING TO THE PFS:

A 55 year old male patient (72" 225 lbs) was treated with Testim, 1 pump each shoulder, (frequency not specified) from approximately 01-APR-2011 to 03-SEP-2013 (discrepant dates reported). Other suspect TRT included Androgel, 1 pump on each shoulder (frequency not specified) (approx 25-AUG-2005 to 01-AUG-2008; and 15-OCT-2013 to 20-MAY-2015) and Androderm daily (approx 25-MAY-2010 to 16-DEC-2010).

The patient experienced a right parietal cerebrovascular infarct/stroke on (b) (6) was hospitalized and treated with warfarin and Aggrenox.

It was reported that the patient experienced a pulmonary embolism (PE) on (b) (6). Symptoms included chest tightness and extreme shortness of breath. Patient was hospitalized and diagnosed with a PE. On (b) (6) patient experienced four days of shortness of breath, went to the hospital and was diagnosed with a PE (hospitalized).

Medical history included back pain, chronic pain syndrome, hypertension, muscle stiffness, sleep disorder, constipation, neuropathy, depression, asthma, erectile dysfunction, anxiety, hyperlipidemia, irritable bowel syndrome, GERD, bipolar disorder.

Concomitant medication included methadone for chronic pain syndrome (approx February 2004 to present), metoprolol for hypertension (June 2005-April 2011; April 2014-present), Carbidopa/Levodopa for muscle stiffness (June 2005-July 2011), Nexium for GERD (June 2005-April 2011), Lyrica for neuropathy (Nov 2005-April 2011; January 2014-present), hydrocodone/APAP for chronic pain syndrome (April 2006-April 2011), HCTZ for hypertension (June 2006-February 2011), simvastatin for hyperlipidemia (November 2006-April 2011), dicyclomine for irritable bowel syndrome (July 2008-December 2010), Doc-Q-Lace for constipation (February 2009 to April 2011), Cymbalta for neuropathy (December 2009 to May 2011; April 2014-present), Lunesta for sleep (April 2010-April 2011; October 2013-present).

ACCORDING TO MEDICAL RECORDS:

Medical records reflect that the patient was hospitalized on (b) (6) with bilateral pulmonary emboli (PE). It was noted the patient reported he had history of known hypercoagulable state, either Protein C or Protein S.

Medical history included depression, reflex sympathetic dystrophy s/p multiple back surgeries, hypertension, restless legs syndrome, osteoarthritis, possible history of seizures-partial, asthma, insomnia.

On (b) (6) the patient was hospitalized with anoxic brain injury following suicide attempt.

ACCORDING TO THE AMENDED PLEADING:

The patient used TRT from approximately 2003 to June 2015. The amended pleading reflected that the patient also used Testim, and that Testim was defective.

The outcome of the events of right parietal cerebrovascular infarct/stroke and PE was not recovered: PFS stated patient's respiratory function suffered due to the pulmonary issues he suffered. Patient continued to have trouble with short term memory. The outcome of the events of suicide attempt and anoxic brain injury was unspecified.

The events of right parietal cerebrovascular infarct/stroke and PE were considered serious due to hospitalization and disability or permanent damage. The events of suicide attempt and anoxic brain injury were considered serious due to hospitalization.

Follow-up was received from an attorney in the form of an amended complaint, PFS and medical records on 27-Dec-2016:

As per the amended complaint, the patient suffered a stroke on (b) (6) bilateral pulmonary emboli on (b) (6) and (b) (6) while using TRT.

The patient was in the hospital following what appeared to be an episode of unstable angina pectoris. He underwent cardiac catheterization on (b) (6) which revealed non-obstructive coronary artery disease. Ultimately he was found to have recurrent pulmonary emboli and potential pulmonary Infarction. He was started on Eliquis (apixaban) therapy and presented for follow up. Overall, the patient felt like his breathing was stabilized. He stated that he was feeling like he was nearing his baseline. He denied any chest pain or pressures, any lower extremity edema, orthopnea or paroxysmal nocturnal dyspnea, any palpitations, significant dizziness, lightheadedness, syncope or presyncope. The pulmonary embolus was related to a long car ride in which he was relatively immobile for a period of three to five days. This episode of pulmonary embolus was found to be on testosterone therapy, and this was since discontinued. Radiology report on (b) (6) revealed multiple bilateral pulmonary emboli. The pulmonary emboli were much more significant in burden. These were seen bilaterally. Previously, this was only in the right pulmonary arteries. Stable atelectasis in the left lung base and mild patchy ground-glass opacification mainly in the right upper lobe consistent with an underlying inflammatory process. Laboratory data on (b) (6) included sodium 136 MEq/L (range 137-145 MEq/L), Potassium was 3.3 MEq/L (3.5-5.1 MEq/L), Carbon dioxide was 21 MEq/L (range (22-30 MEq/L), Glucose was 299 mg/dl (range 74-106 mg/dl), red blood cell was 3.99 M/UL (range 4.00-6.00 M/UL), hemoglobin was 12.3 g/dl (range:13.0-17.0 g/dl), hematocrit was 34.5 % (range 36.0-52.0%), platelet count was 148 K/UL (range was 150-400 K/UL). EKG (Electrocardiogram) on (b) (6) revealed normal sinus rhythm, Nonspecific T-wave flattening in the precordial leads v2, V3, V4, and V5, A non pathologic Q-wave in lead III and Abnormal EKG.

The outcome of the events non-obstructive coronary artery disease and potential pulmonary Infarction was unspecified.

The event of non-obstructive coronary artery disease was considered serious due to hospitalization and the event of potential pulmonary Infarction was considered serious due to serious criterion of medically significance.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?	Comment
Anxiety				

Asthma					
Back pain					
Bipolar disorder					
Chronic pain					
Constipation				UNKNOWN	
Depression					
Erectile dysfunction					
GERD					
Hypercoagulability					EITHER PROTEIN C OR PROTEIN S
Hyperlipidemia					
Hypertension					
Insomnia					
Irritable bowel syndrome					
Muscle stiffness					
Neuropathy					
Osteoarthritis					
Partial seizures				UNKNOWN	
Reflex sympathetic dystrophy					STATUS POST MULTIPLE BACK SURGERIES
Restless legs syndrome					
Sleep disorder				UNKNOWN	

Medical History Product(s)	Start Date	End Date	Indication(s)	MedDRA Preferred Term(s)

***Age in Years displays a mid-value where the Age Unit in the report is in DECADE**

Relevant Laboratory Data:

Test Date	Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail Y/N
(b) (6)	POTASSIUM	3.3	mEq/L	3.5	5.1	N
(b) (6)	HEMOGLOBIN	12.3	mg/dL	13.0	17.0	N
(b) (6)	GLUCOSE	299	mg/dL	74	106	N
(b) (6)	SODIUM	136	mEq/L	137	145	N
(b) (6)	HEMATOCRIT	34.5	%	36.0	52.0	N
(b) (6)	CO2	21	mEq/L	22	30	N
(b) (6)	RBC	3.99	mg/dL	4.00	6.00	N
(b) (6)	PLATELET COUNT	148	K/ul	150	400	N
(b) (6)	EKG					N
(b) (6)	RADIOLOGY					N
(b) (6)	CARDIAC CATHETERIZATION	nonobstructive coronary artery disease				N

Concomitant Products:

#	Product Name	Dose/Frequency	Route	Dosage Text	Indication(s)	Start Date	End Date	Interval 1st Dose to Event
1	CARBIDOPA LEVODOPA	/	UNK		Muscle stiffness	Jun-2005	Jul-2011	
2	METOPROLOL	/	UNK		Hypertension	Jun-2005	Apr-2011	
3	METOPROLOL	/	UNK			Apr-2014		
4	NEXIUM	/	UNK		GERD	Jun-2005	Apr-2011	
5	HYDROCODONE/APAP	/	UNK		Chronic pain	Apr-2006	Apr-2011	
6	CYMBALTA	/	UNK		Neuropathy	Dec-2009	May-2011	
7	LYRICA	/	UNK			Jan-2014		
8	LUNESTA	/	UNK		Sleep disorder NOS	Apr-2010	Apr-2011	

***Age in Years displays a mid-value where the Age Unit in the report is in DECADE**

FDA - Adverse Event Reporting System (FAERS)

Batch Printing Report for Cases

	Product Name	Dose/Frequency	Route	Dosage Text	Indication(s)	Start Date	End Date	Interval 1st Dose to Event
9	SIMVASTATIN	/	UNK		Hyperlipidemia	Nov-2006	Apr-2011	
10	HCTZ	/	UNK		Hypertension	Jun-2006	Feb-2011	
11	DOC-Q-LACE	/	UNK		Constipation	Feb-2009	Apr-2011	
12	DICYCLOMINE	/	UNK		Irritable bowel syndrome	Jul-2008	Dec-2010	
13	LUNESTA	/	UNK			Oct-2013		
14	LYRICA	/	UNK		Neuropathy	Nov-2005	Apr-2011	
15	METHADONE	/	UNK		Chronic pain	Feb-2004		

Reporter Source:

Study Report: **Study Name:** **Study Type:** **Sponsor Study:** **Protocol** **IND #:**

No

Literature Text:

Country of Event: USA **Sender MFR:** ENDO

Reporter Name: (b) (6)
Reporter Org.:
Reporter Street:
Reporter City:
Reporter Zip:
Health Prof.:
Occupation:

Reporter Type:
Reporter Email:
Reporter Phone:
Reporter State: (b) (6)
Reporter Country: UNITED STATES
Sent To:
Identity Disclosed:

***Age in Years displays a mid-value where the Age Unit in the report is in DECADE**

FDA - Adverse Event Reporting System (FAERS)

Batch Printing Report for Cases

Case Information:

Case Id: 12601094 **Version:** 1 **Case Type:** 15-DAY **eSub:** Yes **HP:** **Country:** USA **Outcome(s):** OT,

FDA Rcvd. Date: 28-Jul-2016 **Init FDA Rcvd. Date:** 28-Jul-2016 **Mfr Rcvd. Date:** 26-Jul-2016 **Application Type:** NDA **Application #:** 021015

Mfr. Control #: US-ABBVIE-16P-163-1686412-00

Patient Information:

Patient ID: UNKNOWN **Age:** **Age in Years:** **Sex:** Male **Weight:** **DoB:**

Suspect Products:

#	Product Name	Dose/Frequency	Route	Dosage Text	Indication(s)	Start Date	End Date	Interval 1st Dose to Event	ReC	DeC
1	ANDROGEL	/	TOP		Drug use for unknown indication	2011	2016		NA	No

#	Product Name	Lot#	Exp Date	NDC #	Labeler	OTC
1	ANDROGEL	unknown				

Event Information:

MedDRA © PreferredTerm	Start Date	End Date	Outcomes	Highlighted Terms	ReC
Confusional State			NOT RECOVERED/ NOT RESOLVED	N	NA
Depression			NOT RECOVERED/ NOT RESOLVED	N	NA
Feeling Abnormal			NOT RECOVERED/ NOT RESOLVED	N	NA
Suicidal Ideation			NOT RECOVERED/ NOT RESOLVED	N	NA

Event/Problem Narrative:

Spontaneous report from the USA by a consumer of a male with events of SUICIDAL IDEATION and non-serious CONFUSION, BRAIN FOG and DEPRESSION with ANDROGEL (TESTOSTERONE). There was no reported medical history.

On unknown dates, the patient experienced SUICIDAL IDEATION, CONFUSION, BRAIN FOG and DEPRESSION.

On an unknown date the patient reported trying to taper himself off unknown strength Androgel after being on it for five years. The patient experienced confusion, brain fog, suicidal ideation, and deep dark depression. The patient decline to fill out adverse event report. The primary reporter declined to report the lot number. No further information was provided.

***Age in Years displays a mid-value where the Age Unit in the report is in DECADE**

Causality for ANDROGEL(TESTOSTERONE)

The reporter stated that there is a reasonable possibility that the events of SUICIDAL IDEATION, CONFUSION, BRAIN FOG and DEPRESSION are related to ANDROGEL(TESTOSTERONE).

Relevant Medical History:
Not reported.

Disease/Surgical Procedure	Start Date	End Date	Continuing?	Comment

Medical History Product(s)	Start Date	End Date	Indication(s)	MedDRA Preferred Term(s)

Relevant Laboratory Data:

Test Date	Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail Y/N

Concomitant Products:

#	Product Name	Dose/Frequency	Route	Dosage Text	Indication(s)	Start Date	End Date	Interval 1st Dose to Event

Reporter Source:

Study Report:	Study Name:	Study Type:	Sponsor Study:	Protocol	IND #:
No					

Literature Text:

Country of Event: USA **Sender MFR:** ABBVIE

FDA - Adverse Event Reporting System (FAERS)

Batch Printing Report for Cases

Reporter Name:	Unknown	**Reporter Type:**	
Reporter Org.:		**Reporter Email:**	
Reporter Street:		**Reporter Phone:**	
Reporter City:		**Reporter State:**	
Reporter Zip:		**Reporter Country:**	UNITED STATES
Health Prof.:		**Sent To:**	
Occupation:	CONSUMER OR OTHER NON HEALTH PROFESSIONAL	**Identity Disclosed:**	

***Age in Years displays a mid-value where the Age Unit in the report is in DECADE**

FDA - Adverse Event Reporting System (FAERS)

Batch Printing Report for Cases

Case Information:

Case Id: 12708660 **Version:** 1 **Case Type:** 15-DAY **eSub:** Yes **HP:** **Country:** USA **Outcome(s):** DE

FDA Rcvd. Date: 01-Sep-2016 **Init FDA Rcvd. Date:** 01-Sep-2016 **Mfr Rcvd. Date:** 26-Aug-2016 **Application Type:** ANDA **Application #:** 080911

Mfr. Control #: US-ENDO PHARMACEUTICALS INC.-2016-005404

Patient Information:

Patient ID: Unknown **Age:** 6 DEC **Age in Years:** 55 YR **Sex:** Male **Weight:** **DoB:**

Suspect Products:

#	Product Name	Dose/Frequency	Route	Dosage Text	Indication(s)	Start Date	End Date	Interval 1st Dose to Event	ReC	DeC
1	Testopel	/	UNK		Drug use for unknown indication	Apr-2016		4 Month	NA	NA

#	Product Name	Lot#	Exp Date	NDC #	Labeler	OTC
1	Testopel				AUXILIUM	

Event Information:

MedDRA © PreferredTerm	Start Date	End Date	Outcomes	Highlighted Terms	ReC
Completed Suicide	(b) (6)		FATAL	N	NA
Gun Shot Wound	(b) (6)		FATAL	N	NA

Event/Problem Narrative:

A US spontaneous report was received via a company representative, on behalf of a nurse practitioner, regarding a male in his 50's who experienced completed suicide and gun shot wound while receiving therapy with Testopel for an unspecified indication.

No medical history or concomitant medications were reported.

Therapy with Testopel 75mg pellets was initiated in Apr-2016.

The nurse practitioner reported that the patient committed suicide by shooting himself in the head in (b) (6) while receiving Testopel. The patient was at the morgue on (b) (6) The nurse practitioner stated that the wife of the patient contacted the physician's office to ask if the Testopel pellets could be removed from her husband. It was reported that the wife did not want anyone to know he had been receiving Testopel.

***Age in Years displays a mid-value where the Age Unit in the report is in DECADE**

No reporter causality was provided.

The events of completed suicide and gun shot wound were considered serious due to death.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?	Comment

Medical History Product(s)	Start Date	End Date	Indication(s)	MedDRA Preferred Term(s)

Relevant Laboratory Data:

Test Date	Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail Y/N

Concomitant Products:

#	Product Name	Dose/Frequency	Route	Dosage Text	Indication(s)	Start Date	End Date	Interval 1st Dose to Event

Reporter Source:

Study Report:	Study Name:	Study Type:	Sponsor Study:	Protocol	IND #:
No					

Literature Text:

Country of Event: USA **Sender MFR:** ENDO

***Age in Years displays a mid-value where the Age Unit in the report is in DECADE**

FDA - Adverse Event Reporting System (FAERS)

Batch Printing Report for Cases

Reporter Name:	(b) (6)	**Reporter Type:**	
Reporter Org.:		**Reporter Email:**	
Reporter Street:		**Reporter Phone:**	
Reporter City:		**Reporter State:**	(b) (6)
Reporter Zip:		**Reporter Country:**	UNITED STATES
Health Prof.:		**Sent To:**	
Occupation:		**Identity Disclosed:**	

***Age in Years displays a mid-value where the Age Unit in the report is in DECADE**

FDA - Adverse Event Reporting System (FAERS)

Batch Printing Report for Cases

Case Information:

Case Id: 13152271 **Version:** 1 **Case Type:** 15-DAY **eSub:** Yes **HP:** **Country:** USA **Outcome(s):** OT,

FDA Rcvd. Date: 25-Jan-2017 **Init FDA Rcvd. Date:** 25-Jan-2017 **Mfr Rcvd. Date:** 20-Jan-2017 **Application Type:** NDA **Application #:** 020489

Mfr. Control #: US-ALLERGAN-1702559US

Patient Information:

Patient ID: PRIVACY **Age:** 57 YR **Age in Years:** 57 YR **Sex:** Male **Weight:** **DoB:**

Suspect Products:

#	Product Name	Dose/Frequency	Route	Dosage Text	Indication(s)	Start Date	End Date	Interval 1st Dose to Event	ReC	DeC
1	ANDRODERM	/	TDER		Drug use for unknown indication				Unk	Unk
2	ANDROGEL	/	TOP	UNK	Drug use for unknown indication	Jul-2016	17-Aug-2016		Yes	Yes
3	ANDROGEL	/		UNK					Yes	Yes
4	TESTOSTERONE	/	IM	UNK	Drug use for unknown indication	2015	2016		Unk	Yes

#	Product Name	Lot#	Exp Date	NDC #	Labeler	OTC
1	ANDRODERM				ALLERGAN	
2	ANDROGEL					
3	ANDROGEL					
4	TESTOSTERONE					

Event Information:

MedDRA © PreferredTerm	Start Date	End Date	Outcomes	Highlighted Terms	ReC
Suicidal Ideation	01-Jul-2016	01-Aug-2016	RECOVERED/ RESOLVED		NA

***Age in Years displays a mid-value where the Age Unit in the report is in DECADE**

Event/Problem Narrative:

Country of incidence: UNITED STATES

Initial receipt: 20-JAN-2017. This case also includes information received on 20-JAN-2017, within the same reporting timeframe.

The consumer reported similar events for different patients. This is the 3rd of 3 reports.

A spontaneous report was received via TEVA and AbbVie (MFR Control number: 16P-163-1705768-00) from a 57-year-old male patient who experienced suicidal ideation following the administration of ANDRODERM (testosterone); ANDROGEL (testosterone) and TESTOSTERONE all for an unknown indication.

The patient reported that he used ANDROGEL once before 2 years ago prior to this report in 2015 for 8 months and the medications worked fine. Furthermore ANDROGEL was switched to testosterone injections. The patient stated that he was placed back to ANDROGEL in JUL-2016 and due to lack of effect he kept increasing the dose. In JUL-2016 the patient experienced suicidal ideation. The outcome of the event was resolved on AUG-2016. Moreover on an unspecified date the patient found a sample of ANDRODERM and used it, the patient stated that ANDRODERM patch worked. Dose regimen for ANDORDERM was not reported, transdermal. Dose regimen for ANDROGEL was not reported, topical and dose regimen for TESTOSTERONE injections was not reported, intramuscular. Action taken with ANDRODERM was unknown. Action taken with ANDROGEL and TESTOSTERONE injections were withdrawn. No further information was provided.

Medical history and concomitant medications were not reported.

Related cases: 1702551US and 1702555US: same reporter, different patients and different products.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?	Comment

Medical History Product(s)	Start Date	End Date	Indication(s)	MedDRA Preferred Term(s)

Relevant Laboratory Data:

Test Date	Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail Y/N

***Age in Years displays a mid-value where the Age Unit in the report is in DECADE**

Concomitant Products:

#	Product Name	Dose/Frequency	Route	Dosage Text	Indication(s)	Start Date	End Date	Interval 1st Dose to Event

Reporter Source:

Study Report:	Study Name:	Study Type:	Sponsor Study:	Protocol	IND #:
No					

Literature Text:

Country of Event: USA **Sender MFR:** ALLERGAN

Reporter Name: PRIVACY
Reporter Org.:
Reporter Street:
Reporter City:
Reporter Zip:
Health Prof.:
Occupation: CONSUMER OR OTHER NON HEALTH PROFESSIONAL

Reporter Type:
Reporter Email:
Reporter Phone:
Reporter State:
Reporter Country: UNITED STATES
Sent To:
Identity Disclosed:

***Age in Years displays a mid-value where the Age Unit in the report is in DECADE**

FDA - Adverse Event Reporting System (FAERS)

Batch Printing Report for Cases

Case Information:

Case Id: 13324218 **Version:** 1 **Case Type:** 15-DAY **eSub:** Yes **HP:** **Country:** USA **Outcome(s):** OT,

FDA Rcvd. Date: 10-Mar-2017 **Init FDA Rcvd. Date:** 10-Mar-2017 **Mfr Rcvd. Date:** 03-Mar-2017 **Application Type:** NDA **Application #:** 021015

Mfr. Control #: US-ABBVIE-17P-163-1896471-00

Patient Information:

Patient ID: (b) (6) **Age:** 66 YR **Age in Years:** 66 YR **Sex:** Male **Weight:** **DoB:**

Suspect Products:

#	Product Name	Dose/Frequency	Route	Dosage Text	Indication(s)	Start Date	End Date	Interval 1st Dose to Event	ReC	DeC
1	ANDROGEL	/	TOP		Testosterone low				NA	Yes
2	TESTOSTERONE CREAM	/	UNK		Testosterone low				NA	Yes
3	TESTOSTERONE INJECTIONS	/	UNK		Testosterone low	2016			NA	NA
4	TESTOSTERONE PELLETS	/	UNK		Drug use for unknown indication				NA	Yes

#	Product Name	Lot#	Exp Date	NDC #	Labeler	OTC
1	ANDROGEL	NOT AVAILABLE				
2	TESTOSTERONE CREAM	NOT AVAILABLE				
3	TESTOSTERONE INJECTIONS	NOT AVAILABLE				
4	TESTOSTERONE PELLETS	NOT AVAILABLE				

Event Information:

MedDRA © PreferredTerm	Start Date	End Date	Outcomes	Highlighted Terms	ReC
Depression	01-Jan-2016		NOT RECOVERED/ NOT RESOLVED	N	NA
Feeling Abnormal	01-Jan-2016		NOT RECOVERED/ NOT RESOLVED	N	NA
Hot Flush	01-Jan-2016		NOT RECOVERED/ NOT RESOLVED	N	NA
Hyperhidrosis	01-Jan-2016		NOT RECOVERED/ NOT RESOLVED	N	NA
Suicidal Ideation	01-Jan-2016		NOT RECOVERED/ NOT RESOLVED	N	NA

***Age in Years displays a mid-value where the Age Unit in the report is in DECADE**

MedDRA © PreferredTerm	Start Date	End Date	Outcomes	Highlighted Terms	ReC
Blood Testosterone Decreased			NOT RECOVERED/ NOT RESOLVED	N	NA
Blood Testosterone Increased			RECOVERED/ RESOLVED	N	NA
Polycythaemia			NOT RECOVERED/ NOT RESOLVED	N	NA

Event/Problem Narrative:

Spontaneous report from the USA by a consumer of a 66 year old male with events of SUICIDAL IDEOLOGY, DEPRESSION WORSENED, BRAIN FOG and POLYCYTHEMIA and non-serious HOT FLASHES, SWEATING, TESTOSTERONE INCREASED and TESTOSTERONE DECREASED with ANDROGEL (TESTOSTERONE). There was no reported medical history.

On unknown dates, the patient experienced TESTOSTERONE INCREASED, TESTOSTERONE DECREASED and POLYCYTHEMIA. In 2016, the patient experienced SUICIDAL IDEOLOGY, HOT FLASHES, SWEATING, DEPRESSION WORSENED and BRAIN FOG. On an unknown date, TESTOSTERONE INCREASED resolved. TESTOSTERONE PELLETS (TESTOSTERONE), TESTOSTERONE CREAM (TESTOSTERONE) and TESTOSTERONE INJECTION (TESTOSTERONE) were also considered suspect.

Primary reporter does not have the lot number information because the packaging was discarded.

Causality for ANDROGEL(TESTOSTERONE)

The reporter's causality for the event(s) of SUICIDAL IDEOLOGY, HOT FLASHES, SWEATING, DEPRESSION WORSENED, BRAIN FOG, TESTOSTERONE INCREASED, TESTOSTERONE DECREASED and POLYCYTHEMIA with ANDROGEL(TESTOSTERONE) was no reasonable possibility.

Relevant Laboratory & Other Diagnostic Tests

2016 testosterone: 800 while on testosterone injections
Unknown date testosterone: 1400 while on testosterone pellets
Unknown date testosterone: 300 while on ANDROGEL

Relevant Medical History:

Not reported.

Disease/Surgical Procedure	Start Date	End Date	Continuing?	Comment

***Age in Years displays a mid-value where the Age Unit in the report is in DECADE**

FDA - Adverse Event Reporting System (FAERS)

Batch Printing Report for Cases

Medical History Product(s)	Start Date	End Date	Indication(s)	MedDRA Preferred Term(s)

Relevant Laboratory Data:

Test Date	Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail Y/N
01-Jan-2016	Testosterone					N
	Testosterone					N

Concomitant Products:

#	Product Name	Dose/Frequency	Route	Dosage Text	Indication(s)	Start Date	End Date	Interval 1st Dose to Event

Reporter Source:

Study Report:	Study Name:	Study Type:	Sponsor Study:	Protocol	IND #:
No					

Literature Text:

Country of Event: USA **Sender MFR:** ABBVIE

Reporter Name: PRIVACY
Reporter Org.:
Reporter Street:
Reporter City:
Reporter Zip:
Health Prof.:
Occupation: CONSUMER OR OTHER NON HEALTH PROFESSIONAL

Reporter Type:
Reporter Email:
Reporter Phone:
Reporter State:
Reporter Country: UNITED STATES
Sent To:
Identity Disclosed:

***Age in Years displays a mid-value where the Age Unit in the report is in DECADE**

FDA - Adverse Event Reporting System (FAERS)

Batch Printing Report for Cases

Case Information:

Case Id: 13665923 **Version:** 1 **Case Type:** 15-DAY **eSub:** Yes **HP:** **Country:** USA **Outcome(s):** OT,

FDA Rcvd. Date: 19-Jun-2017 **Init FDA Rcvd. Date:** 19-Jun-2017 **Mfr Rcvd. Date:** 12-Jun-2017 **Application Type:** NDA **Application #:** 022309

Mfr. Control #: US-ABBVIE-17P-163-2006691-00

Patient Information:

Patient ID: (b) (6) **Age:** 56.(b) (6) Y **Age in Years:** 56.(b) (6) Y **Sex:** Male **Weight:** **DoB:** (b) (6)

Suspect Products:

#	Product Name	Dose/Frequency	Route	Dosage Text	Indication(s)	Start Date	End Date	Interval 1st Dose to Event	ReC	DeC
1	ANDROGEL STICK PACK 2.5G	/	TDER	apply one packet (40.5 mg/2.5g) every other day	Drug use for unknown indication		Apr-2017		NA	No

#	Product Name	Lot#	Exp Date	NDC #	Labeler	OTC
1	ANDROGEL STICK PACK 2.5G	unknown				

Event Information:

MedDRA © PreferredTerm	Start Date	End Date	Outcomes	Highlighted Terms	ReC
Blood Testosterone Decreased	19-May-2017		NOT RECOVERED/ NOT RESOLVED	N	NA
Depression			UNKNOWN	N	NA
Suicidal Ideation			UNKNOWN	N	NA

Event/Problem Narrative:

Solicited report from the USA by a consumer of a 56 year old male with events of SUICDAL THOUGHTS and DEPRESSED and non-serious TESTOSTERONE DECREASED with ANDROGEL STICK PACK 2.5G (TESTOSTERONE). Information was also received from a healthcare professional. There was no reported medical history.

On unknown dates, the patient experienced SUICDAL THOUGHTS and DEPRESSED. On 19 May 2017, the patient experienced TESTOSTERONE DECREASED.

The patient reported he has had suicidal thoughts. No further information was provided.

Causality for ANDROGEL STICK PACK 2.5G(TESTOSTERONE)

***Age in Years displays a mid-value where the Age Unit in the report is in DECADE**

The reporter's causality for the event(s) of SUICDAL THOUGHTS and DEPRESSED was not provided. The reporter's causality for the event(s) of TESTOSTERONE DECREASED with ANDROGEL STICK PACK 2.5G(TESTOSTERONE) was no reasonable possibility.
AbbVie's opinion is that the events of SUICDAL THOUGHTS and DEPRESSED are not assessable. AbbVie's opinion is that there is no reasonable possibility that the event of TESTOSTERONE DECREASED is related to ANDROGEL STICK PACK 2.5G(TESTOSTERONE).

Relevant Medical History:

Tobacco, alcohol, medical history and allergy information were not provided.

Disease/Surgical Procedure	Start Date	End Date	Continuing?	Comment

Medical History Product(s)	Start Date	End Date	Indication(s)	MedDRA Preferred Term(s)

Relevant Laboratory Data:

Test Date	Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail Y/N

Concomitant Products:

#	Product Name	Dose/Frequency	Route	Dosage Text	Indication(s)	Start Date	End Date	Interval 1st Dose to Event
1	HCTZ	/			Drug use for unknown indication			
2	VIAGRA	/			Drug use for unknown indication			
3	KALETRA	/			Drug use for unknown indication			

Reporter Source:

Study Report:	Study Name:	Study Type:	Sponsor Study:	Protocol	IND #:
No	FACILITATED COLLECTION				

Literature Text:

Country of Event: USA **Sender MFR:** ABBVIE

***Age in Years displays a mid-value where the Age Unit in the report is in DECADE**

FDA - Adverse Event Reporting System (FAERS)

Batch Printing Report for Cases

Reporter Name:		**Reporter Type:**	
Reporter Org.:		**Reporter Email:**	
Reporter Street:		**Reporter Phone:**	
Reporter City:		**Reporter State:**	
Reporter Zip:		**Reporter Country:**	UNKNOWN
Health Prof.:		**Sent To:**	
Occupation:	CONSUMER OR OTHER NON HEALTH PROFESSIONAL	**Identity Disclosed:**	

Reporter Name:	PRIVACY	**Reporter Type:**	
Reporter Org.:	PRIVACY	**Reporter Email:**	
Reporter Street:		**Reporter Phone:**	
Reporter City:		**Reporter State:**	
Reporter Zip:	PRIVACY	**Reporter Country:**	UNITED STATES
Health Prof.:		**Sent To:**	
Occupation:		**Identity Disclosed:**	

***Age in Years displays a mid-value where the Age Unit in the report is in DECADE**

FDA - Adverse Event Reporting System (FAERS)

Batch Printing Report for Cases

Reporter Name:	PRIVACY PRIVACY	**Reporter Type:**	
Reporter Org.:		**Reporter Email:**	
Reporter Street:	PRIVACY	**Reporter Phone:**	
Reporter City:	PRIVACY	**Reporter State:**	PRIVACY
Reporter Zip:	PRIVACY	**Reporter Country:**	UNITED STATES
Health Prof.:		**Sent To:**	
Occupation:	CONSUMER OR OTHER NON HEALTH PROFESSIONAL	**Identity Disclosed:**	

***Age in Years displays a mid-value where the Age Unit in the report is in DECADE**

Printer: CDPEDQ5
User: SAHOOS
Date - Time: 30-Aug-2017 10:11 AM
Total Number of Cases (Non-Esub): 17
Total Number of Pages: 46
Print Job Number: 14921

Disclaimer:
Submission of a safety report does not constitute an admission that medical personnel, user facility, importer, distributor, manufacturer or product caused or contributed to the event. The information in these reports has not been scientifically or otherwise verified as to a cause and effect relationship and cannot be used to estimate the incidence of these events.

Non-Esub Case ID(s) Printed:
3407382 4015122 4150773 4843586 5022217 5860250 5954475 6138877 7546458 7916353 9027842 10363745 10524469 10676706 11358782 11693245 11934615

Failed Non-Esub Case ID(s):

Total Failed Cases: 0

Individual Safety Report

3424905-3-00-01

MEDWATCH ALZA Drug Experience Report

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Page 1 of 2

FDA Facsimile Approval 12/3/1998
Mfr report# 5700
UF/Dist report#
FDA use only

A. Patient Information

1.Patient ID	2.Age	3.Sex	4.Weight
(b) (6)	43	○ F	169.99 lbs or
In confidence	or Year(s)	◉ M	77.27 kgs
	Date of birth (b) (6)		

B. Adverse event and/or product problem

1. ☑ Adverse event and/or
☐ Product problem (defects/malfunctions)

2.Outcomes attributed to adverse event
- ☐ death
- ☐ life-threatening
- ☑ hospitalization-initial or prolonged
- ☐ disability
- ☐ congenital anomaly
- ☐ required intervention to prevent permanent damage
- ☐ other:

3.Date of event	4.Date of this report
19NOV1999	08DEC1999

5.Describe event or problem

A 43 year old male, with a history of bipolar disorder and end stage liver failure, reported that he was hospitalized for suicidal ideation onset (b) (6) during the use of Testoderm TTS 5mg initiated 10/26/99. Testoderm was discontinued (on or around (b) (6)). The symptoms resolved after discontinuation of the patches and modification of his other psychotropic medications (actual date unknown). He was discharged from the hospital on (b) (6) The patient was unable to provide the dosages of his drugs and requested that his physician not be contacted. No additional information is expected.

DEC 20

6.Relevant test/laboratory data, including dates

unk

7.Other relevant history, including preexisting medical conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

Date unk: end stage liver disease-secondary to Hep C
Date unk: Bi-polar disorder

C. Suspect medication

1.Name (give labeled strength and mfr/labeler, if known)

#1 Testoderm TTS (Testosterone Transdermal System)
#2

2.Dose, frequency and route	3.Therapy dates (if unknown, give duration)
#1 5mg 1x/1Day,transdermal	#1 26OCT1999-19NOV1999
#2	#2

4.Diagnosis for use (indication)
#1 Hypogonadism
#2

5.Event abated after use stopped or dose reduced
#1 ◉ Yes ○ No ○ doesn't apply
#2 ○ Yes ○ No ○ doesn't apply

6.Lot # (if known)	7.Exp. date (if known)
#1 193492	#1 4/00
#2	#2

8.Event reappeared after reintroduction
#1 ○ Yes ○ No ◉ doesn't apply
#2 ○ Yes ○ No ○ doesn't apply

9.NDC # for product problems only (if known)
n/a

10.Concomitant medical products and therapy dates (exclude treatment of event)

PROZAC unk-present
LITHIUM unk-present

(continues...)

G. All manufacturers

1.Contact office-name/address
ALZA Corporation
Medical & Safety Services
1900 Charleston Road
Mountain View, CA 94043

2.Phone number
(888)228-8336

3.Report source (check all that apply)
- ☐ foreign
- ☐ study
- ☐ literature
- ☑ consumer
- ☐ health professional
- ☐ user facility
- ☐ company representative
- ☐ distributor
- ☐ other

4.Date received by manufacturer
08DEC1999

5.
(A) NDA# 20-791
IND#
PLA#
pre-1938 ☐ Yes
OTC product ☐ Yes

6.if IND, protocol #

7.Type of report (check all that apply)
- ☐ 5-day ☑ 15-day
- ☐ 10-day ☐ periodic
- ☑ initial ☐ follow-up

#

8.Adverse event term(s)
DEPRESSION PSYCHOTIC

9.Mfr. report number
5700

E. Initial reporter

1.Name, address and phone #
(b) (6)

2.Health professional?	3.Occupation	4.Initial reporter also sent report to FDA
○ Yes ◉ No	Unknown	○ Yes ○ No ◉ unk

ALZA 3500A Facsimile Form

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer, or product caused or contributed to the event.

DEC 17 1999

25.1/1

Individual Safety Report

3424905-3-00-02

MEDWATCH

ALZA Drug Experience Report

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Page 2 of 2

FDA Facsimile Approval 12/3/1998	
Mfr report#	5700
UF/Dist report#	
FDA use only	

B. Adverse event and/or product problem

5.Describe event or problem

6.Relevant test/laboratory data, including dates

7.Other relevant history, including preexisting medical conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

C. Suspect medication

1.Name (give labeled strength and mfr/labeler, if known)

#3

#4

2.Dose, frequency and route

#3

#4

3.Therapy dates (if unknown, give duration)

#3

#4

4. Diagnosis for use (indication)

#3

#4

5.Event abated after use stopped or dose reduced

#3 ◯ Yes ◯ No ◯ doesn't apply

#4 ◯ Yes ◯ No ◯ doesn't apply

6. Lot # (if known)

#3

#4

7.Exp. date (if known)

#3

#4

8.Event reappeared after reintroduction

#3 ◯ Yes ◯ No ◯ doesn't apply

#4 ◯ Yes ◯ No ◯ doesn't apply

9.NDC # for product problems only (if known)

n/a

10.Concomitant medical products and therapy dates (exclude treatment of event)

(continued)

NEOMYCIN
PREVACID
TRAZADONE

DEC 20

G. All manufacturers

8.Adverse event term(s)

ALZA
3500A
Facsimile Form

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer, or product caused or contributed to the event.

DEC 17 1999

25.1/2

Approved by FDA on 3/22/94

Solvay Pharmaceuticals, Inc.

Domain Facsimile

Individual Safety Report

4223103-3-00-01

Page 1 of 3

Mfr report # TEST00203002722

LIF/Dist report #

FDA Use Only

A. Patient information

1. Patient identifier	2. Age at time of event:	3. Sex	4. Weight
(b) (6) in confidence	* or Date of birth: (b) (6)	☐ female ☒ male	lbs or 67.8 kgs

B. Adverse event or product problem

1. ☒ Adverse event and/or ☐ Product problem (e.g., defects/malfunctions)

2. Outcomes attributed to adverse event (check all that apply)
- ☐ death (mo/day/yr)
- ☐ life-threatening
- ☒ hospitalization - initial or prolonged
- ☐ disability
- ☐ congenital anomaly
- ☐ required intervention to prevent permanent impairment/damage
- ☐ other:

3. Date of event (mo/day/yr): 09/17/2003

4. Date of this report (mo/day/yr): 10/27/2003

5. Describe event or problem

An investigator report was received regarding a 13 year old male patient ((b) (6) (b) (6)) participating in a (b) (6) (b) (6) (b) (6) (b) (6) The patient began the study medication on (b) (6) at (b) (6) g, and later increased to (b) (6) g therapy on (b) (6) The patient experienced suicidal ideation on (b) (6) and was admitted to the hospital. He was treated with Ativan and Zoloft, and remains hospitalized. His most recent testosterone level was 119; all other lab values are within the normal limits. As of (b) (6) (b) (6) the patient remains on the study medication. Follow-up information has been requested. *

6. Relevant tests/laboratory data, including dates

DATE UNKNOWN: Testosterone level: 119 ***ADDITIONAL INFORMATION RECEIVED ON 16 OCT 2003: (b) (6) : Chem 7 WNL, WBC 8.0 H/H, 14.4/42.3, PT 294; LFT alk Phos elevated at 327 but otherwise WNL, TFT wnl, Urinalysis moderate blood, Tox screen negative, Cho: *

7. Other relevant history, including preexisting medical conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

The patient has a history of depression, ADHD, and acute lymphocytic leukemia at age 3, and was treated with chemotherapy and radiation. At the present time, there is no evidence of recurrent lymphocytic leukemia. ***ADDITIONAL INFORMATION RECEIVED ON 16 *

C. Suspect medication(s)

1. Name (give labeled strength & mfr/labeler, if known)
#1 ANDROGEL (TESTOSTERONE)
#2

2. Dose, frequency & route used
#1 *
#2

3. Therapy dates (if unknown, give duration) from/to (or best estimate)
#1 *
#2

4. Diagnosis for use (indication)
#1 *
#2

5. Event abated after use stopped or dose reduced
#1 ☐ yes ☐ no ☒ doesn't apply
#2 ☐ yes ☐ no ☐ doesn't apply

6. Lot # (if known)
#1 NI, NI
#2

7. Exp. date (if known)
#1 NI, NI
#2

8. Event reappeared after reintroduction
#1 ☐ yes ☐ no ☒ doesn't apply
#2 ☐ yes ☐ no ☐ doesn't apply

9. NDC # - for product problems only (if known)
#1 NI
#2

10. Concomitant medical products and therapy dates (exclude treatment of event)

G. All manufacturers

1. Contact office - name/address (& mfring site for devices)
Solvay Pharmaceuticals, Inc.
901 Sawyer Road
Marietta, Georgia 30062

2. Phone number: (770) 578-9000

3. Report source (check all that apply)
- ☐ foreign
- ☒ study
- ☐ literature
- ☐ consumer
- ☒ health professional
- ☐ user facility
- ☐ company representative
- ☐ distributor
- ☐ other:

4. Date received by manufacturer (mo/day/yr): 10/14/2003

5. (A)NDA # 21-015
IND #
PLA #
pre-1938 ☐ yes
OTC product ☐ yes

6. If IND, protocol #

7. Type of report (check all that apply)
- ☐ 5-day ☒ 15-day
- ☐ 10-day ☐ periodic
- ☐ Initial ☒ follow-up # 2

8. Adverse event term(s)
MedDRA Version: MEDDRA 6.0
SUICIDAL IDEATION
MAJOR DEPRESSIVE DISORDER NOS
OBSESSIVE-COMPULSIVE DISORDER
BLOOD ALKALINE PHOSPHATASE *

9. Mfr. report number: TEST00203002722

E. Initial reporter

1. Name, address & phone #
(b) (6)

DSS
OCT 29 2003

2. Health professional? ☒ yes ☐ no

3. Occupation: NI

4. Initial reporter also sent report to FDA ☐ yes ☒ no ☐ unk

OCT 28 2003

FDA
Domain Facsimile of FDA Form 3500A

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

Item completed on continuation pages.

Individual Safety Report

4223103-3-00-02

ay Pharmaceuticals, Inc.

MED WATCH	A.1. Patient Identifier (b) (6)	G.9. Mfr. report number TEST00203002722	Page 2 of 3

A.2. Age at time of event

13 years 73 days

B.5. Describe event or problem

[continuation:]
The investigator's assessment of this case is "unlikely."

***ADDITIONAL INFORMATION RECEIVED 30 SEP 2003: Additional treatment medication of Risperdal was provided. The event ended on (b) (6) and the patient was discharged from the hospital on the same day. He is to remain on Risperdal and Zoloft and to follow-up with outpatient care. Study drug is being continued. The patient is considered to be recovered completely.

***ADDITIONAL INFORMATION RECEIVED 14 OCT 2003: On (b) (6) the study drug was discontinued due to the medications required to treat the event. According to the site, no other information is available at this time.

***ADDITIONAL INFORMATION RECEIVED ON 16 OCT 2003: The date the patient was admitted to the hospital was changed to (b) (6) He was admitted because of an acute onset of suicidal thoughts, experiencing urges to hurt himself, experiencing intense anxiety and escalation of depressive symptoms. Relevant labs included *alkaline phosphatase 327, moderate blood in urine and a negative toxicity screen. He reported that Ativan PRN provided relief for his symptoms. His discharge diagnosis was *major depressive disorder with psychotic features and *obsessive compulsive disorder. Upon discharge from the hospital, the patient reported that his symptoms were much improved, no longer needing PRN medications. He denied suicidal thoughts, had worked on a safety plan and had been able to use support from the staff to reality test and obtain reassurance when feeling anxious. He was discharged home with recommendations for continued therapy for anxiety and depression for possibly adding behavioral therapy to support anxiety management and return to school. The patient was discharged on Zoloft and Risperdal.

***ADDITIONAL INFORMATION RECEIVED ON 23 OCT 2003: The site confirmed the start date of the adverse event is (b) (6) and the elevated alkaline phosphatase of 327 is not clinically significant.

NOTE: *Transcribed event, not originally stated as an adverse event by the reporter.
Corrective Therapy: Ativan and Zoloft

***ADDITIONAL INFORMATION RECEIVED 30 SEP 2003: The patient also received Risperdal.

B.6. Relevant tests/laboratory data ,including dates

[continuation:] 159, HDL 49, LDL 89.

B.7. Other relevant history, including preexisting medical conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

[continuation:] OCT 2003: The patient has no known allergies.
Race: CAUCASIAN

C.2. Dose, frequency & route used (Suspect #1)

0.5 g QD TD, 1.5 g QD TD

DSS

OCT 29 2003

OCT 28 2003

Individual Safety Report

4223103-3-00-03

ıy Pharmaceuticals, Inc.

MED WATCH | (b) (6) | Mfr. report number TEST00203002722 | Page 3 of 3

C.3. Therapy dates (if unknown, give duration) (mo/day/yr) (Suspect #1)

24-JUL-03 to 14-AUG-03, 15-AUG-03 to 12-OCT-03

C.4. Diagnosis for use (indication) (Suspect #1)

LOW TESTOSTERONE (BLOOD TESTOSTERONE DECREASED)

G.8. Adverse event term(s)

[continuation:] INCREASED

E.1. Name, address & phone #

[continuation:] (b) (6) US

Phone: (b) (6)

DSS

OCT 2 9 2003

OCT 2 8 2003

Individual Safety Report

4369507-X-00-01

se by user-facilities,
s and manufacturers for
DATORY reporting

Relsys International, Inc.
FDA Facsimile Approval: 11-JUN-1999

Mfr report # KII-2002-0010355
UF/Dist. report #
FDA Use Only

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

A. Patient information

1. Patient identifier (b) (6) In confidence
2. Age at time of event: 55 Years or Date of birth: (b) (6)
3. Sex: [ ] female [x] male
4. Weight: UNK lbs or UNK kgs

B. Adverse event or product problem

1. [x] Adverse event and/or [ ] Product problem (e.g., defects/malfunctions)

2. Outcomes attributed to adverse event (check all that apply)
[x] death (b) (6) (mo/day/yr)
[ ] life-threatening
[ ] hospitalization - initial or prolonged
[ ] disability
[ ] congenital anomaly
[ ] required intervention to prevent permanent impairment/damage
[ ] other:

3. Date of event (mo/day/yr): UNK
4. Date of this report (mo/day/yr): 05/26/2004

5. Describe event or problem

Suicide[Completed suicide]

Case Description:
A 55-year-old male patient (age and race unspecified) committed suicide on (b) (6) while taking OxyContin (controlled-release oxycodone hydrochloride) 20mg every night (qhs) for an unspecified indication. Route and therapy dates were not specified. The patient was also taking Testoderm (testosterone), Fosamax (alendronate sodium), Indocin (indomethacin), Norco (hydrochloride bitartrate, acetaminophen) and Paxil (paroxetine hydrochloride). Reportedly, the manner of the suicide was unknown. It was also unknown if this event was attributable to OxyContin. This case was reported on 05MAR02 by a physician in the United States of America via a company representative as retrieved from the sales call database. The case became reportable on 13MAY04 when additional information was received from the reporting
continued in additional info section...

6. Relevant tests/laboratory data, including dates
UNKNOWN

7. Other relevant history, including preexisting medical conditions (e.g. allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)
#1 UNK, (UNKNOWN)

C. Suspect medication(s)

1. Name (give labeled strength & mfr/labeler, if known)
#1. OxyContin Tablets(OXYCODON (continued)
#2. TESTOSTERONE(TESTOSTERONE)

2. Dose, frequency & route used
#1. 20 mg, hs, Unknown
#2. UNK (continued)

3. Therapy dates (if unknown, give duration) (mo/day/yr (or best estimate))
#1. UNK
#2. UNK

4. Diagnosis for use (indication)
#1. Drug use for unknown indication
#2. Drug use for unknown indication

5. Event abated after use stopped or dose reduced
#1. [ ] yes [ ] no [x] doesn't apply
#2. [ ] yes [ ] no [x] doesn't apply

6. Lot # (if known)
#1. UNKNOWN
#2. UNKNOWN

7. Exp. date (if known)
#1. UNK
#2. UNK

8. Event reappeared after reintroduction
#1. [ ] yes [ ] no [x] doesn't apply
#2. [ ] yes [ ] no [x] doesn't apply

9. NDC # - for product problems only (if known)

10. Concomitant medical products and therapy dates (exclude treatment of event)
UNKNOWN UNK to UNK

G. All Manufacturers

1. Contact office - name/address (& mfring site for devices)
Purdue Pharma L.P.
One Stamford Forum
Stamford, CT 06901-3431 UNITED STATES

2. Phone number: +1 203 588-8000

3. Report source (check all that apply)
[ ] foreign
[ ] study
[ ] literature
[ ] consumer
[x] health professional
[ ] user facility
[x] company representative
[ ] distributor
[ ] other:

4. Date received by manufacturer (mo/day/yr): 05/13/2004

5. (A)NDA # 20-553
IND #
PLA #
pre-1938 [ ] yes
OTC product [ ] yes

6. If IND, protocol #

7. Type of report (check all that apply)
[ ] 5-day [x] 15-day
[ ] 10-day [ ] periodic
[x] initial [ ] follow-up #

8. Adverse event term(s)
Completed suicide

9. Mfr. report number
KII-2002-0010355

E. Initial reporter

1. Name & address
Name and address withheld.

phone # Withheld

2. Health professional ?
[x] yes [ ] no

3. Occupation
Physician

4. Initial reporter also sent report to FDA
[ ] yes [ ] no [x] unk

FDA
3500A - Facsimile

Submission of a report does not constitute an admisssion that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

DSS

26-May-2004 14:43:07

Individual Safety Report

4369507-X-00-02

mission of a report does not constitute
dmission that medical personnel, user
y, distributor, manufacturer or product
aused or contributed to the event.

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service - Food and Drug Administration

Mfr report #	KII-2002-0010355
UF/Dist. report #	
	FDA Use Only

(continued)

C. Suspect medication(s)

1. Name (give labeled strength & mfr/labeler, if known)
#3. FOSAMAX(ALENDRONATE SODIUM)
#4. INDOCIN(INDOMETACIN)

2. Dose, frequency & route used
#3. UNK (continued)
#4. UNK (continued)

3. Therapy dates (if unknown, give duration)
from/to (or best estimate)
#3. UNK
#4. UNK

4. Diagnosis for use (indication)
#3. Drug use for unknown indication
#4. Drug use for unknown indication

5. Event abated after use stopped or dose reduced
#3. ☐ yes ☐ no ☒ doesn't apply
#4. ☐ yes ☐ no ☒ doesn't apply

6. Lot # (if known) 7. Exp. date (if known)
#3. UNKNOWN #3. UNK
#4. UNKNOWN #4. UNK

8. Event reappeared after reintroduction
#3. ☐ yes ☐ no ☒ doesn't apply
#4. ☐ yes ☐ no ☒ doesn't apply

9. NDC # - for product problems only (if known)
NA

10. Concomitant medical products and therapy dates (exclude treatment of event)
NA

C. Suspect medication(s)

1. Name (give labeled strength & mfr/labeler, if known)
#5. NORCO (continued)
#6. PAXIL (continued)

2. Dose, frequency & route used
#5. UNK (continued)
#6. UNK (continued)

3. Therapy dates (if unknown, give duration)
from/to (or best estimate)
#5. UNK
#6. UNK

4. Diagnosis for use (indication)
#5. Drug use for unknown indication
#6. Drug use for unknown indication

5. Event abated after use stopped or dose reduced
#5. ☐ yes ☐ no ☒ doesn't apply
#6. ☐ yes ☐ no ☒ doesn't apply

6. Lot # (if known) 7. Exp. date (if known)
#5. UNKNOWN #5. UNK
#6. UNKNOWN #6. UNK

8. Event reappeared after reintroduction
#5. ☐ yes ☐ no ☒ doesn't apply
#6. ☐ yes ☐ no ☒ doesn't apply

9. NDC # - for product problems only (if known)
NA

10. Concomitant medical products and therapy dates (exclude treatment of event)
NA

DSS

JUN 0 2 2004

MAY 2 7 2004

26-May-2004 14:43:07

Individual Safety Report

4369507-X-00-03

ission of a report does not constitute
ission that medical personnel, user
distributor, manufacturer or product
sed or contributed to the event.

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service - Food and Drug Administration

Mfr report #	KII-2002-0010355
UF/Dist. report #	
	FDA Use Only

Additional Information

B5. EVENT DESCRIPTION (cont.)

physician. Additional information was also received from an unspecified health professional in the physician's office on 25MAY04. No further information will be requested.

C1. Name (cont.)
Suspect Medication #1: OxyContin Tablets(OXYCODONE HYDROCHLORIDE) CR Tablet
Suspect Medication #5: NORCO(PARACETAMOL, HYDROCODONE BITARTRATE)
Suspect Medication #6: PAXIL(PAROXETINE HYDROCHLORIDE)

C2. Dose, frequency & route used (cont.)
Suspect Medication #2: UNK unk, unk, Unknown
Suspect Medication #3: UNK unk, unk, Unknown
Suspect Medication #4: UNK unk, unk, Unknown
Suspect Medication #5: UNK unk, unk, Unknown
Suspect Medication #6: UNK unk, unk, Unknown

DSS

JUN 0 2 2004

MAY 2 7 2004

JAN 22 1992

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

DRUG EXPERIENCE REPORT
(Drugs and Biologics)

Form Approved by FDA August 16,1988

FDA CONTROL NO

ACCESSION NO 911207078039 22

I. EVENT INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-6. EVENT ONSET MO.	DA.	YR.
(b) (6)	54	M	05	00	1991

7. DESCRIBE EVENT(S) DID NOT WORK, DEPRESSED, FINGERS AND TOES BECAME STIFF, PAIN IN FEET AND LEGS, COMMITTED SUICIDE.
A WOMAN REPORTED THAT HER HUSBAND BECAME DEPRESSED AND DEVELOPED STIFFNESS IN HIS FINGERS AND TOES AND PAIN IN HIS FEET AND LEGS AFTER RECEIVING INJECTIONS OF DEPO-TESTOSTERONE. HE STOPPED THE PRODUCT AFTER 4 OR 5 INJECTIONS BECAUSE AFTER THE FIRST INJECTION THEY DID NOT WORK. HE HAD BEEN PRESCRIBED IBUPROFEN FOR THE PAIN IN HIS FEET AND LEGS. HE HAD RECEIVED HIS FIRST DEPO-TESTOSTERONE INJECTION IN MAY OF 1991 AND APPARENTLY COMMITTED SUICIDE IN (b) (6) THE REPORTER FEELS THAT DEPO-TESTOSTERONE CAUSED THE PROBLEMS THAT RESULTED IN SUICIDE. WE ARE SEEKING INFORMATION FROM THE PATIENT'S PHYSICIAN. THIS REPORT WAS INITIALLY RECEIVED THROUGH THE FDA DRUG QUALITY REPORTING SYSTEM (#92-00771).

8.-12. CHECK ALL APPROPRIATE

- [X] DIED
- [X] TREATED WITH Rx DRUG
- [ ] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

13. RELEVANT TESTS/LABORATORY DATA
UNKNOWN

NO DRUG EFFECT
PAIN
DEPRESSION

II. SUBJECT DRUG(S) INFORMATION

14. SUBJECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*
A DEPO-Testosterone Sterile Solution /TUC/DORS-USP# 92-00771

15. DAILY DOSE
A UNKNOWN

16. ROUTE OF ADMINISTRATION
A UNKNOWN

17. INDICATION(S) FOR USE
A SEXUAL DYSFUNCTION

18. THERAPY DATES *(From/To)*
A 05/08/1991-UNKNOWN

19. THERAPY DURATION
A 5 DOSES APPROX

20. DID EVENT ABATE AFTER STOPPING DRUG?

A	[ ] YES	[ ] NO	[X] NA
B	[ ] YES	[ ] NO	[ ] NA
C	[ ] YES	[ ] NO	[ ] NA

21. DID EVENT REAPPEAR AFTER REINTRODUCTION?

A	[ ] YES	[ ] NO	[X] NA
B	[ ] YES	[ ] NO	[ ] NA
C	[ ] YES	[ ] NO	[ ] NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*
A IBUPROFEN 08/27/1991-09/22/1991
B HYDROCHLOROTHIAZIDE
C CHLORPROPAMIDE

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*
HYPERTENSION; DIABETES; SEXUAL DYSFUNCTION

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*
THE UPJOHN COMPANY
7000 PORTAGE ROAD
KALAMAZOO, MICHIGAN 49001

24a. IND NDA. NO. FOR DRUG
85635

24b. MFR CONTROL NO.
225/85635

24c. DATE RECEIVED BY MANUFACTURER
01/13/1992

24d. REPORT SOURCE *(Check all appropriate)*
[ ] FOREIGN [ ] STUDY [ ] LITERATURE
[ ] HEALTH PROFESSIONAL [X] CONSUMER

25. 15 DAY REPORT
[X] YES [ ] NO

25a. REPORT TYPE
[ ] INITIAL [X] FOLLOWUP

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*
CONSUMER REPORT
(b) (6)

26b. TELEPHONE NO. *(Include area code)*

26c. HAVE YOU ALSO REPORTED THIS EVENT TO THE MANUFACTURER?
[ ] YES [ ] NO

26d. ARE YOU A HEALTH PROFESSIONAL?
[ ] YES [ ] NO

Submission of a report does not necessarily constitute an admission that the drug caused the drug experience

NOTE Required of manufacturers by 21 CFR 314.80

FORM FDA 1639 (5/85) PREVIOUS EDITION IS OBSOLETE

JAN 22 1992

DIRECT SUBMISSION

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE MD 20857

DRUG EXPERIENCE REPORT
(Drugs and Biologics)

Form Approved by FDA August 16 1985

FDA CONTROL NO 808585

ACCESSION NO

I. EVENT INFORMATION

1. PATIENT ID INITIALS *(In Confidence)*: (b) (6)

2. AGE YRS.: UNK

3. SEX: M

4.-6. EVENT ONSET: MO. DA. YR. UNKNOWN

8.-12. CHECK ALL APPROPRIATE

7. DESCRIBE EVENT(S) DEPRESSED, FINGERS AND TOES BECAME STIFF, COMMITTED SUICIDE.

A WOMAN REPORTED THAT HER HUSBAND HAD RECEIVED AT LEAST 4 OR 5 INJECTIONS OF DEPO-TESTOSTERONE. HE BECAME DEPRESSED, EXPERIENCED STIFFNESS IN HIS FINGERS AND TOES, AND EVENTUALLY COMMITTED SUICIDE. THE REPORTER FEELS THAT DEPO-TESTOSTERONE CAUSED THE PROBLEMS THAT RESULTED IN SUICIDE. ADDITIONAL INFORMATION IS BEING SOUGHT.
THIS REPORT WAS FORWARDED TO THE UPJOHN COMPANY BY THE DRUG QUALITY REPORTING SYSTEM OF FDA (DQRS #92-00771).

- [X] DIED
- [ ] TREATED WITH Rx DRUG UNKNOWN
- [ ] RESULTED IN OR PROLONGED INPATIENT HOSPITALIZATION UNKNOWN
- [ ] RESULTED IN PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

13. RELEVANT TESTS/LABORATORY DATA
UNKNOWN

PREVIOUSLY SUBMITTED

II. SUBJECT DRUG(S) INFORMATION

14. SUBJECT DRUG(S) *(Give manufacturer and lot no for vaccines/biologics)*

A DEPO-Testosterone Sterile Solution /TUC/DQRS-USP# 92-00771

20. DID EVENT ABATE AFTER STOPPING DRUG?

A [ ] YES [ ] NO [X] NA
B [ ] YES [ ] NO [ ] NA
C [ ] YES [ ] NO [ ] NA

15. DAILY DOSE
A UNKNOWN

16. ROUTE OF ADMINISTRATION
A UNKNOWN

17. INDICATION(S) FOR USE
A UNKNOWN

21. DID EVENT REAPPEAR AFTER REINTRODUCTION?

A [ ] YES [ ] NO [X] NA
B [ ] YES [ ] NO [ ] NA
C [ ] YES [ ] NO [ ] NA

18. THERAPY DATES *(From/To)*
A UNKNOWN

19. THERAPY DURATION
A UNKNOWN

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*
UNKNOWN

23. OTHER RELEVANT HISTORY *(eg diagnoses allergies, pregnancy with LMP etc)*
UNKNOWN

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*
THE UPJOHN COMPANY
7000 PORTAGE ROAD
KALAMAZOO, MICHIGAN 49001

24a. IND/NDA. NO. FOR DRUG: 85635

24b. MFR CONTROL NO.: 225/85635

24c. DATE RECEIVED BY MANUFACTURER: 12/04/1991

24d. REPORT SOURCE *(Check all appropriate)*: [ ] FOREIGN [ ] STUDY [ ] LITERATURE [ ] HEALTH PROFESSIONAL [X] CONSUMER

25. 15 DAY REPORT: [X] YES [ ] NO

25a. REPORT TYPE: [X] INITIAL [ ] FOLLOWUP

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*
CONSUMER REPORT
(b) (6)

26b. TELEPHONE NO. *(Include area code)*

26c. HAVE YOU ALSO REPORTED THIS EVENT TO THE MANUFACTURER? [ ] YES [ ] NO

26d. ARE YOU A HEALTH PROFESSIONAL? [ ] YES [ ] NO

Submission of this report does not necessarily constitute an admission that the drug caused the drug experience

NOTE Required of manufacturers by 21 CFR 314 80

FORM FDA 1639 (5 85)

PREVIOUS EDITION IS OBSOLETE

8085 85

THE UPJOHN COMPANY

7000 Portage Road
Kalamazoo, MI 49001-0199

Pharmaceutical Regulatory Affairs Div.
Jill E. Robinson, Manager
7031-298-142
Worldwide Pharmacovigilance Unit
Telephone No. 1-800-253-8600 (Ext. 9-8549)

January 22, 1992

Central Document Room
Center of Drug Evaluation & Research
Food and Drug Administration
Park Building, Room 2-14
12420 Parklawn Drive
Rockville, MD 20852

15 DAY ALERT REPORT

Re: NDA #85-635
DEPO®-Testosterone Sterile Solution
Mfg. Control No. 225/85635
Direct Submission Follow-up

Dear Sir/Madam:

The attached Drug Experience Report (Form FDA 1639) for the above named product is being forwarded, in duplicate, in compliance with the provisions of 21 CFR 314.80(c)1.

Sincerely,

THE UPJOHN COMPANY

Jill E. Robinson
Manager, Worldwide Pharmacovigilance I

(b) (6)

Enclosures

(b) (6)

JAN 22 1992

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

DRUG EXPERIENCE REPORT
(Drugs and Biologics)

Form Approved by FDA August 16,1988

FDA CONTROL NO

ACCESSION NO 911207078039 22

I. EVENT INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)*: (b) (6)

2. AGE YRS.: 54

3. SEX: M

4.-6. EVENT ONSET: MO. 05 DA. 00 YR. 1991

8.-12. CHECK ALL APPROPRIATE
- [X] DIED
- [X] TREATED WITH Rx DRUG
- [ ] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- [ ] RESULTED IN PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

7. DESCRIBE EVENT(S) DID NOT WORK, DEPRESSED, FINGERS AND TOES BECAME STIFF, PAIN IN FEET AND LEGS, COMMITTED SUICIDE.
A WOMAN REPORTED THAT HER HUSBAND BECAME DEPRESSED AND DEVELOPED STIFFNESS IN HIS FINGERS AND TOES AND PAIN IN HIS FEET AND LEGS AFTER RECEIVING INJECTIONS OF DEPO-TESTOSTERONE. HE STOPPED THE PRODUCT AFTER 4 OR 5 INJECTIONS BECAUSE AFTER THE FIRST INJECTION THEY DID NOT WORK. HE HAD BEEN PRESCRIBED IBUPROFEN FOR THE PAIN IN HIS FEET AND LEGS. HE HAD RECEIVED HIS FIRST DEPO-TESTOSTERONE INJECTION IN MAY OF 1991 AND APPARENTLY COMMITTED SUICIDE IN (b) (6) THE REPORTER FEELS THAT DEPO-TESTOSTERONE CAUSED THE PROBLEMS THAT RESULTED IN SUICIDE. WE ARE SEEKING INFORMATION FROM THE PATIENT'S PHYSICIAN. THIS REPORT WAS INITIALLY RECEIVED THROUGH THE FDA DRUG QUALITY REPORTING SYSTEM (#92-00771).

13. RELEVANT TESTS/LABORATORY DATA
UNKNOWN

NO DRUG EFFECT
PAIN
DEPRESSION

II. SUBJECT DRUG(S) INFORMATION

14. SUBJECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*
A DEPO-Testosterone Sterile Solution /TUC/DORS-USP# 92-00771

15. DAILY DOSE
A UNKNOWN

16. ROUTE OF ADMINISTRATION
A UNKNOWN

17. INDICATION(S) FOR USE
A SEXUAL DYSFUNCTION

18. THERAPY DATES *(From/To)*
A 05/08/1991-UNKNOWN

19. THERAPY DURATION
A 5 DOSES APPROX

20. DID EVENT ABATE AFTER STOPPING DRUG?
A [ ] YES [ ] NO [X] NA
B [ ] YES [ ] NO [ ] NA
C [ ] YES [ ] NO [ ] NA

21. DID EVENT REAPPEAR AFTER REINTRODUCTION?
A [ ] YES [ ] NO [X] NA
B [ ] YES [ ] NO [ ] NA
C [ ] YES [ ] NO [ ] NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*
A IBUPROFEN 08/27/1991-09/22/1991
B HYDROCHLOROTHIAZIDE
C CHLORPROPAMIDE

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*
HYPERTENSION; DIABETES; SEXUAL DYSFUNCTION

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*
THE UPJOHN COMPANY
7000 PORTAGE ROAD
KALAMAZOO, MICHIGAN 49001

24a. IND NDA. NO. FOR DRUG: 85635

24b. MFR CONTROL NO.: 225/85635

24c. DATE RECEIVED BY MANUFACTURER: 01/13/1992

24d. REPORT SOURCE *(Check all appropriate)*
[ ] FOREIGN [ ] STUDY [ ] LITERATURE
[ ] HEALTH PROFESSIONAL [X] CONSUMER

25. 15 DAY REPORT
[X] YES [ ] NO

25a. REPORT TYPE
[ ] INITIAL [X] FOLLOWUP

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*
CONSUMER REPORT
(b) (6)

26b. TELEPHONE NO. *(Include area code)*

26c. HAVE YOU ALSO REPORTED THIS EVENT TO THE MANUFACTURER?
[ ] YES [ ] NO

26d. ARE YOU A HEALTH PROFESSIONAL?
[ ] YES [ ] NO

Submission of a report does not necessarily constitute an admission that the drug caused the drug experience

NOTE Required of manufacturers by 21 CFR 314.80

FORM FDA 1639 (5/85) PREVIOUS EDITION IS OBSOLETE

JAN 22 1992

DIRECT SUBMISSION

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE MD 20857

DRUG EXPERIENCE REPORT
(Drugs and Biologics)

Form Approved by FDA August 16 1985

FDA CONTROL NO 808585

ACCESSION NO

I. EVENT INFORMATION

1. PATIENT ID INITIALS *(In Confidence)*: (b) (6)

2. AGE YRS.: UNK

3. SEX: M

4.-6. EVENT ONSET: MO. DA. YR. UNKNOWN

8.-12. CHECK ALL APPROPRIATE

7. DESCRIBE EVENT(S) DEPRESSED, FINGERS AND TOES BECAME STIFF, COMMITTED SUICIDE.

A WOMAN REPORTED THAT HER HUSBAND HAD RECEIVED AT LEAST 4 OR 5 INJECTIONS OF DEPO-TESTOSTERONE. HE BECAME DEPRESSED, EXPERIENCED STIFFNESS IN HIS FINGERS AND TOES, AND EVENTUALLY COMMITTED SUICIDE. THE REPORTER FEELS THAT DEPO-TESTOSTERONE CAUSED THE PROBLEMS THAT RESULTED IN SUICIDE. ADDITIONAL INFORMATION IS BEING SOUGHT.
THIS REPORT WAS FORWARDED TO THE UPJOHN COMPANY BY THE DRUG QUALITY REPORTING SYSTEM OF FDA (DQRS #92-00771).

- [X] DIED
- [ ] TREATED WITH Rx DRUG UNKNOWN
- [ ] RESULTED IN OR PROLONGED INPATIENT HOSPITALIZATION UNKNOWN
- [ ] RESULTED IN PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

13. RELEVANT TESTS/LABORATORY DATA
UNKNOWN

PREVIOUSLY SUBMITTED

II. SUBJECT DRUG(S) INFORMATION

14. SUBJECT DRUG(S) *(Give manufacturer and lot no for vaccines/biologics)*
A DEPO-Testosterone Sterile Solution /TUC/DQRS-USP# 92-00771

15. DAILY DOSE
A UNKNOWN

16. ROUTE OF ADMINISTRATION
A UNKNOWN

17. INDICATION(S) FOR USE
A UNKNOWN

18. THERAPY DATES *(From/To)*
A UNKNOWN

19. THERAPY DURATION
A UNKNOWN

20. DID EVENT ABATE AFTER STOPPING DRUG?

A	YES	NO	[X] NA
B	YES	NO	NA
C	YES	NO	NA

21. DID EVENT REAPPEAR AFTER REINTRODUCTION?

A	YES	NO	[X] NA
B	YES	NO	NA
C	YES	NO	NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*
UNKNOWN

23. OTHER RELEVANT HISTORY *(eg diagnoses allergies, pregnancy with LMP etc)*
UNKNOWN

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*
THE UPJOHN COMPANY
7000 PORTAGE ROAD
KALAMAZOO, MICHIGAN 49001

24a. IND/NDA. NO. FOR DRUG
85635

24b. MFR CONTROL NO.
225/85635

24c. DATE RECEIVED BY MANUFACTURER
12/04/1991

24d. REPORT SOURCE *(Check all appropriate)*
- [ ] FOREIGN
- [ ] STUDY
- [ ] LITERATURE
- [ ] HEALTH PROFESSIONAL
- [X] CONSUMER

25. 15 DAY REPORT
- [X] YES
- [ ] NO

25a. REPORT TYPE
- [X] INITIAL
- [ ] FOLLOWUP

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*
CONSUMER REPORT
(b) (6)

26b. TELEPHONE NO. *(Include area code)*

26c. HAVE YOU ALSO REPORTED THIS EVENT TO THE MANUFACTURER?
- [ ] YES
- [ ] NO

26d. ARE YOU A HEALTH PROFESSIONAL?
- [ ] YES
- [ ] NO

Submission of this report does not necessarily constitute an admission that the drug caused the drug experience

NOTE Required of manufacturers by 21 CFR 314 80

FORM FDA 1639 (5 85)

PREVIOUS EDITION IS OBSOLETE

8085 85

THE UPJOHN COMPANY

7000 Portage Road
Kalamazoo, MI 49001-0199

Pharmaceutical Regulatory Affairs Div.
Jill E. Robinson, Manager
7031-298-142
Worldwide Pharmacovigilance Unit
Telephone No. 1-800-253-8600 (Ext. 9-8549)

January 22, 1992

Central Document Room
Center of Drug Evaluation & Research
Food and Drug Administration
Park Building, Room 2-14
12420 Parklawn Drive
Rockville, MD 20852

15 DAY ALERT REPORT

Re: NDA #85-635
DEPO®-Testosterone Sterile Solution
Mfg. Control No. 225/85635
Direct Submission Follow-up

Dear Sir/Madam:

The attached Drug Experience Report (Form FDA 1639) for the above named product is being forwarded, in duplicate, in compliance with the provisions of 21 CFR 314.80(c)1.

Sincerely,

THE UPJOHN COMPANY

Jill E. Robinson
Manager, Worldwide Pharmacovigilance I

(b) (6)

Enclosures

(b) (6)

900614

THE UPJOHN COMPANY

7000 Portage Road
Kalamazoo, MI 49001-0199

US Pharmaceutical Regulatory
Affairs Division

Office of
J.R. Assenzo, Ph.D.
Executive Director

Telephone No. (616) 329-8216

December 18, 1991

Central Document Room
Center for Drug Evaluation & Research
Food and Drug Administration
Park Building, Room 2-14
12420 Parklawn Drive
Rockville, Maryland 20852

15 DAY ALERT REPORT

Re: NDA 85-635
DEPO®-Testosterone Sterile Solution
Mfr. Control No. 225/85635 - Direct Submission

Gentlemen:

The attached Drug Experience Report (Form FDA 1639) for the above is being forwarded, in duplicate, in compliance with the provisions of 21 CFR 314.80(c)(1).

Sincerely,

THE UPJOHN COMPANY

J.R. Assenzo, Ph.D.
Executive Director
US Pharmaceutical Regulatory Affairs

JRA (b) (6)
att.
(b) (6)

E 3105

DIRECT SUBMISSION

5597601 DEPO-Testosterone SS 225

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

DRUG EXPERIENCE REPORT
(Drugs and Biologics)

Form Approved by FDA August 16,1985

DEC 18 1991

FDA CONTROL NO. 800614

ACCESSION NO. 911207 0978 03924

I. EVENT INFORMATION

1. PATIENT ID/INITIALS *(In Confidence)*	2. AGE YRS.	3. SEX	4.-5. EVENT ONSET MO.	DA.	YR.
(b) (6)	UNK	M	UNKNOWN		

8.-12. CHECK ALL APPROPRIATE

- [X] DIED
- [ ] TREATED WITH Rx DRUG UNKNOWN
- [ ] RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION UNKNOWN
- [ ] RESULTED IN PERMANENT DISABILITY
- [ ] NONE OF THE ABOVE

7. DESCRIBE EVENT(S) DEPRESSED, FINGERS AND TOES BECAME STIFF, COMMITTED SUICIDE.

A WOMAN REPORTED THAT HER HUSBAND HAD RECEIVED AT LEAST 4 OR 5 INJECTIONS OF DEPO-TESTOSTERONE. HE BECAME DEPRESSED, EXPERIENCED STIFFNESS IN HIS FINGERS AND TOES, AND EVENTUALLY COMMITTED SUICIDE. THE REPORTER FEELS THAT DEPO-TESTOSTERONE CAUSED THE PROBLEMS THAT RESULTED IN SUICIDE. ADDITIONAL INFORMATION IS BEING SOUGHT.
THIS REPORT WAS FORWARDED TO THE UPJOHN COMPANY BY THE DRUG QUALITY REPORTING SYSTEM OF FDA (DQRS #92-00771).

Suicide attempt
depression psychotic
hypertonia

13. RELEVANT TESTS/LABORATORY DATA
UNKNOWN

II. SUBJECT DRUG(S) INFORMATION

14. SUBJECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*

A DEPO-Testosterone Sterile Solution /TUC/DQRS-USP# 92-00771

15. DAILY DOSE
A UNKNOWN

16. ROUTE OF ADMINISTRATION
A UNKNOWN

17. INDICATION(S) FOR USE
A UNKNOWN

18. THERAPY DATES *(From/To)*
A UNKNOWN

19. THERAPY DURATION
A UNKNOWN

20. DID EVENT ABATE AFTER STOPPING DRUG?

A.	[ ] YES	[ ] NO	[X] NA
B.	[ ] YES	[ ] NO	[ ] NA
C.	[ ] YES	[ ] NO	[ ] NA

21. DID EVENT REAPPEAR AFTER REINTRODUCTION?

A.	[ ] YES	[ ] NO	[X] NA
B.	[ ] YES	[ ] NO	[ ] NA
C.	[ ] YES	[ ] NO	[ ] NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*
UNKNOWN

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*
UNKNOWN

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*
THE UPJOHN COMPANY
7000 PORTAGE ROAD
KALAMAZOO, MICHIGAN 49001

01/13/92

24a. IND/NDA. NO. FOR DRUG
85635

24b. MFR CONTROL NO.
225/85635

24c. DATE RECEIVED BY MANUFACTURER
12/04/1991

24d. REPORT SOURCE *(Check all appropriate)*
[ ] FOREIGN [ ] STUDY [ ] LITERATURE
[ ] HEALTH PROFESSIONAL [X] CONSUMER

25. 15 DAY REPORT
[X] YES [ ] NO

25a. REPORT TYPE
[X] INITIAL [ ] FOLLOWUP

NOTE: Required of manufacturers by 21 CFR 314.80.

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*
CONSUMER REPORT
(b) (6)

26b. TELEPHONE NO. *(Include area code)*

26c. HAVE YOU ALSO REPORTED THIS EVENT TO THE MANUFACTURER?
[ ] YES [ ] NO

26d. ARE YOU A HEALTH PROFESSIONAL?
[ ] YES [X] NO

Submission of a report does not necessarily constitute an admission that the drug caused the drug experience.

FORM FDA 1639 (5/85) PREVIOUS EDITION IS OBSOLETE.

DEC 26 PM 3:31

6634201 DEPO-Testosterone SS 272

DEPARTMENT OF HEALTH HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-736)
ROCKVILLE, MD 20857

DRUG EXPERIENCE REPORT
(Drugs and Biologics)

Form Approved by FDA August 16,1985

FDA CONTROL NO. 135299 JUN 16 1993

ACCESSION NO.

I. EVENT INFORMATION

1. PATIENT ID/INITIALS (In Confidence)	2. AGE YRS.	3. SEX	4.-6. EVENT ONSET MO.	DA.	YR.
(b) (6)	UNK	M	UNKNOWN		

7. DESCRIBE EVENT(S) INCREASED DEPRESSION AND SUICIDE ATTEMPT

THIS PATIENT COMPLAINED TO HIS PHYSICIAN OF DEPRESSION DUE TO LOSS OF SEXUAL FUNCTION. HE WAS TREATED WITH DEPO-TESTOSTERONE AND SEVERAL OTHER MEDICATIONS. HE NOW ALLEGES THIS TREATMENT LEAD TO FURTHER DEPRESSION AND A SECOND SUICIDE ATTEMPT.

depression psychotic.
suicide attempt

8.-12. CHECK ALL APPROPRIATE

- ☐ DIED
- ☐ TREATED WITH Rx DRUG UNKNOWN
- ☐ RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION UNKNOWN
- ☐ RESULTED IN PERMANENT DISABILITY
- ☐ NONE OF THE ABOVE

13. RELEVANT TESTS/LABORATORY DATA
UNKNOWN

II. SUBJECT DRUG(S) INFORMATION

14. SUBJECT DRUG(S) *(Give manufacturer and lot no. for vaccines/biologics)*

A DEPO-Testosterone Sterile Solution /TUC

15. DAILY DOSE	16. ROUTE OF ADMINISTRATION
A UNKNOWN	A UNKNOWN

17. INDICATION(S) FOR USE
A LOSS OF SEXUAL FUNCTION,DEPRESSION

18. THERAPY DATES (From/To)	19. THERAPY DURATION
A UNKNOWN	A UNKNOWN

20. DID EVENT ABATE AFTER STOPPING DRUG?

*A.	☐ YES	☐ NO	☐ NA
B.	☐ YES	☐ NO	☐ NA
C.	☐ YES	☐ NO	☐ NA

*-UNKNOWN

21. DID EVENT REAPPEAR AFTER REINTRODUCTION?

*A.	☐ YES	☐ NO	☐ NA
B.	☐ YES	☐ NO	☐ NA
C.	☐ YES	☐ NO	☐ NA

*-UNKNOWN

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION *(Exclude those used to treat reaction)*

B estradiol cypionate
HCG
C HYDROXYPROGESTERONE
D. gonadotropin, chorionic, human

23. OTHER RELEVANT HISTORY *(e.g. diagnoses, allergies, pregnancy with LMP etc.)*
DEPRESSION; PREVIOUS SUICIDE ATTEMPT; SHOULDER PROBLEM;

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER *(Include Zip Code)*
THE UPJOHN COMPANY
7000 PORTAGE ROAD
KALAMAZOO, MICHIGAN 49001

24a. IND/NDA. NO. FOR DRUG	24b. MFR CONTROL NO.
85635	272/85635

24c. DATE RECEIVED BY MANUFACTURER	24d. REPORT SOURCE (Check all appropriate)
05/14/1993	☐ FOREIGN ☐ STUDY ☐ LITERATURE ☒ HEALTH PROFESSIONAL ☐ CONSUMER

25. 15 DAY REPORT	25a. REPORT TYPE
☐ YES ☒ NO	☒ INITIAL ☐ FOLLOWUP

NOTE: Required of manufacturers by 21 CFR 314.80.

V. INITIAL REPORTER *(In confidence)*

26.-26a. NAME AND ADDRESS OF REPORTER *(Include Zip Code)*
(b) (6)

26b. TELEPHONE NO. *(Include area code)*
UNKNOWN

26c. HAVE YOU ALSO REPORTED THIS EVENT TO THE MANUFACTURER?
☐ YES ☐ NO N/A

26d. ARE YOU A HEALTH PROFESSIONAL?
☒ YES ☐ NO N/A

Submission of a report does not necessarily constitute an admission that the drug caused the drug experience.

Individual Safety Report

4736461-8-00-01

The FDA Medical Products Reporting Program

uxilium Pharmaceuticals, Inc.

For use by user-facilities, distributors and manufacturers for MANDATORY reporting

FDA Facsimile Approval: May 02 2003

Mfr report # 190705001/225 AE

UF/Dist report #

FDA Use Only

A. Patient information

1. Patient Identifier	2. Age at time of event	3. Sex	4. Weight
UNK in confidence	41-years-old or Date of birth: (b) (6)	☐ female ☒ male	UNK lbs or _____ kgs

B. Adverse event or product problem

1. ☒ Adverse event and/or ☐ Product problem (e.g., defects/malfunctions)

2. Outcomes attributed to adverse event (check all that apply)

- ☐ death _____ (mo/day/yr)
- ☐ life-threatening
- ☐ hospitalization - initial or prolonged
- ☐ disability
- ☐ congenital anomaly
- ☒ required intervention to prevent permanent impairment/damage
- ☐ other: _____

3. Date of event	4. Date of this report
(mo/day/yr) 07/??/2005	(mo/day/yr) 08/02/2005

5. Describe event or problem

A physician reported to a company representative that a 41-year-old male patient with gastroesophageal reflux disease and erectile dysfunction was placed on therapy with Testim 50 mg daily on 25APR05 for the treatment of hypogonadism. Concomitant medications included lansoprazole (Prevacid). In early July 2005, approximately two and a half months after initiating therapy with Testim, the patient developed marked depression with accompanying suicidal ideation. The physician reported that the patient had an excellent clinical response to Testim for the hypogonadism and erectile dysfunction and refused to discontinue therapy. The patient was treated with escitalopram oxalate (Lexapro) for the depression and his symptoms resolved. Therapy with Testim was continued. At the time of the report, no further information was available.

6. Relevant tests/laboratory data, including dates

UNK

DSS

AUG 05 2005

7. Other relevant history, including preexisting medical conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

Medical History: UNK

Concurrent Conditions: Gastroesophageal reflux disease; Erectile dysfunction

C. Suspect medication(s)

1. Name (give labeled strength & mfr/labeler, if known)

#1 Testim® 1% CIII

#2

2. Dose, frequency & route used

#1 50 mg, Daily, Transdermal

#2

3. Therapy dates (if unknown, give duration) from/to or best estimate

#1 04/25/2005 - CONT

#2 _____ - _____

4. Diagnosis for use (indication)

#1 Hypogonadism

#2

5. Event abated after use stopped or dose reduced

#1 ☐ yes ☐ no ☒ doesn't apply

#2 ☐ yes ☐ no ☐ doesn't apply

6. Lot # (if known)

#1 UNK

#2

7. Exp. Date (if known)

#1 UNK

#2

8. Event reappeared after reintroduction

#1 ☐ yes ☐ no ☒ doesn't apply

#2 ☐ yes ☐ no ☐ doesn't apply

9. NDC # - for product problems only (if known)

- -

10. Concomitant medical products and therapy dates (exclude treatment of event)

Prevacid

G. All manufacturers

1. Contact office - name/address (& mfring site for devices)

Auxilium Pharmaceuticals, Inc.
40 Valley Stream Parkway
Malvern, PA 19355

2. Phone number: 484-321-5900

3. Report source (check all that apply)

- ☐ foreign
- ☐ study
- ☐ literature
- ☐ consumer
- ☒ health professional
- ☐ user facility
- ☒ company representative
- ☐ distributor
- ☐ other

4. Date received by manufacturer: 07/19/2005 (mo/day/yr)

5. (A)NDA # 21-454
IND # _____
PLA # _____
Pre-1938 ☐ yes
OTC product ☐ yes

6. If IND, protocol #

7. Type of report (check all that apply)

- ☐ 5-day ☒ 15-day
- ☐ 10-day ☐ periodic
- ☒ Initial ☐ follow-up # _____

8. Adverse event term(s)

Suicidal ideation; Depression

AUG - 4 2005

9. Mfr. Report number: 190705001/225 AE

E. Initial reporter

1. Name & address

(b) (6)

Phone # (b) (6)

IQA

2. Health professional?	3. Occupation	4. Initial reporter also sent report to FDA
☒ yes ☐ no	Physician	☐ yes ☒ no ☐ unk

FDA 3500A Facsimile (04/03)

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

Individual Safety Report

5007484-9-00-01

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

For use by user-facilities, ...stributors and manufacturers for MANDATORY reporting
Watson Laboratories, Inc

Relsys International, Inc.
FDA Facsimile Approval: 11-JUN-1999

Mfr report # 2005-04814
UF/Dist. report #
FDA Use Only

A. Patient information

1. Patient identifier (b) (6) in confidence
2. Age at time of event: 54 Years or Date of birth: UNK
3. Sex: [ ] female [X] male
4. Weight: UNK lbs or UNK kgs

B. Adverse event or product problem

1. [X] Adverse event and/or [ ] Product problem (e.g., defects/malfunctions)

2. Outcomes attributed to adverse event (check all that apply)
[ ] death (mo/day/yr)
[ ] life-threatening
[ ] hospitalization - initial or prolonged
[ ] disability
[ ] congenital anomaly
[ ] required intervention to prevent permanent impairment/damage
[X] other: Medically Significant

3. Date of event (mo/day/yr): --/--/2001
4. Date of this report (mo/day/yr): 05/16/2006

5. Describe event or problem

suicial depression[Depression suicidal]
violent outbursts/ aggression[Aggression]
antisocial / does not speak[Antisocial behaviour]
Confusion[Confusional state]
Thinking abnormalities[Thinking abnormal]

Case Description:
Date of initial report: 12-DEC-2005 A woman reported that her 54-year-old husband (Patient Initials: (b) (6)) who is using twice his prescribed dose of Androderm, is experiencing suicidal depression, violent outbursts and aggression which is causing her to fear for her own safety.

During a fight with the wife the patient yelled out in anger "no wonder I want to kill myself !" The patient's behavior has changed after he began Androderm. He is highly antisocial, sometimes not speaking a word to his wife all day. The
continued in additional info section...

6. Relevant tests/laboratory data, including dates
NI

7. Other relevant history, including preexisting medical conditions (e.g. allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)
#1 UNK, Current Condition (Diabetes, testosterone deficiency, erectile dysfunction)
#2 UNK, Historical Drug (Testosterone injections used in the past. Uknown dose & duration of therapy)

C. Suspect medication(s)

1. Name (give labeled strength & mfr/labeler, if known)
#1. Androderm (Watson Laboratories) (continued)
#2.

2. Dose, frequency & route used
#1. 2 Patch, (continued)
#2.

3. Therapy dates (if unknown, give duration) (from/to (or best estimate))
#1. --/--/2001 to Ongoing
#2.

4. Diagnosis for use (indication)
#1. testosterone deficiency
#2.

5. Event abated after use stopped or dose reduced
#1. [ ] yes [ ] no [X] doesn't apply
#2. [ ] yes [ ] no [ ] doesn't apply

6. Lot # (if known)
#1. unknown
#2.

7. Exp. date (if known)
#1. UNK
#2.

8. Event reappeared after reintroduction
#1. [ ] yes [ ] no [X] doesn't apply
#2. [ ] yes [ ] no [ ] doesn't apply

9. NDC # - for product problems only (if known)

10. Concomitant medical products and therapy dates (exclude treatment of event)
VIAGRA (SILDENAFIL CITRATE) UNK to ongoing
GLUCOVANCE (GLIBENCLAMIDE) UNK to ongoing
continued in additional info section...

G. All Manufacturers

1. Contact office - name/address (& mfring site for devices)
Watson Laboratories, Inc.
311 Bonnie Circle
Corona, CA 92880 UNITED STATES

2. Phone number: 9512701400

3. Report source (check all that apply)
[ ] foreign
[ ] study
[ ] literature
[Y] consumer
[Y] health professional
[ ] user facility
[ ] company representative
[ ] distributor
[ ] other:

4. Date received by manufacturer (mo/day/yr): 05/05/2006

5. (A)NDA # 020-489
IND #
PLA #
pre-1938 [ ] yes
OTC product [ ] yes

6. If IND, protocol #

7. Type of report (check all that apply)
[ ] 5-day [Y] 15-day
[ ] 10-day [ ] periodic
[ ] initial [Y] follow-up # 1

8. Adverse event term(s)
Depression suicidal, Aggression, Antisocial behaviour, Confusional state, Thinking abnormal, Anger

9. Mfr. report number
2005-04814

E. Initial reporter

1. Name & address
(b) (6)
UNITED STATES

phone # (b) (6)

MAY 17 2006

2. Health professional ?
[X] yes [ ] no

3. Occupation
Physician

4. Initial reporter also sent report to FDA
[ ] yes [X] no [ ] unk

FDA
3500A - Facsimile

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

DSS

MAY 18 2006

16-May-2006 10:50:10

Medication and Device Experience Report

Individual Safety Report

5007484-9-00-02

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

Watson Laboratories, Inc

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service - Food and Drug Administration

Mfr report # 2005-04814

UF/Dist. report #

FDA Use Only

[redacted]

B5. EVENT DESCRIPTION (cont.)

patient uses 2 patches per day of Androderm 5mg, according to the wife. The patient has been on testosterone injection in the past without these adverse events, although the dose is unknown to the reporter.

Additional information obtained: The patient's physician (current urologist) was contacted and notified of the wife's report of the patient's suicidal depression and violent aggression. The physician felt that the police should be contacted to seize the patient so that he can be taken to a mental hospital for evaluation. The local police was notified and a police report was filed.

The patient was last seen by the urologist on 28-FEB-2005, and the chart notes had no mention of change in the patient's behavior. At that visit the patient was given a prescription for Androderm with 1 year's worth of refills. The patient has a history of erectile dysfunction for which he has tried Viagra, Cialis and Levitra.

The physician stated that he prescribed Androderm 1 patch per day, not 2 patches per day. The physician was unaware that the patient had been using 2 patches per day, as described by his wife.

A testosterone level had been ordered in July 2004, however no results were received by the physician's office, and it is unknown if the patient had ever gone to the lab for a blood draw. The physician was not able to provide a lab result for the latest testosterone level measured.

The urologist is unaware of any other medical conditions in this patient other than diabetes, impotence and testosterone deficiency.

Additional information received on 13-DEC-2005. The patient's wife called back and left the following message on voicemail. The label on the patient's Androderm box reads "Use 2 patches every night." The identity of the prescribing doctor on the label of this Androderm box was not provided in the voicemail, however, the wife had mentioned in her previous report that the husband receives Androderm from one physician only.

Additional information received on 14-DEC-2005. The wife confirmed that the prescription label on the most current Androderm box has instructions to use 2 patches per day, and that the patient's current urologist name was printed on the label. There are no more refills remaining. The wife requested that the police not be contacted anymore because the husband is not an immediate threat to himself or to others, contrary to her initial report.

Additional information received on 05-MAY-2006. The wife reported that her husband is experiencing confusion, thinking abnormalities, and he gets angry while on Androderm and that all the events are still continuing. Reporter still continues to express concern for her husband's well being.

Comment:
This case involves dosing (10 mg/ day) which is not addressed in the US label.

C1. Name (cont.)
Suspect Medication #1: Androderm (Watson Laboratories)(TESTOSTERONE) Transdermal Patch, 5mg

C2. Dose, frequency & route used (cont.)
Suspect Medication #1: 2 Patch, daily, Transdermal

C10. CONCOMITANT MEDICAL PRODUCTS

ACTOS /USA/ (PIOGLITAZONE HYDROCHLORIDE) UNK to ongoing

MAY 17 2006

DSS

MAY 18 2006

Individual Safety Report

5108206-3-00-01

MEDWATCH

FORM FDA 3500A (10/05)

For use by user-facilities, importers, distributors and manufacturers for MANDATORY reporting

FDA Facsimile Approval: 05/09/2006 (ArisGlobal, LLC)

Mfr Report # 2006-BP-10602RO (0)

UF/Importer Report #

FDA Use Only

A. PATIENT INFORMATION

1. Patient Identifier	2. Age at Time of Event: / Date of Birth:	3. Sex	4. Weight
(b) (6) In confidence	UNK / Unk	☐ Female ☒ Male	Unk lbs / Unk kgs

B. ADVERSE EVENT OR PRODUCT PROBLEM

1. ☒ Adverse Event and/or ☐ Product Problem (e.g., defects/malfunctions)

2. Outcomes Attributed to Adverse Event (Check all that apply)

☒ Death: (b) (6) (mm/dd/yyyy)
☐ Life-threatening
☐ Hospitalization - initial or prolonged
☐ Required Intervention to Prevent Permanent Impairment/Damage (Devices)
☐ Disability or Permanent Damage
☐ Congenital Anomaly/Birth Defect
☐ Other serious (Important Medical Events)

3. Date of Event (mm/dd/yyyy)	4. Date of This Report (mm/dd/yyyy)
08/01/2006	09/11/2006

5. Describe Event or Problem

11-SEP-2006 Initial report per US Mail from Solvay Pharmaceuticals MCN # 00206002504

Event: Completed suicide

Solvay forwarded a report where a male patient (b) (6) with a previous history of suicide attempts died as a result of a completed suicide on (b) (6) He was using Lithium Carbonate and Androgel at the time of his death.

Additional information requested.

6. Relevant Tests/Laboratory Data, Including Dates

7. Other Relevant History, Including Preexisting Medical Conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

Risk Factors : Drug abuse
Past Disease:
SUICIDE ATTEMPT (Unk)

Concurrent Disease:
DEPRESSION (Unk) (Continuing: Unk)

Submission of a report does not constitute an admission that medical personnel, user facility, importer, distributor, manufacturer or product caused or contributed to the event.

3500A Facsimile

C. SUSPECT PRODUCT(S)

1. Name (Give labeled strength & mfr/labeler)

#1 Lithium Carbonate Capsules USP, 300 mg(LITHIUM CARBONATE)

#2 ANDROGEL 1 (TESTOSTERONE GEL 1%) (TESTOSTERONE) Cont...

2. Dose, Frequency & Route Used	3. Therapy Dates (If unknown, give duration) from/to (or best estimate)
#1 NR (NR), PO	#1 NR
#2 1% topical gel (see text), TO	#2 NR

4. Diagnosis for Use (Indication)	5. Event Abated After Use Stopped or Dose Reduced?
#1 DEPRESSION	#1 ☐ Yes ☐ No ☒ Doesn't Apply
#2 DEPRESSION	#2 ☐ Yes ☐ No ☒ Doesn't Apply

6. Lot #	7. Exp. Date	8. Event Reappeared After Reintroduction?
#1 Unk	#1 Unk	#1 ☐ Yes ☐ No ☒ Doesn't Apply
#2 Unk	#2 Unk	#2 ☐ Yes ☐ No ☒ Doesn't Apply

9. NDC # or Unique ID

10. Concomitant Medical Products and Therapy Dates (Exclude treatment of event)

1) NR

G. ALL MANUFACTURERS

1. Contact Office - Name/Address (and Manufacturing Site for Devices)

Roxane Laboratories, Inc.
1809 Wilson Road
Columbus, OH 16532
UNITED STATES
(Printing Unit)

2. Phone Number: Cont...

3. Report Source (Check all that apply)
☐ Foreign
☐ Study
☐ Literature
☐ Consumer
☒ Health Professional
☐ User Facility
☐ Company Representative
☐ Distributor
☐ Other:

4. Date Received by Manufacturer (mm/dd/yyyy): 09/11/2006

5. (A)NDA #: 17-812
IND #:
STN #:
PMA/510(k) #:

6. If IND, Give Protocol #

7. Type of Report (Check all that apply)
☐ 5-day ☐ 30-day
☐ 7-day ☐ Periodic
☐ 10-day ☒ Initial
☒ 15-day ☐ Follow-up #

Combination Product ☐ Yes
Pre-1938 ☐ Yes
OTC Product ☐ Yes

9. Manufacturer Report Number: 2006-BP-10602RO (0)

8. Adverse Event Term(s)
1) Completed suicide

E. INITIAL REPORTER

1. Name and Address

Solvay Pharmaceuticals, Inc
MCN # 00206002504
GA
US

Phone #

2. Health Professional?	3. Occupation	4. Initial Reporter Also Sent Report to FDA
☒ Yes ☐ No	Manufacturer	☐ Yes ☐ No ☒ Unk.

DSS

SEP 15 2006

SEP 18 2006

5108206-3-00-02

Mfr. Report # : 2006-BP-10602RO(0)

Date of This Report : 09/11/2006

C. SUSPECT PRODUCT(S) (Cont...)

Seq No.	: 2
C.1 Suspect Product	: ANDROGEL 1 (TESTOSTERONE GEL 1%) (TESTOSTERONE)
C.3 Therapy Dates (or duration)	: 1) 11/?/2005 - Unk

G. ALL MANUFACTURERS

G.2 Phone Number

(614) 276-4000

SEP 15 2006

DSS

SEP 18 2006

CaseID: 7546458

FDA Facsimile Approval: 05/09/2006 (ArisGlobal, LLC)

6920229-8-00-01

MEDWATCH

FORM FDA 3500A (1/09)

user-facilities, importers, distributors and manufacturers for MANDATORY reporting

Mfr Report # 201004025

UF/Importer Report #

FDA Use Only

A. PATIENT INFORMATION

1. Patient Identifier: (b) (6) — In confidence

2. Age at Time of Event: 46 Y or Date of Birth: (b) (6)

3. Sex: ☐ Female ☒ Male

4. Weight: 175 lbs or ____ kgs

B. ADVERSE EVENT OR PRODUCT PROBLEM

1. ☒ Adverse Event and/or ☐ Product Problem (e.g., defects/malfunctions)

2. Outcomes Attributed to Adverse Event (Check all that apply)

- ☐ Death: ____ (mm/dd/yyyy)
- ☐ Life-threatening
- ☒ Hospitalization - initial or prolonged
- ☐ Required Intervention to Prevent Permanent Impairment/Damage (Devices)
- ☐ Disability or Permanent Damage
- ☐ Congenital Anomaly/Birth Defect
- ☐ Other serious (Important Medical Events)

3. Date of Event (mm/dd/yyyy): 07/??/2009

4. Date of This Report (mm/dd/yyyy): 08/05/2010

5. Describe Event or Problem

A report was received regarding a 47-year-old male, with a history of depression, sleep apnea, and anxiety, who was placed on Testim (testosterone) gel 50 mg daily starting in Mar-2008 (exact date unknown) for the treatment of low testosterone. Concomitant medications included duloxetine (Cymbalta), and alprazolam (Xanax).

In (b) (6) (exact date not known), the patient experienced depression with suicidal ideation "that goes up and down." Prior to starting Testim, his depression was controlled by duloxetine; however, the medication was no longer effective after starting therapy with Testim. In Dec-2009 (exact date unknown), he was switched from duloxetine to quetiapine (Seroquel). His depression remained unchanged, and citalapram (Celexa) was added to treatment regimen.

In Jan-2010 (exact date unknown), he began to experience a headache. In Feb-2010 (exact date unknown), he experienced worsening of his sleep apnea. Therapy with Testim was

Cont...

6. Relevant Tests/Laboratory Data, Including Dates

Unknown

D33

AUG 10 2010

Cont...

7. Other Relevant History, Including Preexisting Medical Conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

Concurrent Disease:
Depression[10012378] (??/??/1993 -)
(Continuing: Yes)
Sleep apnoea syndrome[10040979] (Continuing: Yes)
Anxiety[10002855] (Continuing: Yes)

Submission of a report does not constitute an admission that medical personnel, user facility, importer, distributor, manufacturer or product caused or contributed to the event.

3500A Facsimile

C. SUSPECT PRODUCT(S)

1. Name (Give labeled strength & mfr/labeler)
#1 Testim(testosterone)
#2

Cont...

2. Dose, Frequency & Route Used
#1 50 mg, 1 in 1 D, Transdermal
#2

3. Therapy Dates (If unknown, give duration) from/to (or best estimate)
#1 ??/??/2007 - 11/??/2009
#2

4. Diagnosis for Use (Indication)
#1 Blood testosterone decreased[10005814]
#2

5. Event Abated After Use Stopped or Dose Reduced?
#1 ☐ Yes ☒ No ☐ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply

6. Lot #
#1
#2

7. Exp. Date
#1
#2

8. Event Reappeared After Reintroduction?
#1 ☒ Yes ☐ No ☐ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply

9. NDC # or Unique ID

10. Concomitant Medical Products and Therapy Dates (Exclude treatment of event)

1) Seroquel(QUETIAPINE)	12/??/2009	Stopped
2) Celexa(CITALOPRAM HYDROBROMIDE)	04/05/2010	Stopped
3) Cymbalta(DULOXETI-		

Cont...

G. ALL MANUFACTURERS

1. Contact Office - Name/Address (and Manufacturing Site for Devices)
Auxilium Pharmaceuticals, Inc.
40 Valley Stream Parkway
Malvern, PA 19355
USA
(Initial Unit)

2. Phone Number: 484-321-5928

3. Report Source (Check all that apply)
☐ Foreign ☐ Study ☐ Literature ☒ Consumer ☐ Health Professional ☐ User Facility ☐ Company Representative ☐ Distributor ☐ Other:

4. Date Received by Manufacturer (mm/dd/yyyy): 07/28/2010

5. (A)NDA # 21-454
IND #
STN #
PMA/510(k) #

6. If IND, Give Protocol #

7. Type of Report (Check all that apply)
☐ 5-day ☐ 30-day ☐ 7-day ☐ Periodic ☐ 10-day ☒ Initial ☒ 15-day ☐ Follow-up # ____

Combination Product ☐ Yes
Pre-1938 ☐ Yes
OTC Product ☐ Yes

9. Manufacturer Report Number: 201004025

8. Adverse Event Term(s)
1) Anxiety
2) Depression

Cont...

E. INITIAL REPORTER

1. Name and Address
CONFIDENTIAL
USA

Phone # CONFDENTIAL

2. Health Professional? ☐ Yes ☒ No

3. Occupation

4. Initial Reporter Also Sent Report to FDA ☐ Yes ☐ No ☒ Unk.

Reference ID: 4146835

AUG 09 2010

B. ADVERSE EVENT OR PRODUCT PROBLEM

B.5 Describe Event or Problem (Cont...)

tapered to 75 percent of a tube daily starting on 05-Apr-2010 for ten days, then to 50 percent of a tube starting on 15-Apr-2010 for ten days, and finally he tapered down until there was almost nothing to apply. His last dose of Testim was on 26-Apr-2010.

At the time of reporting, therapy with Testim had been discontinued and the events of depression with suicidal ideation that went up and down and headache were unchanged. The event of sleep apnea had worsened. No other information was available.

On 28-Jul-2010, additional information was received which corrected the patient's age to 46 years at the time of the newly-reported events occurring in 2009. He admitted to changing endocrinologists, psychiatrists, and concomitant medications multiple times since 2009. He suffered from depression 17 years ago in 2003 and this restarted approximately one year ago in 2009. He was placed on Testim (testosterone) gel 50 mg daily for the treatment of low testosterone approximately two and one half to three years ago in 2007 (unknown exact dates or timeframe). Concomitant medications at the time of reporting included mirtazapine (Remeron), valporate semisodium (Depakote), clonazepam (Klonopin), escitalopram (Lexapro), aripiprozole (Abilify), and lorazepam (ativan).

In approximately Jul-2009 the patient began to feel depressed and experienced "up and down" experiences with Testim every day. Since 2009, he would feel anxious approximately ten minutes to two hours after applying Testim in the morning. As the day would progress he felt depressed until approximately 8PM (local time), then he would feel normal. Approximately eight months ago in (b) (6) he checked himself into a psychiatric hospital for treatment. During his hospitalization he discontinued Testim and stated he felt worse while he was off Testim therapy. He was discharged eight days later and he restarted Testim therapy (exact dates or timeframe unknown). After restarting Testim therapy, he remained depressed. Per his initial report in 26-Apr-2010, he had begun tapering off of Testim and his last dose was on 26-Apr-2010. He did not provide tapering details in his report received on 28-Jul-2010.

The consumer was a poor historian and provided contradictory event specific information in relation to his report received on 26-Apr-2010.

At the time of reporting, it was believed that therapy with Testim was discontinued and the events of anxiety and depression were unresolved. No further information was available.

B.6 Relevant Tests/Laboratory Data, Including Dates (Cont...)

Lab Result :

Test name	Test date	Test result	Normal value
Testosterone	07/??/2009	300-400 unknown exact date, while on testim therapy	
testosterone	07/??/2010	275 unknown exact date, while on testim therapy	

C. SUSPECT PRODUCT(S) (Cont...)

Seq No.	:1
C.1 Suspect Product	:Testim(testosterone)
C.2 Dose, Frequency & Route Used	:2) 50 mg, 1 in 1 D, Transdermal 3) Transdermal
C.3 Therapy Dates (or duration)	:2) 12/??/2009 3) 04/16/2010 - 04/26/2010
C.5 Dechallenge	:2) -ve :3) UNK :4) UNK :5) UNK :6) N/A
C.8 Rechallenge	:2) +ve :3) UNK :4) UNK :5) UNK :6) N/A

DSS

AUG 10 2010

C.10 Concomitant Medical Products and Therapy Dates

Seq No.	:1
Concomitant Medical Product	:Seroquel(QUETIAPINE)
Dose, Frequency & Route Used	:1) 300 mg
Diagnosis for Use (Indication)	:1) Depression[10012378]

AUG 09 2010

Seq No.	:2
Concomitant Medical Product	:C elexa(CITALOPRAM HYDROBROMIDE)
Dose, Frequency & Route Used	:1) 10 mg
Diagnosis for Use (Indication)	:1) Depression[10012378]
Seq No.	:3
Concomitant Medical Product	:C ymbalta(DULOXETINE HYDROCHLORIDE)
Therapy Dates	:1) ??/??/2005 - 12/??/2009
Diagnosis for Use (Indication)	:1) Depression[10012378]
Seq No.	:4
Concomitant Medical Product	:X anax(ALPRAZOLAM)
Therapy Dates	:1) 04/05/2010 Stopped
Diagnosis for Use (Indication)	:1) Anxiety[10002855]
Seq No.	:5
Concomitant Medical Product	:R emeron(MIRTAZAPINE)
Dose, Frequency & Route Used	:1) 30 mg, Every morning
Therapy Dates	:1) 07/??/2010 Ongoing
Diagnosis for Use (Indication)	:1) Depression[10012378]
Seq No.	:6
Concomitant Medical Product	:K lonopin(CLONAZEPAM)
Dose, Frequency & Route Used	:1) 1 mg, At bedtime
Therapy Dates	:1) 07/??/2010 Ongoing
Seq No.	:7
Concomitant Medical Product	:L exapro(ESCITALOPRAM OXALATE)
Dose, Frequency & Route Used	:1) 20 mg, Every morning
Therapy Dates	:1) 07/??/2010 Ongoing
Diagnosis for Use (Indication)	:1) Depression[10012378]
Seq No.	:8
Concomitant Medical Product	:A bilify(ARIPIPRAZOLE)
Dose, Frequency & Route Used	:1) 1 mg
Therapy Dates	:1) 07/??/2010 Ongoing
Diagnosis for Use (Indication)	:1) Depression[10012378]
Seq No.	:9
Concomitant Medical Product	:A tivan(LORAZEPAM)
Dose, Frequency & Route Used	:1) 1.5 mg, As required
Therapy Dates	:1) 07/??/2010 Ongoing
Seq No.	:1 0
Concomitant Medical Product	:D epakote(VALPROATE SEMISODIUM)
Dose, Frequency & Route Used	:1) 500 mg, Every morning
Therapy Dates	:1) 07/??/2010 Ongoing
Diagnosis for Use (Indication)	:1) Depression[10012378]

G. ALL MANUFACTURERS

G.8 Adverse Event Term(s)

3) Suicidal ideation
4) Headache
5) Sleep apnoea syndrome
6) Incorrect dose administered

Pharmacovigilance comments:

Pharmacovigilance comments: Inconsistencies between the original and follow-up reports are noted including 1) dates of start of Testim therapy and 2) omission of his hospitalization in the original report.

DSS

AUG 10 2010

AUG 0 9 2010

Individual Safety Report

7419790-9-00-01

LUNTARY reporting of
ents, product problems and
product use errors

Page ___ of ___ CDER

Form Approved: OMB No. 0910-0291 Expires: 12/31/2011
See OMB statement on reverse.

CaseID: 7419790

FDA USE ONLY

Triage unit sequence # 450714

A. PATIENT INFORMATION

1. Patient Identifier	2. Age at Time of Event, or Date of Birth:	3. Sex	4. Weight
(b) (6) In confidence	59	☐ Female ☑ Male	___ lb or ___ kg

B. ADVERSE EVENT, PRODUCT PROBLEM OR ERROR

Check all that apply:

1. ☑ Adverse Event ☐ Product Problem *(e.g., defects/malfunctions)*
   ☐ Product Use Error ☐ Problem with Different Manufacturer of Same Medicine

2. Outcomes Attributed to Adverse Event *(Check all that apply)*
   ☑ Death: (b) (6) *(mm/dd/yyyy)* ☐ Disability or Permanent Damage
   ☑ Life-threatening ☐ Congenital Anomaly/Birth Defect
   ☐ Hospitalization - initial or prolonged ☐ Other Serious (Important Medical Events)
   ☐ Required Intervention to Prevent Permanent Impairment/Damage (Devices)

3. Date of Event *(mm/dd/yyyy)*	4. Date of this Report *(mm/dd/yyyy)*
03/23/2011	04/06/2011

5. Describe Event, Problem or Product Use Error

HAD BEEN USING TESTIM FOR ONLY A COUPLE OF WEEKS IN ADDITION TO ANTIDEPRESSANTS AND ANTIPSYCHOTICS. SEEMED TO BE IMPROVING WHEN HE ATTEMPTED SUICIDE (DIED THE FOLLOWING DAY).

CONCERN HEIGHTENED BECAUSE OF SIMILAR SUICIDE ATTEMPT BY ANOTHER PATIENT THE SAME WEEK (ONLY TIMING ✓ TESTIM IN COMMON)

6. Relevant Tests/Laboratory Data, Including Dates

RECEIVED
APR 13 2011
MEDWATCH CTU

7. Other Relevant History, Including Preexisting Medical Conditions *(e.g., allergies, race, pregnancy, smoking and alcohol use, liver/kidney problems, etc.)*

DEPRESSION

C. PRODUCT AVAILABILITY

Product Available for Evaluation? *(Do not send product to FDA)*

☐ Yes ☑ No ☐ Returned to Manufacturer on: ___ *(mm/dd/yyyy)*

D. SUSPECT PRODUCT(S)

1. Name, Strength, Manufacturer *(from product label)*
   #1 TESTIM
   #2

2. Dose or Amount	Frequency	Route
#1		
#2		

3. Dates of Use *(If unknown, give duration) from/to (or best estimate)*
   #1
   #2

4. Diagnosis or Reason for Use *(Indication)*
   #1
   #2

6. Lot #	7. Expiration Date
#1	#1
#2	#2

5. Event Abated After Use Stopped or Dose Reduced?
   #1 ☐ Yes ☐ No ☐ Doesn't Apply
   #2 ☐ Yes ☐ No ☐ Doesn't Apply

8. Event Reappeared After Reintroduction?
   #1 ☐ Yes ☐ No ☐ Doesn't Apply
   #2 ☐ Yes ☐ No ☐ Doesn't Apply

9. NDC # or Unique ID

E. SUSPECT MEDICAL DEVICE

1. Brand Name
2. Common Device Name
3. Manufacturer Name, City and State

RECEIVED
APR 13 2011
MEDWATCH CTU

4. Model #	Lot #	5. Operator of Device
Catalog #	Expiration Date *(mm/dd/yyyy)*	☐ Health Professional ☐ Lay User/Patient ☐ Other:
Serial #	Other #	

6. If Implanted, Give Date *(mm/dd/yyyy)*	7. If Explanted, Give Date *(mm/dd/yyyy)*

8. Is this a Single-use Device that was Reprocessed and Reused on a Patient?
   ☐ Yes ☐ No

9. If Yes to Item No. 8, Enter Name and Address of Reprocessor

F. OTHER (CONCOMITANT) MEDICAL PRODUCTS

Product names and therapy dates *(exclude treatment of event)*

UNKNOWN BECAUSE I AM NOT A PRESCRIBER.

DSS

APR 13 2011

G. REPORTER *(See confidentiality section on back)*

1. (b) (6)

Phone (b) (6)

E-mail (b) (6)

2. Health Professional?	3. Occupation	4. Also Reported to:
☑ Yes ☐ No	PSYCHOLOGIST	☐ Manufacturer ☐ User Facility ☐ Distributor/Importer

5. If you do NOT want your identity disclosed to the manufacturer, place an "X" in this box: ☒

PLEASE TYPE OR USE BLACK INK

Reference ID: 4146835

FORM FDA 3500 (1/09) Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

Individual Case Safety Report

CDER

9027842-01-00-01

U.S. Depar

The FDA
Adverse Event Reporting Program

reporting of
t problems and
errors

Form Approved: OMB No. 0910-0291, Expires: 10/31/08
See OMB statement on reverse.

FDA USE ONLY
Triage unit sequence # 499909

A. PATIENT INFORMATION

1. Patient Identifier	2. Age at Time of Event, or Date of Birth:	3. Sex	4. Weight
(b) (6) In confidence	(b) (6) 56 Years	☐ Female ☑ Male	280 lb or ____ kg

B. ADVERSE EVENT, PRODUCT PROBLEM OR ERROR

Check all that apply:

1. ☑ Adverse Event ☐ Product Problem *(e.g., defects/malfunctions)*
☐ Product Use Error ☐ Problem with Different Manufacturer of Same Medicine

2. Outcomes Attributed to Adverse Event *(Check all that apply)*
☐ Death: ____ *(mm/dd/yyyy)* ☐ Disability or Permanent Damage
☑ Life-threatening ☐ Congenital Anomaly/Birth Defect
☐ Hospitalization - initial or prolonged ☐ Other Serious (Important Medical Events)
☐ Required Intervention to Prevent Permanent Impairment/Damage (Devices)

3. Date of Event *(mm/dd/yyyy)*	4. Date of this Report *(mm/dd/yyyy)*
12/01/2012	01/11/2013

5. Describe Event, Problem or Product Use Error

My Urologist had prescribed Androderm transdermal patches for me so that the dosage could be increased to 6mgs. I had been on 5mgs of Testim but that was insufficient so I started on two Androderm patches one that was 2mgs and one that was 4mgs. A little more than a week after starting Androderm I started getting depressed, but I thought it might just be me feeling down. It continued to get worse. I started thinking bad thoughts like suicide. For some reason I thought it might be the Androderm because the depression soon started after beginning taking Androderm. One night I was sitting in my living and I started thinking about putting on my

More

6. Relevant Tests/Laboratory Data, Including Dates

CTU

JAN 15 2013

More

7. Other Relevant History, Including Preexisting Medical Conditions *(e.g., allergies, race, pregnancy, smoking and alcohol use, liver/kidney problems, etc.)*

More

C. PRODUCT AVAILABILITY

Product Available for Evaluation? *(Do not send product to FDA)*
☐ Yes ☑ No ☐ Returned to Manufacturer on: ____ *(mm/dd/yyyy)*

D. SUSPECT PRODUCT(S)

1. Name, Strength, Manufacturer *(from product label)*
#1 Androderm 2mg Watson
#2 Androderm 4mg Watson

2.	Dose or Amount	Frequency	Route
#1	2mg patch	1xday	Transdermal
#2	4mg patch	1xday	Transderma l

3. Dates of Use *(If unknown, give duration) from/to (or best estimate)*
#1 11/30/2012 -- 12/21/2012
#2 --

4. Diagnosis or Reason for Use *(Indication)*
#1 Very low testosterone levels
#2

5. Event Abated After Use Stopped or Dose Reduced?
#1 ☑ Yes ☐ No ☐ Doesn't Apply
#2 ☑ Yes ☐ No ☐ Doesn't Apply

8. Event Reappeared After Reintroduction?
#1 ☐ Yes ☐ No ☑ Doesn't Apply
#2 ☐ Yes ☐ No ☑ Doesn't Apply

6. Lot #	7. Expiration Date
#1	#1
#2	#2

9. NDC # or Unique ID

E. SUSPECT MEDICAL DEVICE

1. Brand Name
2. Common Device Name
3. Manufacturer Name, City and State

4. Model #	Lot #	5. Operator of Device
Catalog #	Expiration Date *(mm/dd/yyyy)*	☐ Health Professional ☐ Lay User/Patient ☐ Other:
Serial #	Other #	

6. If Implanted, Give Date *(mm/dd/yyyy)*	7. If Explanted, Give Date *(mm/dd/yyyy)*

8. Is this a Single-use Device that was Reprocessed and Reused on a Patient?
☐ Yes ☐ No

9. If Yes to Item No. 8, Enter Name and Address of Reprocessor

F. OTHER (CONCOMITANT) MEDICAL PRODUCTS

Product names and therapy dates *(exclude treatment of event)*

More

G. REPORTER *(See confidentiality section on back)*

1. Name and Address
(b) (6)

USS JAN 15 2013

Phone (b) (6)
E-mail (b) (6)

2. Health Professional?	3. Occupation	4. Also Reported to:
☐ Yes ☑ No		☐ Manufacturer ☐ User Facility ☐ Distributor/Importer

5. If you do NOT want your identity disclosed to the manufacturer, place an "X" in this box: ☐

FORM FDA 3500 (8/05) **Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.**

Individual Case Safety Report

9027842-01-00-02

VATCH

sionals of adverse events and product problems

: Submission - Page 2

B5. Describe event or problem continued

coat to go outside to walk in front of a truck!!!!! I realized I was in danger and my next thought was to take the patches off and keep them off. The next couple of days were a struggle and then I finally started feeling better on Dec. 24th. I called my urologist Dr. (b) (6) 5 times and left messages 4 times stating that I was having trouble with the Androderm and that suicide thoughts were part of the equation. I never heard back from her so I asked my GP Dr (b) (6) if he could change the prescription to Fortesta gel and he did. Everything is back to normal now. I just received a letter today form Medicare thst they wont pay for the Fortesta, they did pay for the Androderm, but I guess this is no concern for you's. Just can't go back on Androderm.

DSS
JAN 15 2013

FDA Facsimile Approval: 05/09/2006 (ArisGlobal, LLC)

...ual Case Safety Report

10363745-01-00-01

...or use by user-facilities, ...ers, distributors and manufacturers MANDATORY reporting

Mfr Report # 201407069 (0)

UF/Importer Report #

FDA Use Only

A. PATIENT INFORMATION

1. Patient Identifier	2. Age at Time	3. Sex	4. Weight
(b) (6) In confidence	of Event: 37 Y or Date of Birth:	☐ Female ☒ Male	____ lbs or ____ kgs

B. ADVERSE EVENT OR PRODUCT PROBLEM

1. ☒ Adverse Event and/or ☐ Product Problem (e.g., defects/malfunctions)

2. Outcomes Attributed to Adverse Event (Check all that apply)

- ☒ Death: (b) (6) (mm/dd/yyyy)
- ☒ Life-threatening
- ☐ Hospitalization - initial or prolonged
- ☐ Required Intervention to Prevent Permanent Impairment/Damage (Devices)
- ☐ Disability or Permanent Damage
- ☐ Congenital Anomaly/Birth Defect
- ☐ Other serious (Important Medical Events)

3. Date of Event (mm/dd/yyyy)	4. Date of This Report (mm/dd/yyyy)
	07/23/2014

5. Describe Event or Problem

On 21-Jul-2014, an initial spontaneous medically confirmed report was received from a physician via a sales representative concerning a 37-year-old male patient with a past history of depression and substance abuse, who was prescribed Testim (testosterone gel) therapy on 1-Jun-2013 for an indication of low testosterone. (Total daily dose, route of administration, dates/duration of therapy and indication not reported). Concomitant medications included cabergoline.

The physician informed the sales representative that the male patient had committed suicide in (b) (6) while using Testim.

On 21-Jul-2014, additional information was received from the patient's physician, who provided the patient's ID, age, medical history, product information and concomitant medications. She provided the cause of death as suicide.

No further information was received. The physician has declined to be contacted

Cont...

6. Relevant Tests/Laboratory Data, Including Dates

7. Other Relevant History, Including Preexisting Medical Conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

Concurrent Disease:
Depression[10012378]
Substance abuse[10066169]

Submission of a report does not constitute an admission that medical personnel, user facility, importer, distributor, manufacturer or product caused or contributed to the event.

3500A Facsimile

C. SUSPECT PRODUCT(S)

1. Name (Give labeled strength & mfr/labeler)
#1 Testim(testosterone)
#2

2. Dose, Frequency & Route Used	3. Therapy Dates (If unknown, give duration) from/to (or best estimate)
#1 1 in 1 D, Transdermal	#1 06/01/2013 -
#2	#2

4. Diagnosis for Use (Indication)	5. Event Abated After Use Stopped or Dose Reduced?
#1 Blood testosterone decreased[10005814]	#1 ☐ Yes ☐ No ☒ Doesn't Apply
#2	#2 ☐ Yes ☐ No ☐ Doesn't Apply

6. Lot #	7. Exp. Date	8. Event Reappeared After Reintroduction?
#1	#1	#1 ☐ Yes ☐ No ☒ Doesn't Apply
#2	#2	#2 ☐ Yes ☐ No ☐ Doesn't Apply

9. NDC # or Unique ID

10. Concomitant Medical Products and Therapy Dates (Exclude treatment of event)
1) CABERGOLINE(CABER-GOLINE) 06/??/2013 -

Cont...

G. ALL MANUFACTURERS

1. Contact Office - Name/Address (and Manufacturing Site for Devices)

Auxilium Pharmaceuticals Inc.
Global Drug Safety
640 Lee Road
Chesterbrook,PA 19087
USA
(Printing Unit)

2. Phone Number: 484-321-5928

3. Report Source (Check all that apply)
- ☐ Foreign
- ☐ Study
- ☐ Literature
- ☐ Consumer
- ☒ Health Professional
- ☐ User Facility
- ☒ Company Representative
- ☐ Distributor
- ☐ Other:

4. Date Received by Manufacturer (mm/dd/yyyy): 07/21/2014

5. (A)NDA #: 21-454
IND #:
STN #:
PMA/510(k) #:

6. If IND, Give Protocol #

7. Type of Report (Check all that apply)
- ☐ 5-day ☐ 30-day
- ☐ 7-day ☐ Periodic
- ☐ 10-day ☒ Initial
- ☒ 15-day ☐ Follow-up #

Combination Product ☐ Yes
Pre-1938 ☐ Yes
OTC Product ☐ Yes

DSS

AUG 04 2014

9. Manufacturer Report Number: 201407069 (0)

8. Adverse Event Term(s)
1) COMMITTED SUICIDE WHILE

Cont...

E. INITIAL REPORTER

1. Name and Address
(b) (6)
USA

Phone #

AUG 01 2014

2. Health Professional?	3. Occupation	4. Initial Reporter Also Sent Report to FDA
☒ Yes ☐ No	Physician	☐ Yes ☐ No ☒ Unk.

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10363745-01-00-02

2

Mfr. Report # : 201407069(0)

Date of This Report : 07/23/2014

B.

Describe Event or Problem (Cont...)

further by Auxilium regarding the adverse event.

C.10 Concomitant Medical Products and Therapy Dates

Seq No.	: 1
Concomitant Medical Product	: CABERGOLINE(CABERGOLINE)
Diagnosis for Use (Indication)	: 1) Hyperprolactinaemia[10020737]

G. ALL MANUFACTURERS

G.8 Adverse Event Term(s)

1) COMMITTED SUICIDE WHILE USING TESTIM (Completed suicide)

Pharmacovigilance comments:

Comment: The primary event of completed suicide has insufficient information provided in the report for a complete assessment.

10524469-01-00-01

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MEDWATCH

The FDA Safety Information and Adverse Event Reporting Program

For VOLUNTARY reporting of adverse events, product problems and product errors

FDA USE ONLY

Triage unit sequence #

A. PATIENT INFORMATION

1. Patient Identifier: (b) (6)	2. Age at Time of Event: 64	3. Sex: MALE	4. Weight (kg): 109.4

B. ADVERSE EVENT, PRODUCT PROBLEM OR ERROR

Check all that apply:

1. ■ Adverse Event
   ■ Product Use Errors
   ■ Product Problem (e.g., defects/malfunctions)
   ■ Problem with Different Mfgr of Same

2. Outcomes Attributed to Adverse Event (check all that apply)
   ■ Death _____
   ■ Life-Threatening
   ■ Hospitalization - initial or prolonged
   ■ Required Intervention to Prevent Permanent Impairment/Damage (Devices)
   ■ Disability or Permanent Damage
   ■ Congenital Anomaly/Birth Defect
   ■ Other Serious (Important Medical Events)

3. Date of Event (mm/dd/yyyy): 08/15/2014 (exact)	4. Date of this Report (mm/dd/yyyy) 9/5/2014

5. Describe Event, Problem or Product Use Error

Narrative: Patient had been started on androgel from a community PCP one week prior to being admitted acute inpatient psychiatry for SI. Patient reported that his depression began to worsen after initaitaiton of testoterone. His wife came to visit while inpatient and stated patient has been having serious mood swings for the past week. Symptoms resolved after discontinuation of drug.

Symptoms: Symptoms: 1. Agitation, 2. Suicidal Ideation, Mood swings

6. Relevant Tests/Laboratory Data, Including Dates

Date: 04/28/2014 Specimen: urine
testosterone: 41.67ng/dL

7. Other Relevant history, Including Preexisting Medical Conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, liver/kidney problems, etc.)
Active problems - Computerized Problem List is the source for the following:

1. Hypertension Nos echo-1/121. Estimated LVEF is 60%.
2. Hyperlipidemia Nec/Nos
3. Obesity, Unsp
4. Dm, Type 2, Controlled

CTU
OCT 15 2014

DSS
OCT 15 2014

10524469-01-00-02

5. Backache Nos
6. DJD, UNSPECIFIED cervical mri- severe l and mild r c6-7 nerrowing, mod l c5-6 mri-4/10-mild spondylosis t10-11, no compression/spinal sten retrolisthesis with midline annular bulging l5s1 unchang 02
7. Hypothyroidism Nos
8. Depressive Disorder Nec
9. Family History of Ischemic Heart Disease
10. Colon Polyps
11. PTSD
12. Chronic Pain due to trauma
13. Pain in joint involving lower leg
14. Continuous opioid dependence

C. PRODUCT AVAILABILITY

Product Available for Evaluation? (Do not send product to FDA)

☐ Yes ■ No ☐ Returned to Mfgr on _____

D. SUSPECT PRODUCT(S)

1. Name, Strength, Manufacturer (from product label)

#1: TESTOSTERONE

#2:

2. Dose or Amount	Frequency	Route
#1		
#2 MG		PO

3. Dates of Use (If unknown, give duration)

from/to (or best estimate)

#1 08/08/2014 thru 08/16/2014

#2 thru

5. Event Abated After Use Stopped or Dose Reduced?

#1 Yes

#2 No

4. Diagnosis for Use (indication)

#1 , Low testoterone

#2

8. Event Reappeared After Reintroduction?

#1 N/A

#2 No

6. Lot #:	7. Expiration Date	9. NDC Number or Unique ID
#1	#1	#1
#2	#2	#2

E. SUSPECT MEDICAL DEVICE

(Section intentionally left blank)

F. OTHER (CONCOMITANT) MEDICAL PRODUCTS

(Section intentionally left blank)

G. REPORTER

1. Name and Address

10524469-01-00-03

(b) (6)
(b) (6)

Phone #: (b) (6) E-mail: email address not found

2. Health Professional? Yes 3. Occupation: Pharmacist 4. Also Reported to:

- Manufacturer
- User Facility
- Distributor/importer

5. If you do not want your identity disclosed to the manufacturer, place an 'x' in this box. ■

FORM vaADERS-3500 (03/2008) *Adapted from FORM FDA 3500 (10/08) for use in auto-faxing vaADERS ADR reports to MedWatch*

[redacted]
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CDER

CaseID: 10676706

1/4

U.S. Department of Health and Human Services

Internet Consumer Report

Individual Case Safety Report

Form Approved: OMB No. 0910-0291, Expires: 12/31/2011
See OMB statement on reverse.

...ting of ...blems and

FDA USE ONLY
Triage unit sequence # 5766679

10676706-01-00-01

1. (b) (6)	Date of Birth: 32 Years (b) (6)	☐ Female ☑ Male	200 lb or ____ kg
In confidence			

	Dose or Amount	Frequency	Route
#1	6 pumps	Once daily	Applied to a surface, usually the skin
#2			

B. ADVERSE EVENT, PRODUCT PROBLEM OR ERROR

Check all that apply:

1. ☑ Adverse Event ☐ Product Problem (e.g., defects/malfunctions)
☐ Product Use Error ☐ Problem with Different Manufacturer of Same Medicine

2. Outcomes Attributed to Adverse Event (Check all that apply)
☐ Death: ____ (mm/dd/yyyy)
☑ Disability or Permanent Damage
☑ Life-threatening
☐ Congenital Anomaly/Birth Defect
☑ Hospitalization - Initial or prolonged
☐ Other Serious (Important Medical Events)
☐ Required Intervention to Prevent Permanent Impairment/Damage (Devices)

3. Date of Event (mm/dd/yyyy)	4. Date of this Report (mm/dd/yyyy)
12/13/2014	12/22/2014

5. Describe Event, Problem or Product Use Error
See page 2 for complete text.

6. Relevant Tests/Laboratory Data, Including Dates
See page 3 for complete text.

7. Other Relevant History, Including Preexisting Medical Conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, liver/kidney problems, etc.)
See page 4 for complete text.

C. PRODUCT AVAILABILITY

Product Available for Evaluation? (Do not send product to FDA)
☑ Yes ☐ No ☐ Returned to Manufacturer on: ____ (mm/dd/yyyy)

D. SUSPECT PRODUCT(S)

1. Name, Strength, Manufacturer (from product label)
#1 Name: Androgel
Strength: 1.25g
Manufacturer: Abbvie Inc.

#2 Name:
Strength:
Manufacturer:

3. Dates of Use (If unknown, give duration) from/to (or best estimate)
#1 03/01/2011 - 12/13/2014
#2

4. Diagnosis or Reason for Use (Indication)
#1 Erectile Dysfunction, low testosterone
#2

5. Event Abated After Use Stopped or Dose Reduced?
#1 ☑ Yes ☐ No ☐ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply

8. Event Reappeared After Reintroduction?
#1 ☐ Yes ☐ No ☑ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply

6. Lot #	7. Expiration Date
#1 90626	#1 10/31/2016
#2	#2

9. NDC # or Unique ID
0051-8462-33

E. SUSPECT MEDICAL DEVICE

1. Brand Name

CTU

2. Common Device Name

DEC 23 2014

3. Manufacturer Name, City and State

4. Model #	Lot #	5. Operator of Device
Catalog #	Expiration Date (mm/dd/yyyy)	☐ Health Professional ☐ Lay User/Patient ☐ Other:
Serial #	Other #	

6. If Implanted, Give Date (mm/dd/yyyy)	7. If Explanted, Give Date (mm/dd/yyyy)

8. Is this a Single-use Device that was Reprocessed and Reused on a Patient?
☐ Yes ☐ No

9. If Yes to Item No. 8, Enter Name and Address of Reprocessor

F. OTHER (CONCOMITANT) MEDICAL PRODUCTS

Product names and therapy dates (exclude treatment of event)

G. REPORTER (See confidentiality section on back)

1. Name and Address
(b) (6)

DSS
DEC 23 2014

Phone #	E-mail
(b) (6)	(b) (6)

2. Health Professional?	3. Occupation	4. Also Reported to:
☐ Yes ☐ No		☐ Manufacturer ☐ User Facility ☐ Distributor/Importer

5. If you do NOT want your identity disclosed to the manufacturer, place an "X" in this box: ☐

PLEASE TYPE OR USE BLACK INK

FORM FDA 3500 (1/09) Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

Reference ID: 4146835

B.5. Describe Event or Problem *(continued)*

I have been taking Androgel for nearly 4 years. I began with the 1% concentration at 1 pump daily and was increased at nearly every follow up visit over the years until the eventual dosage was 6 pumps of the 1.62% concentration. Beginning in the late spring of 2014, I began noticing general depressive symptoms, which I reported to my doctor in mid June 2014. At that time, I was prescribed and using 4 pumps daily of the 1.62% concentration. My doctor was unaware of the possibility of depression or mood changes that could result from using Androgel. I informed him that it was listed as a side effect in the literature of the medication that said I needed to tell my doctor immediately about. I was prescribed an antidepressant (Wellbutrin, 150mg 12 hour, once daily) and the Androgel prescription was left unchanged. Roughly two months later, in August 2014, my Androgel prescription was increased once again. This time, my prescription was increased to 6 pumps daily of the 1.62% concentration. The reasoning was that I was still experiencing erectile dysfunction (ED), which was the original reason behind why it was prescribed in the first place, along with the fact that my testosterone level was very low. Over the course of the four years, my ED never improved and my T-Levels remained very low. I expressed to the urologist, a second doctor, my concerns that Androgel was causing depression. He also stated he doubted Androgel could cause depression, even though I mentioned the literature to him as well. In early November 2014, I began experiencing very depressive episodes. Eventually, in November 2014, I called my primary physician's office and notified them that I needed to see someone immediately because I was experiencing depression with suicidal thoughts. I saw the first doctor I could see that day, which was not my normal physician, but in the same office. I again expressed my concern that Androgel was causing the depression. This new doctor also stated she was unaware of that being a possible side effect, even though I again cited the medication's literature. She adjusted the antidepressant (Wellbutrin) to 150mg 24 hour, once daily. I have never experienced depression before or have had and depressive episodes prior to June 2014. Unfortunately, the depression got very severe and eventually led to an increased number of days of agitation, irritability, low moods, and depression until I eventually attempted suicide on (b) (6) I was admitted to a psychiatric hospital for 8 days. At this point, I immediately discontinued the Androgel. The psychiatrists were also unaware of the possible side effect of depression in Androgel's literature. I have been off the antidepressant and Androgel now since (b) (6) I am no longer feeling depressed or suicidal. Androgel never helped with my ED symptoms either. It is important to note that Androgel 1.62%, 4 pumps daily was the only medication I was taking at the time of initial onset of depressive symptoms in the spring of 2014. The depression became worse after the Androgel prescription was increased to 6 pumps daily of the 1.62% concentration in August 2014. This medication's (Androgel) deadly side effect is not adequately presented to doctors by the manufacturer. I am reporting this deadly side effect so that the FDA has a record of such an occurrence. Please advise the manufacturer to provide better precautions to healthcare providers. I was nearly killed as a result of this side effect.

Individual Case Safety Report

10676706-01-00-02

DSS

DEC 23 2014

B.6. Relevant Tests/Laboratory Data, Including Dates *(continued)*

I regularly (roughly every six months) got blood tests to check for my testosterone levels. They increased only slightly and remained too low at many times, which is why the medication was consistently increased in concentration and dosage over the last four years.

Individual Case Safety Report

10676706-01-00-03

B.7. Other Relevant History, Including Preexisting Medical Conditions *(e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.) (continued)*

Race:White
Medical Conditions: Hypogonadism, sleep apnea

Allergies: None

Important Information: 4-5 beers weekly, non-smoker

RX Meds: CPAP for sleep apnea

OTC Meds: None

Form Approved: OMB No. 0910-0291
Expiration Date: 6/30/2015
(See PRA Statement on preceding general information page)

MEDWATCH Consumer Voluntary Reporting (FORM FDA 3500B)

1/3

Section A – About the Problem

What kind of problem was it? *(Check all that apply)*

- [x] Were hurt or had a bad side effect *(including new or worsening symptoms)*
- [ ] Used a product incorrectly which could have or led to a problem
- [ ] Noticed a problem with the quality of the product
- [ ] Had problems after switching from one product maker to another maker

Did any of the following happen? *(Check all that apply)*

- [ ] Hospitalization – admitted or stayed longer
- [ ] Required help to prevent permanent harm *(for medical devices only)*
- [ ] Disability or health problem
- [ ] Birth defect
- [ ] Life-threatening
- [x] ~~Death *(include date)*~~ (b) (6)
- [ ] Other serious/important medical incident *(Please describe below)*

DSS
AUG 7 2015

CTU
AUG – 7 2015

Date the problem occurred *(mm/dd/yyyy)*

used Androgel from about 2011 to time of death

Tell us what happened and how it happened. *(Include as many details as possible)*

My son used Androgel for Low T for about two years. During that time he became more and more depressed, suffered from insomnia, loss of muscle strength, loss of energy. The depression got so bad that he committed suicide. I've not reported this sooner because it's been very painful for me to lose my only son caused by the very medicine he was taking.

Continuation Page

List any relevant tests or laboratory data if you know them. *(Include dates)*

My son lived in (b) (6) and I live in (b) (6) so I don't know the doctors he went to see for lab test

Continuation Page

For a problem with a product, including

- prescription or over-the-counter medicine
- biologics, such as human cells and tissues used for transplantation (for example, tendons, ligaments, and bone) and gene therapies
- nutrition products, such as vitamins and minerals, herbal remedies, infant formulas, and medical foods
- cosmetics or make-up products
- foods (including beverages and ingredients added to foods)

Go to Section B

DSS
AUG 7 2015

For a problem with a medical device, including

- any health-related test, tool, or piece of equipment
- health-related kits, such as glucose monitoring kits or blood pressure cuffs
- implants, such as breast implants, pacemakers, or catheters
- other consumer health products, such as contact lenses, hearing aids, and breast pumps

Go to Section C (Skip Section B)

For more information, visit *http://www.fda.gov/MedWatch*

Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

11358782-01-00-02

Sec

Name of the product as it appears on the box, bottle,
Androgel 1.62%

Name of the company that makes the product
I believe its Abbvie

Expiration date *(mm/dd/yyyy)*	Lot number	NDC number

Strength *(for example, 250 mg per 500 mL or 1 g)*	Quantity *(for example, 2 pills, 2 puffs, or 1 teaspoon, etc.)*	Frequency *(for example, twice daily or at bedtime)*	How was it taken or used *(for example, by mouth, by injection, or on the skin)*?
	cream	once a day	on the skin every morning

Date the person first started taking or using the product *(mm/dd/yyyy)*: 01/01/2011

Date the person stopped taking or using the product *(mm/dd/yyyy)*: Nov 5 2013

Why was the person using the product *(such as, what condition was it supposed to treat?)*

Low T

Did the problem stop after the person reduced the dose or stopped taking or using the product? ☐ Yes ☐ No

Did the problem return if the person started taking or using the product again?

☐ Yes ☐ No ☐ Didn't restart

Do you still have the product in case we need to evaluate it? *(Do not send the product to FDA. We will contact you directly if we need it.)*

☐ Yes ☒ No

Go to Section D (Skip Section C)

Section C – About the Medical Device

Name of medical device

Name of the company that makes the medical device

Other identifying information *(The model, catalog, lot, serial, or UDI number, and the expiration date, if you can locate them)*

Was someone operating the medical device when the problem occurred?

☐ Yes
☐ No

If yes, who was using it?

☐ The person who had the problem
☐ A health professional *(such as a doctor, nurse, or aide)*
☐ Someone else *(Please explain who)*

DSS
AUG 7 2015

For implanted medical devices ONLY *(such as pacemakers, breast implants, etc.)*

Date the implant was put in *(mm/dd/yyyy)*	Date the implant was taken out *(If relevant) (mm/dd/yyyy)*

Go to Section D

Section D – About the Person Who Had the Problem

Person's Initials	Sex	Age *(at time the problem occurred)* or Birth Date	Weight *(Specify lbs or kg)*	Race
(b) (6)	☐ Female ☒ Male	(b) (6)	150 ??	white

List known medical conditions *(such as diabetes, high blood pressure, cancer, heart disease, or others)*

he had no other conditions

Please list all allergies *(such as to drugs, foods, pollen, or others)*.

none

List any other important information about the person *(such as smoking, pregnancy, alcohol use, etc.)*

did not use rec drugs or any other meds

List all current prescription medications and medical devices being used.

Continuation Page

List all over-the-counter medications and any vitamins, minerals, supplements, and herbal remedies being used.

???

Continuation Page

Go to Section E

Section E – About the Person Filling Out This Form

We will contact you only if we need additional information. Your name will not be given out to the public.

Last name	First name
(b) (6)	(b) (6)

Number/Street	City and State/Province
(b) (6)	(b) (6)

Country	ZIP or Postal code
USA	(b) (6)

Telephone number	Email address	Today's date *(mm/dd/yyyy)*
(b) (6)	(b) (6)	7-28-15

Did you report this problem to the company that makes the product (the manufacturer)?

☐ Yes ☒ No

May we give your name and contact information to the company that makes the product (manufacturer) to help them evaluate the product? ☐ Yes ☒ No

Send This Report by Mail or Fax

Keep the product in case the FDA wants to contact you for more information. Please do not send products to the FDA. Mail or fax the form to:

Mail:	**Fax:**
MedWatch Food and Drug Administration 5600 Fishers Lane Rockville, MD 20857	1-800-332-0178 (toll-free)

DSS
AUG 7 2015

Thank you for helping us protect the public health.

11693245-01-00-01

CaseID: 11693245

1/4 622079

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Form Approved: OMB No. 0910-0291
Expiration Date: 6/30/2015
(See PRA Statement on preceding general information page)

MEDWATCH Consumer Voluntary Reporting (FORM FDA 3500B)

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Section A – About the Problem

What kind of problem was it? *(Check all that apply)*

- [X] Were hurt or had a bad side effect *(including new or worsening symptoms)*
- [ ] Used a product incorrectly which could have or led to a problem
- [ ] Noticed a problem with the quality of the product
- [ ] Had problems after switching from one product maker to another maker

Did any of the following happen? *(Check all that apply)*

- [X] Hospitalization – admitted or stayed longer
- [ ] Required help to prevent permanent harm *(for medical devices only)*
- [X] Disability or health problem
- [ ] Birth defect
- [X] Life-threatening
- [ ] Death *(Include date)*: _____
- [ ] Other serious/important medical incident *(Please describe below)*

CTU

NOV – 2 2015

Date the problem occurred *(mm/dd/yyyy)*
02/25/2015 to date

Tell us what happened and how it happened. *(Include as many details as possible)*

On 02/23/2015, received 200 mg. shot of testosterone cypionate in left buttock. On (b) (6) serious adverse effects began: nausea, insomnia, muscular pain (burning/buzzing), hot flashes, chills, [illegible] Continuation Page

List any relevant tests or laboratory data if you know them. *(Include dates)*

Blood testing from (b) (6) to date, showing gross fluctuation in hormone levels after the shot, & induced hypogonadism for a time. Continuation Page

For a problem with a product, including

- prescription or over-the-counter medicine
- biologics, such as human cells and tissues used for transplantation (for example, tendons, ligaments, and bone) and gene therapies
- nutrition products, such as vitamins and minerals, herbal remedies, infant formulas, and medical foods
- cosmetics or make-up products
- foods (including beverages and ingredients added to foods)

Go to Section B

DSS
NOV – 2 2015

For a problem with a medical device, including

- any health-related test, tool, or piece of equipment
- health-related kits, such as glucose monitoring kits or blood pressure cuffs
- implants, such as breast implants, pacemakers, or catheters
- other consumer health products, such as contact lenses, hearing aids, and breast pumps

Go to Section C (Skip Section B)

For more information, visit *http://www.fda.gov/MedWatch*

Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

(Continuation)

Loss of sensation in my testes; impotence; retraction of penis; severe anxiety and depression developed with time, as the severe effects lasted 2 full weeks. After that time, I continued to suffer sexual dysfunction as well as incurred apparently long-term adverse alterations to my sexual apparatus: Chronic & extreme retraction of genitalia (shrinkage of testes), loss of pleasurable sensation in my skin throughout my body but especially genital. Testes ascend into body when orgasm (never did so before). Prostate & testes sensitive or dull ache. Prostate & testes shrunk, per urologist exam. Problems described have persisted mostly unabated to date — Some improvement (fluctuating from time to time). [redacted] Due to the nature, extent and duration of these health problems, I have suffered horrible anxiety and depression. Required 3 E.R. visits in [redacted] (b) (6) and one DSS admission to hospital (incl - one day Wash - 2 20 psych-ward for suicidal ideation). I need to make known the dangers of testosterone replacement, especially via injection! The medical profession is too enamored of this fad. No one else must suffer like I have!

11693245-01-00-03

About the Products

(1) Name of the product as it appears on the box, bottle, or package *(Include as many names as you see)*

Testosterone Cypionate 200 mg.

Name of the company that makes the product

unknown

Expiration date *(mm/dd/yyyy)*	Lot number	NDC number
?	?	?

Strength *(for example, 250 mg per 500 mL or 1 g)*	Quantity *(for example, 2 pills, 2 puffs, or 1 teaspoon, etc.)*	Frequency *(for example, twice daily or at bedtime)*	How was it taken or used *(for example, by mouth, by injection, or on the skin)?*
200 mg.	one injection (deep muscle)	one time only	Injected into left buttock

Date the person first started taking or using the product *(mm/dd/yyyy)*: 02/23/2015

Date the person stopped taking or using the product *(mm/dd/yyyy)*: 02/23/2015

Why was the person using the product *(such as, what condition was it supposed to treat?)*

Misdiagnosis of secondary hypogonadism (male); In truth was transient due to length illness

Did the problem stop after the person reduced the dose or stopped taking or using the product? ☐ Yes ☒ No

Did the problem return if the person started taking or using the product again? ☐ Yes ☐ No ☒ Didn't restart

Do you still have the product in case we need to evaluate it? *(Do not send the product to FDA. We will contact you directly if we need it.)* ☐ Yes ☒ No

➡ *Go to Section D (Skip Section C)*

Section C – About the Medical Device

Name of medical device

Name of the company that makes the medical device

Other identifying information *(The model, catalog, lot, serial, or UDI number, and the expiration date, if you can locate them)*

Was someone operating the medical device when the problem occurred? ☐ Yes ☐ No

If yes, who was using it?

☐ The person who had the problem

☐ A health professional *(such as a doctor, nurse, or aide)*

☐ Someone else *(Please explain who)*

For implanted medical devices ONLY *(such as pacemakers, breast implants, etc.)*

Date the implant was put in *(mm/dd/yyyy)*	Date the implant was taken out *(If relevant) (mm/dd/yyyy)*

DSS NOV - 2 2015

➡ *Go to Section D*

622079

11693245-01-00-04

Person Who Had the Problem

Person's Initials	Sex	Age (at time the problem occurred) or Birth Date	Weight (Specify lbs or kg)	Race
(b) (6)	☐ Female ☒ Male	55	210 lbs.	White

List known medical conditions *(such as diabetes, high blood pressure, cancer, heart disease, or others)*
Severe hip arthritis (bi-lateral); Chronic nausea/insomnia; Anxiety; Depression

Please list all allergies *(such as to drugs, foods, pollen, or others)*. Severe allergy to poison ivy
Minor environmental allergies;

List any other important information about the person *(such as smoking, pregnancy, alcohol use, etc.)*
Suffering 3 years from dental malocclusion due to prior dentist error. Failure to improve led to prescriptions which caused chronic nau

List all current prescription medications and medical devices being used.
Norco; Fioricet (rare); Arimedex (trial); Zofran (rare)

Continuation Page

List all over-the-counter medications and any vitamins, minerals, supplements, and herbal remedies being used.
Herbal teas; fish oil, Vitamin B Complex, Zinc; Probiotics

Continuation Page

Go to Section E

Section E – About the Person Filling Out This Form

We will contact you only if we need additional information. Your name will not be given out to the public.

Last name	First name
(b) (6)	(b) (6)

Number/Street	City and State/Province
(b) (6)	(b) (6)

Country	ZIP or Postal code
USA	(b) (6)

Telephone number	Email address	Today's date *(mm/dd/yyyy)*
(b) (6)	(b) (6)	10 [redacted] 2015

Did you report this problem to the company that makes the product (the manufacturer)?
☐ Yes ☒ No

May we give your name and contact information to the company that makes the product (manufacturer) to help them evaluate the product? ☐ Yes ☒ No

Send This Report by Mail or Fax

Keep the product in case the FDA wants to contact you for more information. Please do not send products to the FDA.
Mail or fax the form to:

Mail:	**Fax:**
MedWatch Food and Drug Administration 5600 Fishers Lane Rockville, MD 20857	1-800-332-0178 (toll-free)

F DSS
NOV - 8 2015

Thank you for helping us protect the public health.

For more information, visit *http://www.fda.gov/MedWatch*

Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

CaseID: 11934615

U.S. Department of Health and Human Services

Internet Consumer Report

CDER

Compounding

Form Approved: OMB No. 0910-0291 Expires: 12/31/2011
See OMB statement on reverse.

Individual Case Safety Report

11934615-01-00-01

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oblems and
rs

12

FDA USE ONLY	
Triage unit sequence #	033594

	Dose or Amount	Frequency	Route
	10 PELLETS	--	Given into/Under the skin
#2			

(b) (6)	Date of Birth: 46 Years (b) (6)	☐ Female ☑ Male	190 lb or kg
In confidence			

B. ADVERSE EVENT, PRODUCT PROBLEM OR ERROR

Check all that apply:

1. ☑ Adverse Event ☐ Product Problem *(e.g., defects/malfunctions)*
☐ Product Use Error ☑ Problem with Different Manufacturer of Same Medicine

2. Outcomes Attributed to Adverse Event *(Check all that apply)*
☐ Death: _____ *(mm/dd/yyyy)*
☑ Life-threatening
☑ Hospitalization - initial or prolonged
☐ Required Intervention to Prevent Permanent Impairment/Damage (Devices)
☑ Disability or Permanent Damage
☐ Congenital Anomaly/Birth Defect
☐ Other Serious (Important Medical Events)

3. Date of Event *(mm/dd/yyyy)*	4. Date of this Report *(mm/dd/yyyy)*
10/12/2015	01/18/2016

5. Describe Event, Problem or Product Use Error

See additional page(s) for complete text.

CTU
JAN 20 2016

6. Relevant Tests/Laboratory Data, Including Dates

See additional page(s) for complete text.

7. Other Relevant History, Including Preexisting Medical Conditions *(e.g., allergies, race, pregnancy, smoking and alcohol use, liver/kidney problems, etc.)*

See additional page(s) for complete text.

C. PRODUCT AVAILABILITY

Product Available for Evaluation? *(Do not send product to FDA)*

☐ Yes ☑ No ☐ Returned to Manufacturer on: _____ *(mm/dd/yyyy)*

D. SUSPECT PRODUCT(S)

1. Name, Strength, Manufacturer *(from product label)*

#1 Name: Testosterone
Strength: 87.5 MG pellet
Manufacturer: US Compounding Pharmacy

DSS
JAN 20 2016

#2 Name:
Strength:
Manufacturer:

3. Dates of Use *(If unknown, give duration) from/to (or best estimate)*	5. Event Abated After Use Stopped or Dose Reduced?
#1 10/12/2015 - 01/04/2016	#1 ☑ Yes ☐ No ☐ Doesn't Apply
#2	#2 ☐ Yes ☐ No ☐ Doesn't Apply
4. Diagnosis or Reason for Use *(Indication)*	8. Event Reappeared After Reintroduction?
#1 Testosterone (sterile) pellets to treat low testosterone	#1 ☐ Yes ☐ No ☑ Doesn't Apply
#2	#2 ☐ Yes ☐ No ☐ Doesn't Apply
6. Lot # #1 . #2	7. Expiration Date #1 #2
	9. NDC # or Unique ID 62295290201

E. SUSPECT MEDICAL DEVICE

1. Brand Name

2. Common Device Name

CTU
JAN 20 2016

3. Manufacturer Name, City and State

4. Model #	Lot #	5. Operator of Device
Catalog #	Expiration Date *(mm/dd/yyyy)*	☐ Health Professional ☐ Lay User/Patient ☐ Other:
Serial #	Other #	

6. If Implanted, Give Date *(mm/dd/yyyy)*	7. If Explanted, Give Date *(mm/dd/yyyy)*

8. Is this a Single-use Device that was Reprocessed and Reused on a Patient?
☐ Yes ☐ No

9. If Yes to Item No. 8, Enter Name and Address of Reprocessor

F. OTHER (CONCOMITANT) MEDICAL PRODUCTS

Product names and therapy dates *(exclude treatment of event)*

See additional page(s) for complete text.

G. REPORTER *(See confidentiality section on back)*

1. Name and Address
(b) (6)

Phone # (b) (6)	E-mail (b) (6)

2. Health Professional?	3. Occupation	4. Also Reported to:
☐ Yes ☐ No		☐ Manufacturer ☐ User Facility ☐ Distributor/Importer

5. If you do NOT want your identity disclosed to the manufacturer, place an "X" in this box: ☐

PLEASE TYPE OR USE BLACK INK

FORM FDA 3500 (1/09) Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

Reference ID: 4146835

B.

I had used testosterone implants for 3-4 years with great success and no issues but in the spring of 2015 my urologist informed me that they were no longer available. In August 2015, he notified me that the pellets were available from an online pharmacy, (b) (6) Pharmacy. My doctor sent the prescription to the pharmacy but my insurance would not cover the medicine. I paid out of pocked and the medicine was shipped to me. I made an appointment with my urologist and the pellets were implanted on 10/12/15. Within 2 weeks I was experiencing sleeplessness and increased anxiety. I went to my family physician on 10/29/15 and received a prescription for a mild sleep aid (Klonopin, .5mg) and an anxiety medicine (Lexapro, 10mg). I began these medications on 10/31/15. My anxiety continued to increase and I had a severe panic attack on 11/9/15. On (b) (6) I went to the ER with extreme anxiety and panic, as well as the beginnings of paranoia. I was admitted to an outpatient therapy program on 11/11/15, increased Lexapro to 20mg and added Seroquel, taking away the Klonopin. On (b) (6) I was back at the ER with even worse anxiety, paranoia, and borderline mania. I was admitted to an inpatient facility for 4 days, released on (b) (6) and readmitted on (b) (6) - (b) (6) Although 'stabilized' at release, I was very depressed, still paranoid, and still had anxiety. The depression worsened until I was taken to the ER again on (b) (6) as my family feared I was suicidal and would do harm to myself. I was admitted back into the hospital for another 10 days. This was a total of 32 days in the hospital behaviorial unit, and a total of 12-13 weeks before I began to feel 'normal' again. When I saw my psychiatrist on 1/11/16, and we discussed the situation that had taken place it was the professional medical opinion that this experience was a direct result of a severe adverse reaction to the Testopel Implants and advised me to report this to the FDA. Negative things experienced during this experience: extreme insomnia, extreme and increasing anxiety, paranoia, mania, suicidal ideation, extreme depression, itching /scratchy skin (but no evident rash), weight loss, diarrhea, fatigue, loss of appetite, feelings of sadness, back pain, muscle aches, headaches, increased urination, nightmares/abnormal dreams, mood swings. This was an absolutely horrible experience for me and for my family. We did not think about the implants during this crisis until we were several weeks in.

B.6. **Relevant Tests/Laboratory Data, Including Dates** *(continued)*

Unfortunately, the only lab tests taken were the routine blood screens for illegal drugs.

B.7. **Other Relevant History, Including Preexisting Medical Conditions** *(e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.) (continued)*

Race: White

Medical Conditions: None other than low testosterone.

Allergies: No known allergies before this experience. Assumed initial reaction was an allergic reaction to the Lexapro.

Important Information: Non-smoker, no illegal drugs, minimal alcohol use.

F. Concomitant Medical Products and Therapy Dates (Exclude treatment of event) *(continued)*

RX Meds: Current medications, because of the physcological experience. Seroquel 150MG/day; Zoloft 200 MG/day; Klonopin .5MG x3/day. • Omeprazole 20mg, 1 tablet daily - take for heartburn • Fluticasone Popionate, 60 mcg/spray - 1 per nostril daily - take for allergy ...

OTC Meds: None at this time. Was taking One-a-Day Active before this incident.

APPEARS THIS WAY ON ORIGINAL

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

RACHNA KAPOOR
08/30/2017

NEHA GADA
08/30/2017

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: July 21, 2017

From: Fred Senatore, MD, PhD, FACC
Clinical Reviewer
Division of Cardiovascular and Renal Products / CDER

Through: Martin Rose, MD, JD, Team Leader
Norman Stockbridge, MD, PhD, Division Director
Division of Cardiovascular and Renal Products / CDER

To: Jeannie Roule, RPM
Division of Reproductive and Urological Products / CDER

Subject: NDA 209863: Cumulative Distribution Curve review of ambulatory blood pressure monitoring (ABPM) data from Antares Pharma's phase-3 study (QST-15-005).

This memo responds to your consult to us requesting our review of the sponsor's response to an information request related to ABPM data from the phase-3 study QST-15-005.

DCRP received and reviewed the following materials:

- Your consult request dated 19 July 2017.
- Our previous consult to you dated 03 March 2017 for NDA 209863.
- NDA submission package: \\CDSESUB1\evsprod\NDA209863\209863.enx. Submissions # 0017 and # 0010 contained the sponsor's responses pertinent to the information request concerning ABPM data.

Background

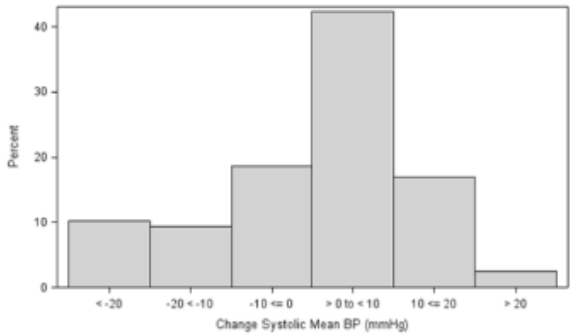
The Division of Cardiovascular and Renal Products (DCRP) was consulted in February 2017 to evaluate blood pressure results from two phase 3 studies: QST-13-003 and QST-15-005.

A summary of the mean systolic blood pressures (SBP), mean diastolic blood pressures (DBP), and changes from baseline for both phase 3 studies and the integrated summary of safety (ISS) are found in Table 1. For the combined cohort of both trials in the ISS, the overall mean baseline SBP and DBP were 126 mmHg and 79 mmHg, respectively. At the end of 26 week, the overall mean baseline SBP and DBP were 131 mmHg and 81 mmHg, respectively. The mean SBP rose by 4 mmHg and the mean DBP rose by 2 mmHg. These changes in the ISS were similar to those seen in the individual phase 3 studies.

In the 26-week single arm QST-15-005 study of 133 hypogonadal males (113 completed), blood pressure was measured by ABPM at 3 distinct 24-hour time periods: baseline, week-6, and week-12. Blood pressure readings beyond week-12 in this study were measured by sphygmomanometry. The overall results showed no consistent or strong relationship between blood pressure changes and testosterone concentration and was unaffected by dipper status (fall in blood pressure at night compared to daytime).

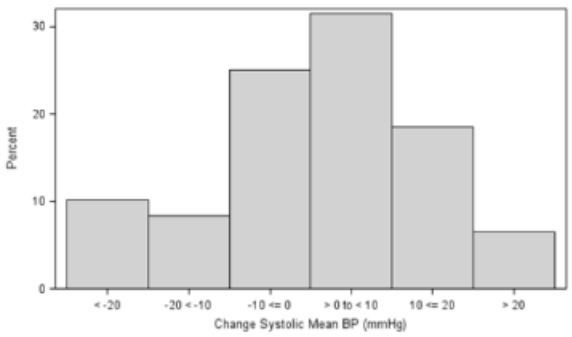
The ABPM report displayed bar graphs showing the percent of subjects at various bracketed changes from baseline in SBP and DBP at week-6 and week-12. The changes ranged from < 20 mmHg reduction in blood pressure to > 20 mmHg increase in blood pressure as illustrated in the figures immediately below taken from the ABPM report and discussed in detail in the previous consult. The tails of the distributions suggested that more subjects had a reduction in both SBP and DBP than an increase both at week-6 and week-12. Moreover, there was an empirical shift in the distributions to the left from week-6 to week-12, suggesting further reductions in both SBP and DBP.

Figure 5. Change from baseline in 24-hour mean SBP at week-6



Source: ABPM Monitoring Report, Appendix in QST-15-005 CSR

Figure 6. Change from baseline in 24-hour mean SBP at week-12



Source: ABPM Monitoring Report, Appendix in QST-15-005 CSR

To establish a better insight on the relationship between the overall mean rise in blood pressure and the distribution of blood pressure changes displayed in the bar graphs for week-6 and week-12 from the phase-3 study QST-15-005, we requested cumulative distribution curves. We also requested a description of blood pressure management during the course of the study and how that might have affected the distribution of mean changes from baseline blood pressure.

The Division of Urological and Reproductive Products submitted an information request to Antares on our behalf. Additionally, the Division of Urological and Reproductive Products asked Antares to eliminate all subjects who did not have at least 18 recordable measurements per 24 hours of measurements (i.e., “18-hour rule) and perform a sensitivity analysis on the remaining subjects. This was based on our previous recommendation in our consult dated 15 January 2016 that at least 18 recordable ABPM measurements over a 24-hour period were required for optimal ABPM data acquisition. In this consult, we review this new information.

Cumulative Distribution Function for Changes in Blood Pressure

Antares Pharma provided cumulative distribution function (CDF) curves for SBP and DBP for both week-6 and week-12 from the phase 3 study QST-15-005.

In response to the request to perform a sensitivity analysis, Antares eliminated subjects who did not meet the 18-hour rule at their baseline from the analysis at all visits. Other subjects who did not meet the 18-hour rule only post-baseline were eliminated from the analysis of those affected visits.

There were 110 subjects who had ABPM measurements (SN # 17, module 5.3.5.1, Listing 16.2.6.1). Of these, 59 did not have at least 18 recordable ABPM measurements per 24-hour period. Of these 59 subjects, 32 subjects failed to have the requisite number of ABPM measurements in each of the 3 visits (i.e., baseline, week-6 and week-12). These 32 subjects were therefore eliminated from the analysis of all 3 visits

because they were missing baseline data. The 18-hour rule was violated in 11 subjects at week-6. These subjects were therefore excluded from the analysis of the week-6 data only. The 18-hour rule was violated in 16 subjects at week-12. These subjects were therefore excluded from the analysis of the week-12 data only. There were no reported non-analyzable subjects who had acceptable baseline ABPM data but violated the 18-hour rule at both week-6 and week12. The sensitivity analysis was therefore performed on 78 subjects (per protocol population).

Antares responded to our IR regarding BP medication management during the course of the study and how that might have affected the ABPM data (Sn # 0010 / module 5.3.5.1 / CSR study QST-15-005). Antares stated that 6 subjects in QST-15-005 received a dose change or new BP medications:

- (b) (6): Losartan added
- (b) (6): Zestoretic, Diltiazem, Metoprolol, Amlodipine, and Verapamil all added within a 1-2 month period and all discontinued within 1-2 months.
- (b) (6): Atenolol added and discontinued the same day.
- (b) (6): Enalaprilat and Hydralazine added the same day and both discontinued the next day.
- (b) (6): Atenolol replaced Metoprolol.
- (b) (6): Furosemide added for 2 weeks and discontinued, added again 2 weeks later for 2 weeks and discontinued.

I compared these 6 subjects with those 110 subjects who had ABPM data (listing 16.2.6.1, SN # 17-module 5.3.5.1). Subject (b) (6) was excluded from the analysis for all visits. Subjects (b) (6) and (b) (6) were excluded from the analysis for week-6. Subject (b) (6) was excluded from the analysis for week-12. Subject (b) (6) was included in the analysis for all visits. Subject (b) (6) was inexplicably not found on table 16.2.6.1.

Antares provided a table of the screening and the three qualification systolic and diastolic blood pressures measurements of the 6 subjects who had a change in blood pressure medications (shown immediately below). The data showed an increase in pre-treatment SBP and DBP for 4 subjects.

Blood pressure (mm/Hg) values prior to receiving testosterone in QST-15-005

Patient no.	Screening Systolic	Visit Q1 Systolic	Visit Q2 Systolic	Visit Q3 Systolic	Day 1 Systolic	Screening Diastolic	Visit Q1 Diastolic	Visit Q2 Diastolic	Visit Q3 Diastolic	Day 1 Diastolic
(b) (6)	129	129	141	146	143	88	88	89	97	99
	122	122	129	137	142	77	77	82	87	83
	107	107	138	125	144	75	75	88	87	93
	121	121	116		137	75	75	76		86
	132	132	132	126	128	86	86	86	80	88
	132	130	130	111	129	82	82	80	77	80

Source: Response to the February 24, 2017 filing communication where reviewer issues were identified (Sn # 0010 / module 5.3.5.1 / CSR study QST-15-005)

Reviewer Comment: The implication of this table provided by Antares in response to our IR regarding subjects who had BP medications is that the rise in SBP and DBP was not testosterone-related. The relationship between the blood pressures displayed here and the timing of the blood pressure medication management was not explicitly provided. Further changes in blood pressure beyond day #1 were not explicitly provided in this response. Of the 6 subjects, only 1 had ABPM data analyzed for all three time periods and 3 had ABPM data analyzed for two time periods. Because this was a non-controlled study, I cannot rule out testosterone as the cause of blood pressure increases during the course of the study. I also cannot rule out the possibility that providing blood pressure medications may have attenuated increases in blood pressure due to testosterone whereby the blood pressure rise might have been greater if left untreated. The overall results are not likely to have been significantly impacted by the administration of blood pressure medications because of the small sample size.

The ABPM measurements for SBP and DBP at baseline, week-6, and week-12 (overall, awake and asleep) for the ITT population are shown in Table 2. The sensitivity analysis of the same data is shown in Table 3. The sample sizes decreased from baseline to week-12 in both the ITT and sensitivity analysis.

Reviewer Comment: I compiled the data in these tables from Tables 14.2.3.7 and 14.2.3.8 (same table numbers) found in SN#0001 for the ITT population and SN#0017 for the sensitivity analysis, respectively. I rounded the numbers (i.e. SBP, DBP, standard deviation, and change from baseline) to the nearest 10th.

For the ITT population, the overall change in mean SBP from baseline to week-6 was 4 mmHg. There were no further increases in mean SBP between week-6 and week-12. The overall changes in mean DBP from baseline to week-6 and to week-12 were 1 mmHg and 2 mmHg, respectively. This was consistent with the overall mean rise in

SBP/DBP reported in the ISS. This rise in BP appeared to be driven by awake-hours. The results of the sensitivity analysis were similar to that from the ITT population.

There were inexplicable but inconsequential discrepancies in sample size between blood pressure measurements and change-from-baseline calculations within a given time period. For example, in Table 2, 105 subjects had ABPM measurements during awake-hours on week-6, but the mean change from baseline for both SBP and DBP were calculated in 102 subjects at that time period. It is unclear why awake-ABPM data were not analyzed in 3 subjects that apparently had ABPM data. There was a similar 3-subject discrepancy at week-12 for awake-hours. There was a 6-subject discrepancy between the number of subjects at week-6 providing asleep-ABPM data (n=98) and the number of subjects whose asleep-ABPM data were analyzed at that timepoint (n=92). At week-12, there was a 5-subject discrepancy between the number of subjects providing asleep-ABPM data (n=95) and the number of subjects whose asleep-ABPM data were analyzed (n= 90).

The CDF curves for the week-6 and week-12 SBP changes from baseline for the ITT population are shown in Figure 1 and Figure 2, respectively. The CDF curves for the week-6 and week-12 SBP changes for the per protocol population are shown in Figure 3 and Figure 4, respectively.

The CDF curves for the week-6 and week-12 DBP changes from baseline for the ITT population are shown in Figure 5 and Figure 6, respectively. The CDF curves for the week-6 and week-12 DBP changes for the per protocol population are shown in Figure 7 and Figure 8, respectively.

The percentage of subjects with a change from baseline data from these CDF curves was estimated by manual measurements. Antares provided the mean change and standard deviation for SBP and DBP at both week # 6 and week # 12 for the ITT and per protocol population. These data are shown in Table 4.

The data shows the following for the ITT population (n=110 at baseline, n= 106 at week # 6 and n=98 at week # 12) and the Per Protocol population (n=78 at baseline, n= 67 at week # 6 and n= 62 at week #12):

- **Week # 6 SBP**: The mean change in SBP was + 3.5 mmHg (SD 10 mmHg). Approximately 35% of the ITT cohort had no change in or reduced SBP measurements at week-6. Approximately 60% of the ITT cohort had between 0 and 20 mmHg increase in SBP at week-6. The sensitivity analysis showed similar results for the per protocol cohort.

- **Week # 12 SBP**: The mean change in SBP was + 3.7 mmHg (SD 11 mmHg). Approximately 35% of the ITT cohort had no change in or reduced SBP measurements at week-12. Approximately 60% of the ITT cohort had between 0 and 20 mmHg increase in SBP at week-12. The sensitivity analysis showed similar results for the per protocol cohort.

- **Week # 6 DBP**: The mean change in DBP was + 1.2 mmHg (SD 5 mmHg). Approximately 40% of the ITT cohort had no change in or reduced DBP measurements at week-6. Approximately 60% of the ITT cohort had between 0 and 10 mmHg increase in DBP at week-6. The sensitivity analysis showed that 36% of the per-protocol subjects had no change in or a reduced DBP, and 50% had increases of 0-5 mmHg in DBP.

- **Week # 12 DBP**: The mean change in DBP was + 1.3 mmHg (SD 6 mmHg). Approximately 40% of the ITT cohort had no change in or reduced DBP measurements at week-12. Approximately 60% of the ITT cohort had between 0 and 20 mmHg increase in DBP at week-12. The sensitivity analysis showed that 37% of the per-protocol subjects had no change in or a reduced DBP, and 60% had increases of 0-10 mmHg in DBP.

DCRP Assessment

The increases in blood pressure were well below the mean of 140/90 mmHg defined as the boundary for blood pressure management (8th Joint National Committee Guidelines for the Management of Hypertension- http://www.nmhs.net/documents/27JNC8HTNGuidelinesBookBooklet.pdf).

The CDF curves suggested a normal distribution of subjects around the mean without a group of hyper-responders driving the overall small mean effect.

The noted discrepancies in the database were small in number and therefore inconsequential. The modifications in blood pressure management were also inconsequential because of the small sample size.

Increases in blood pressure throughout the course of the study could reasonably be attributable to testosterone because there was no control arm in the Phase 3 studies. The largest increases in blood pressure from baseline generally occurred at week #6, with a smaller increments at week # 12.

DCRP Conclusion

One can expect a 4 mmHg rise in SBP and a 2 mmHg rise in DBP when prescribed QuickShotTM Testosterone (QST). This elevation in blood pressure may not be

detectable with respect to the usual variation in daily blood pressure and may be clinically irrelevant for those with low baseline blood pressures.

There is no distinguishable outlier group that drove the overall small increment in blood pressure following initiation of QST

As the mean baseline blood pressure increases, there could be a modest increase in cardiovascular risk. Consider restricting the use of this product in patients diagnosed with an elevated mean blood pressure.

Appendix-Tables and Figures

Table 1. Summary of Blood Pressures for studies QST-13-003, QST-15-005, and the ISS

			SBP (mm Hg)			DBP (mmHg)		
Study	N	Duration	Baseline	Endpoint	Δ from Bl	Baseline	Endpoint	Δ from Bl
003	150	52 wks	127	131	4	80	81	1
005	133	26 wks	126	129	3	78	80	2
ISS	283	26 wks	126	131	4	79	81	2

Source: Study 003: Table 14.3.4.3.5 CSR; Study 005: Table 14.3.4.7.1 CSR; ISS: Table 35.8.1 ISS document

Table 2. Mean Systolic and Diastolic Blood ABPM Pressures

Timepoint	N	Mean SBP (SD)	SBP mean Δ BL (SD)	Mean DBP (SD)	DBP mean Δ BL (SD)
Overall					
Baseline (BL)	110	124 (11)	---	78 (6)	---
Week 6	106	128 (11)	4 (10)	79 (6)	1 (5)
Week 12	98	128 (12)	4 (11)	80 (6)	1 (6)
Awake					
Baseline (BL)	106	126 (11)	---	79 (6)	---
Week 6	105	129 (12)	4 (10)*	80 (6)	1 (5)*
Week 12	98	130 (12)	4 (11)**	81 (6)	2 (6)**
Asleep					
Baseline (BL)	101	118 (18)	---	73 (9)	
Week 6	98	119 (16)	1 (17)***	74 (8)	0.4 (9)***
Week 12	95	120 (20)	2 (22)****	74 (9)	0 (10)****

Δ BL = change from baseline, SD= standard deviation; SBP, DBP and Δ BL are in mmHg;
*(n=102), ** (n=95), *** (n=92), **** (n=90)

Source: Source: Review compilation of data from Table 14.2.3.7 and 14.2.3.8 located in \\CDSESUB1\evsprod\NDA209863\209863.enx., SN # 0001/ module 5.3.5.1/ Study Body Report/ Expert ABPM Report

Table 3. Sensitivity Analysis: Mean Systolic and Diastolic Blood ABPM Pressures

Timepoint	N	Mean SBP (SD)	SBP mean Δ BL (SD)	Mean DBP (SD)	DBP mean Δ BL (SD)
Overall					
Baseline (BL)	78	124 (11)	---	78 (5)	---
Week 6	67	126 (10)	3 (8)	79 (5)	1 (3)
Week 12	62	128 (10)	4 (10)	80 (5)	2 (5)
Awake					
Baseline (BL)	75	125 (11)	---	79 (5)	---
Week 6	66	128 (10)	3 (9)	80 (5)	1 (4)*
Week 12	62	130 (10)	4 (10)	81 (5)	2 (5)**
Asleep					
Baseline (BL)	77	117 (17)	---	73 (9)	
Week 6	63	118 (14)	2 (17)	74 (8)	2 (8)
Week 12	62	118 (17)	1 (20)	73 (7)	0 (9)

Δ BL = change from baseline, SD= standard deviation; SBP, DBP and Δ BL are in mmHg;
* (n=65), ** (n=60)

Source: Review compilation of data from Table 14.2.3.7 and 14.2.3.8 located in \\CDSESUB1\evsprod\NDA209863\209863.enx., SN # 0017 /module 5.3.5.1 / Study Body Report / Tables

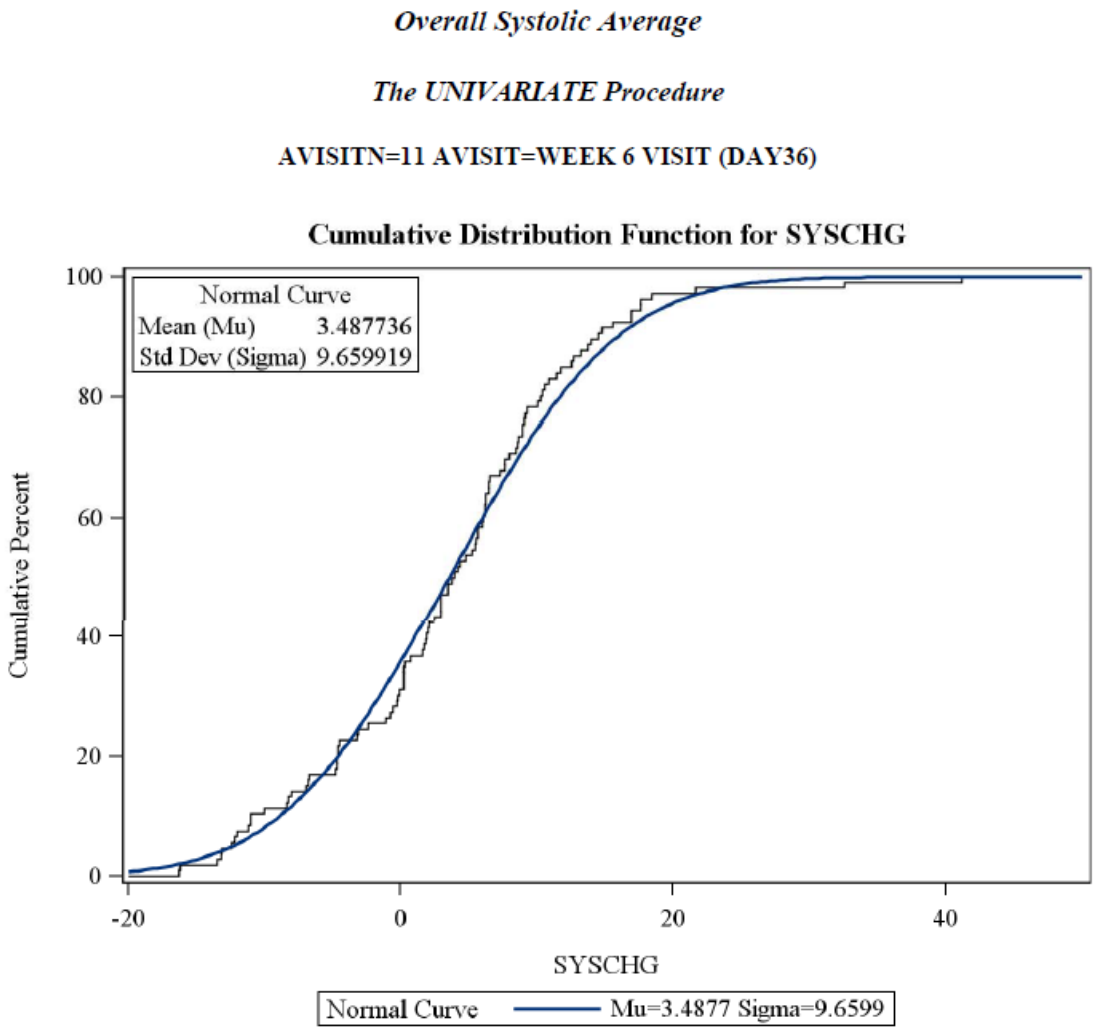
Table 4. Percent subjects with reductions and increases in BP from baseline

Timepoint	N	Mean SBP Δ BL (SD) (mmHg)	% Subjects Reduced or No Change in SBP	% Subjects with 0-20 mmHg increase in SBP	Mean DBP Δ BL (SD) (mmHg)	% Subjects Reduced or No Change in DBP	% Subjects with 0-20 mmHg increase in DBP
	ITT Population						
Week 6	106	+ 3.5 (10)	35	60	+1.2 (5)	40	60*
Week 12	98	+ 3.7 (11)	40	55	+1.3 (6)	40	60
	Per Protocol (Subjects Compliant with 18-hour Rule)						
Week 6	67	+3.0 (8)	35	60	1.1 (3)	36	50**
Week 12	62	+3.9 (10)	35	60	1.5 (5)	37	60*

*Increase in DBP between 0—10 mmHg; **Increase in DBP between 0—5 mmHg

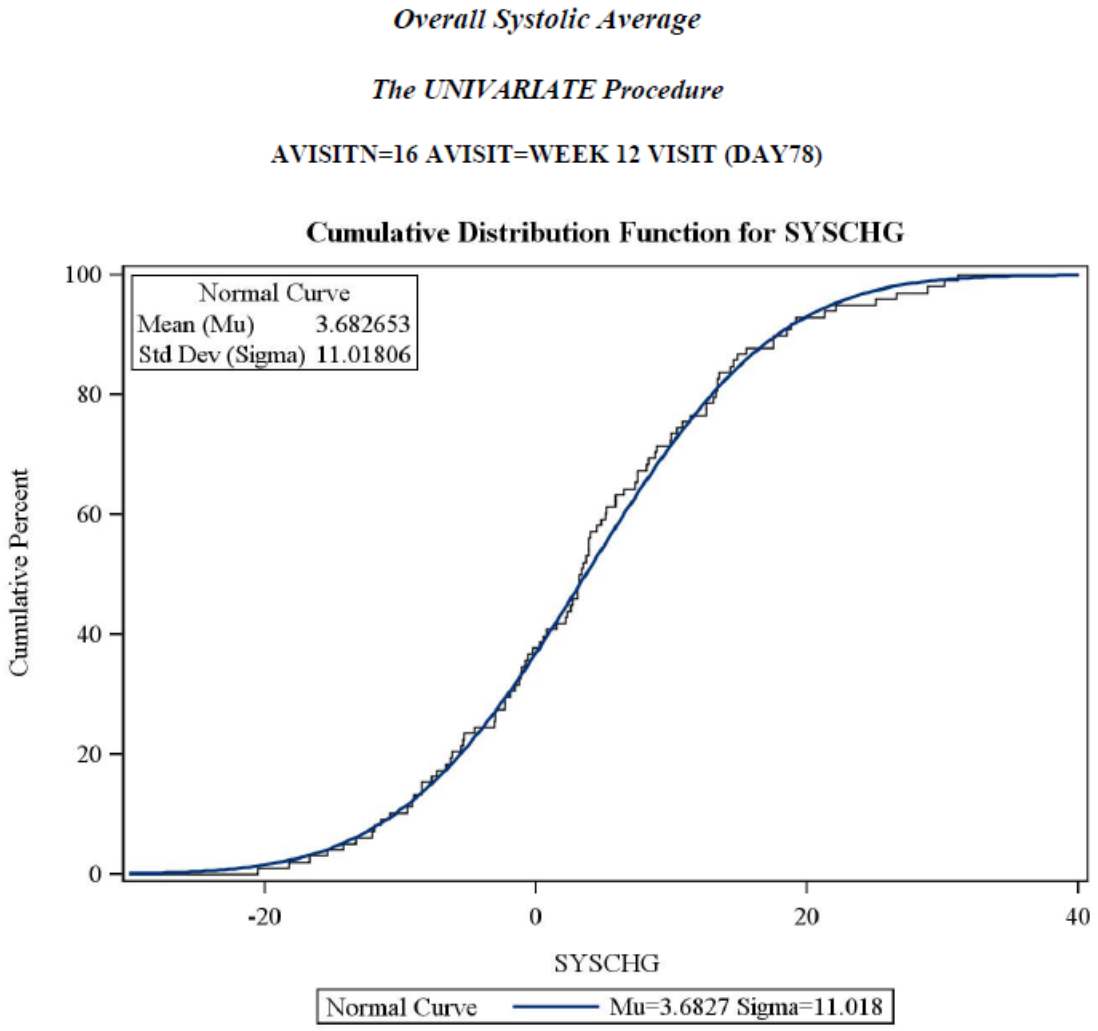
Source: Sample size from Table 2 and Table 3 in this review; Mean changes from baseline and standard deviation directly from the CDF curves; % subjects with reductions or increases in blood pressure manually estimated from the CDF curves.

Figure 1. CDF-SBP Week 6 (Study QST-15-005)



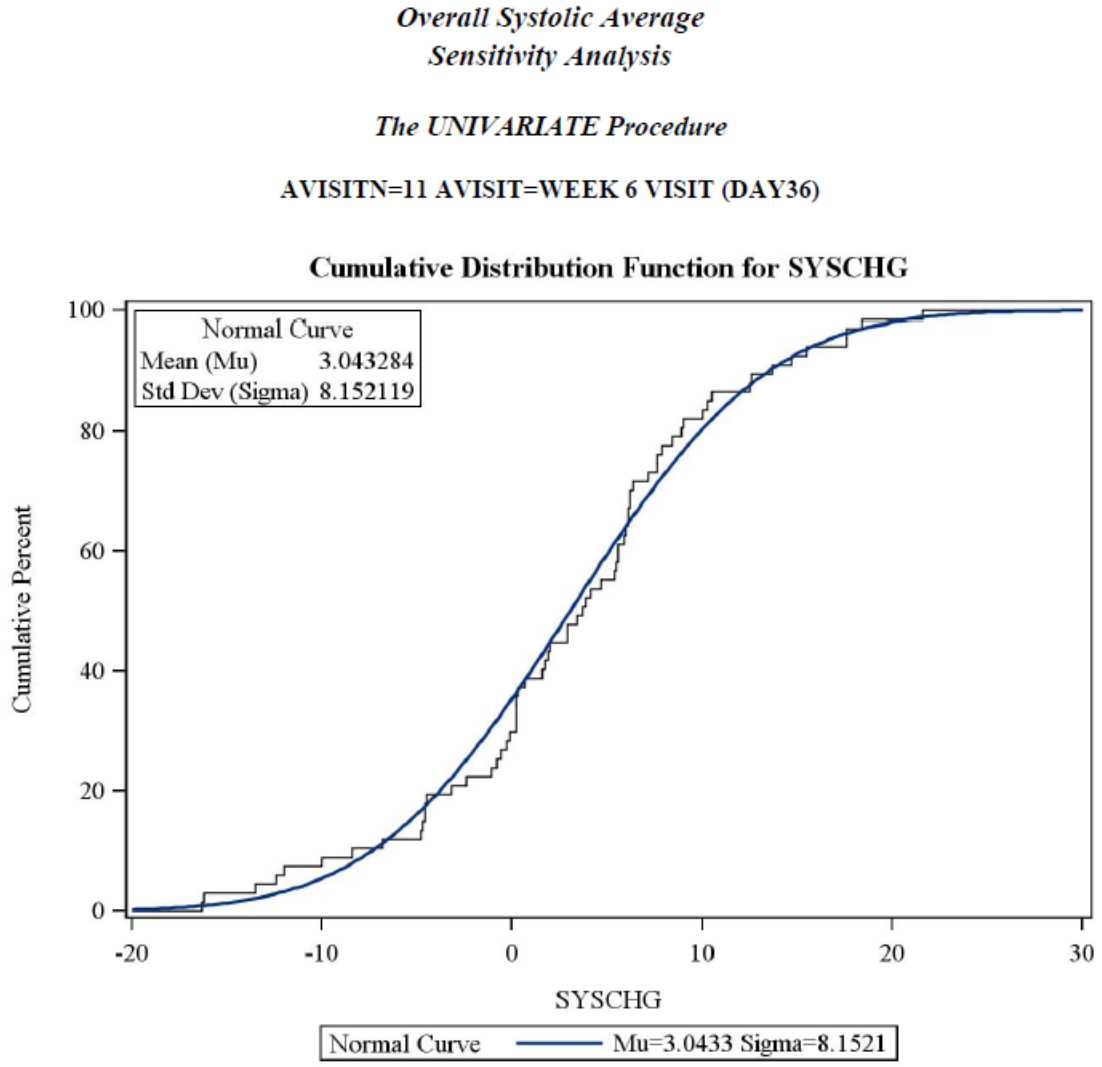
Source: Submission # 0017 Module 5.3.5.1

Figure 2. CDF-SBP Week 12 (Study QST-15-005)



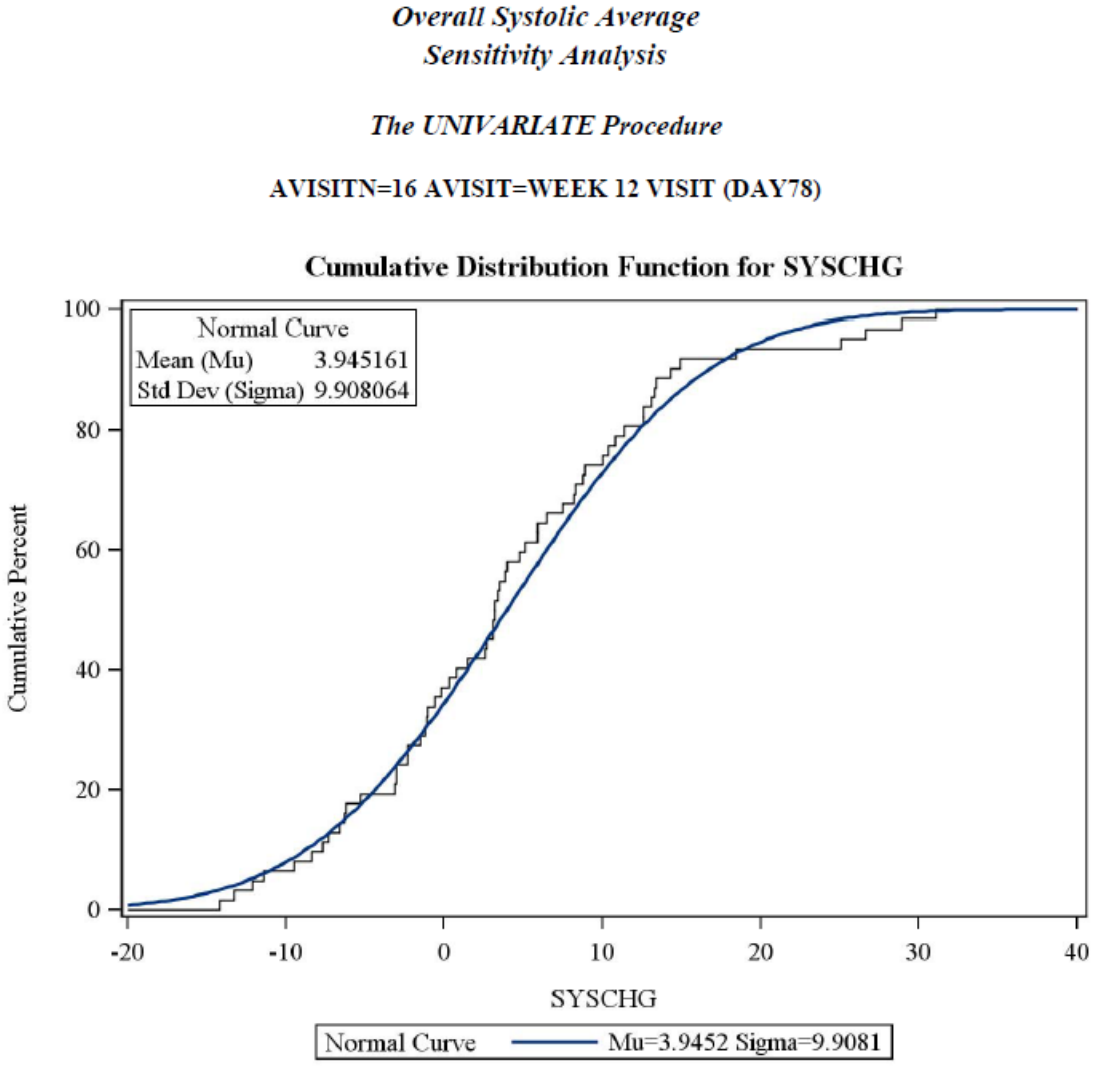
Source: Submission # 0017 Module 5.3.5.1

Figure 3. CDF-SBP Week 6 (Study QST-15-005)-Sensitivity Analysis



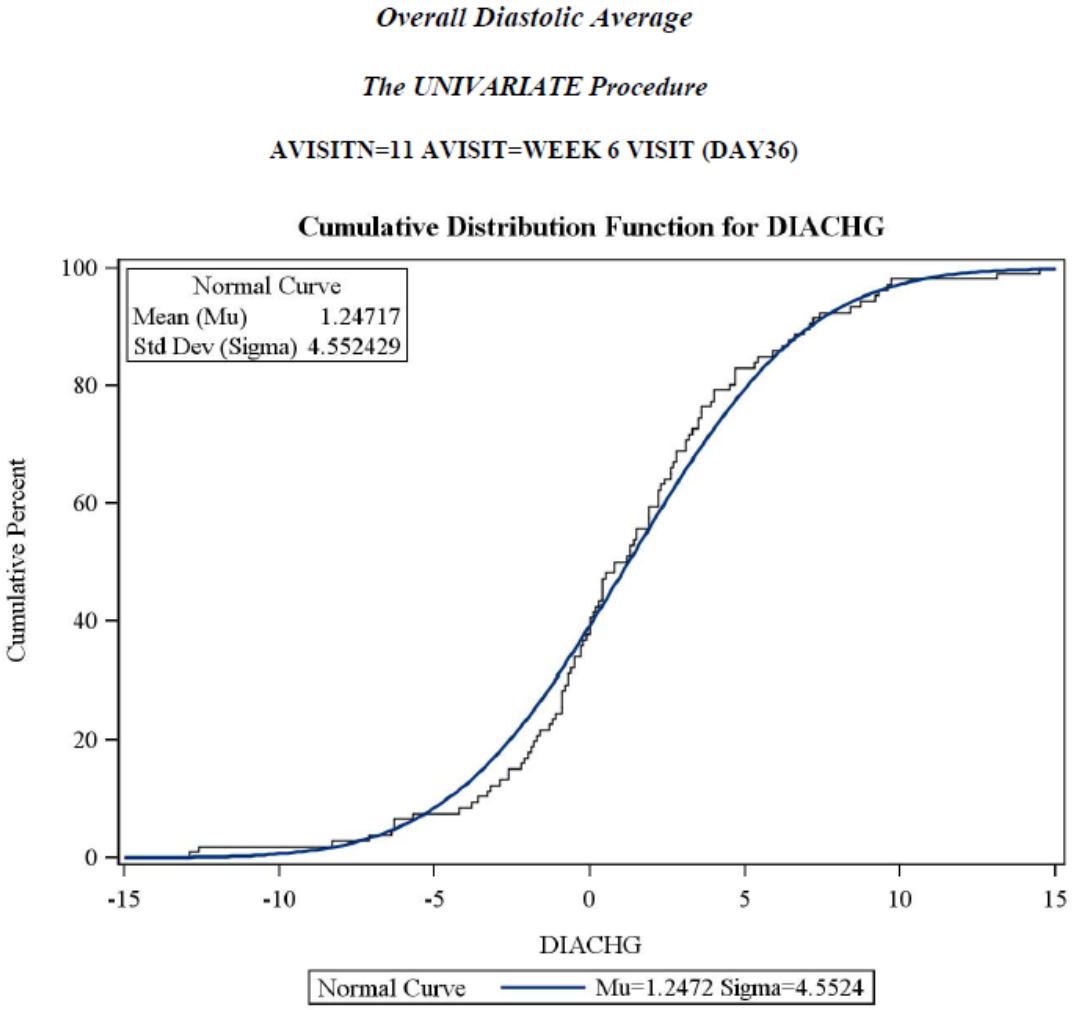
Source: Submission # 0017 Module 5.3.5.1

Figure 4. CDF-SBP Week 12 (Study QST-15-005)-Sensitivity Analysis



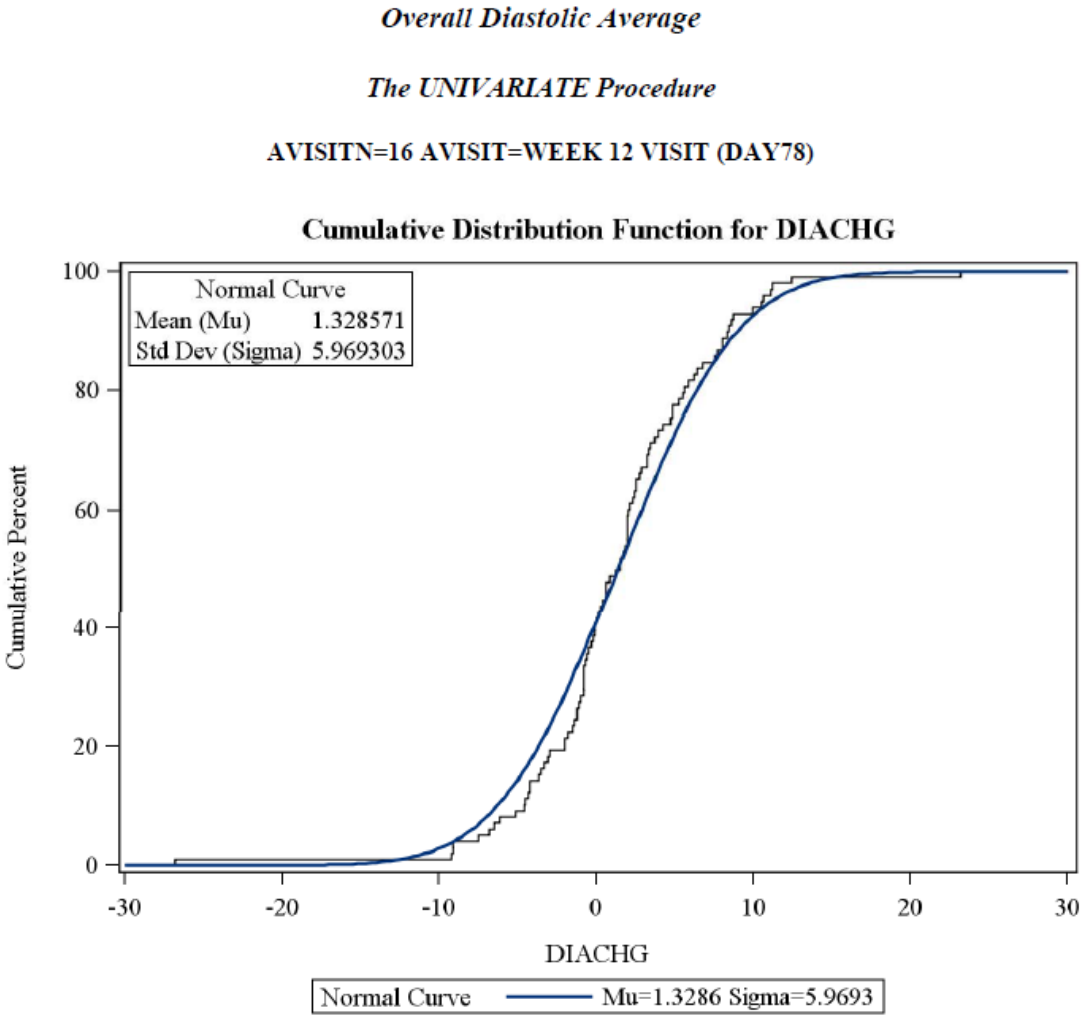
Source: Submission # 0017 Module 5.3.5.1

Figure 5. CDF-DBP Week 6 (Study QST-15-005)



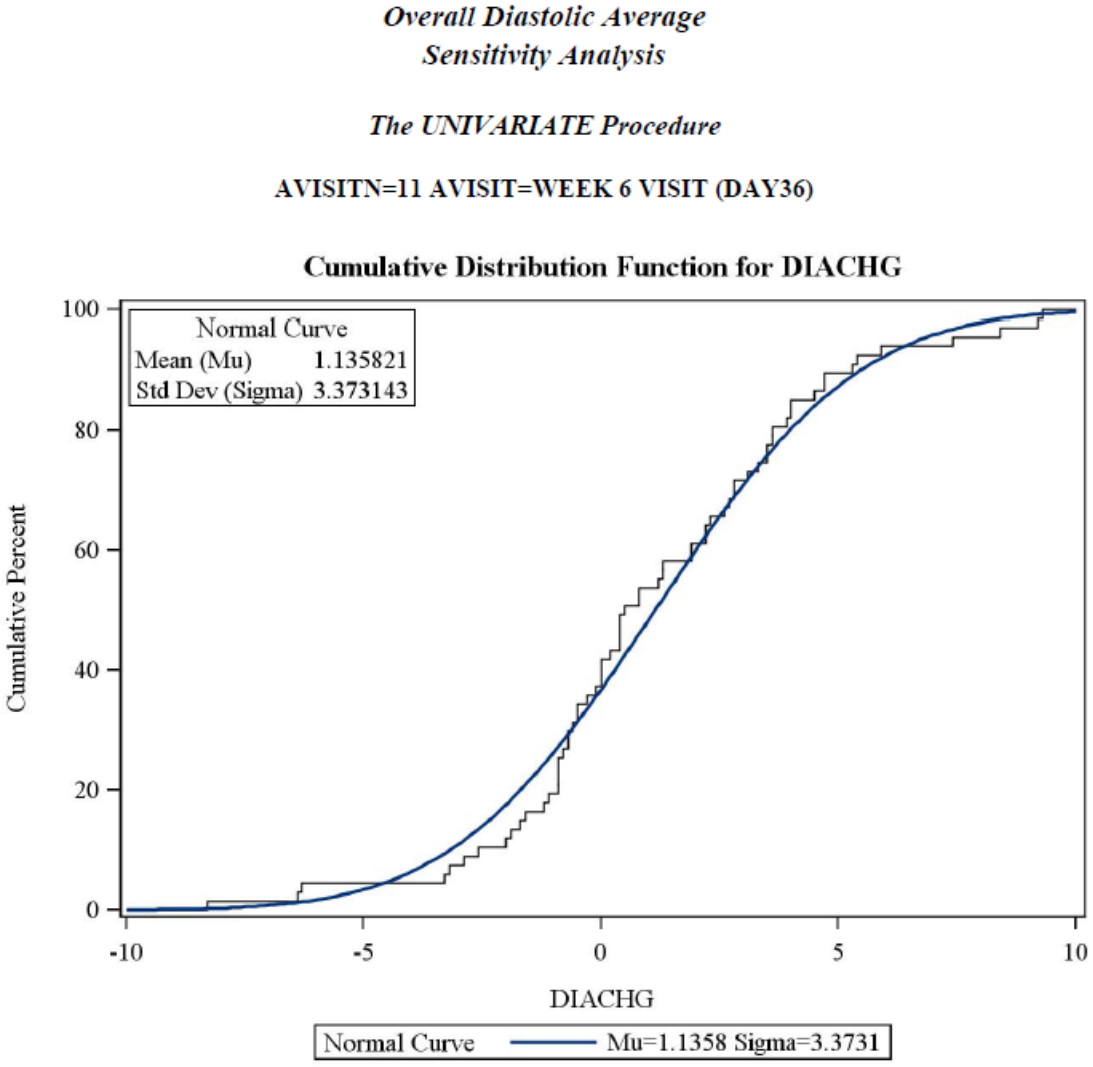
Source: Submission # 0017 Module 5.3.5.1

Figure 6. CDF-SBP Week 12 (Study QST-15-005)



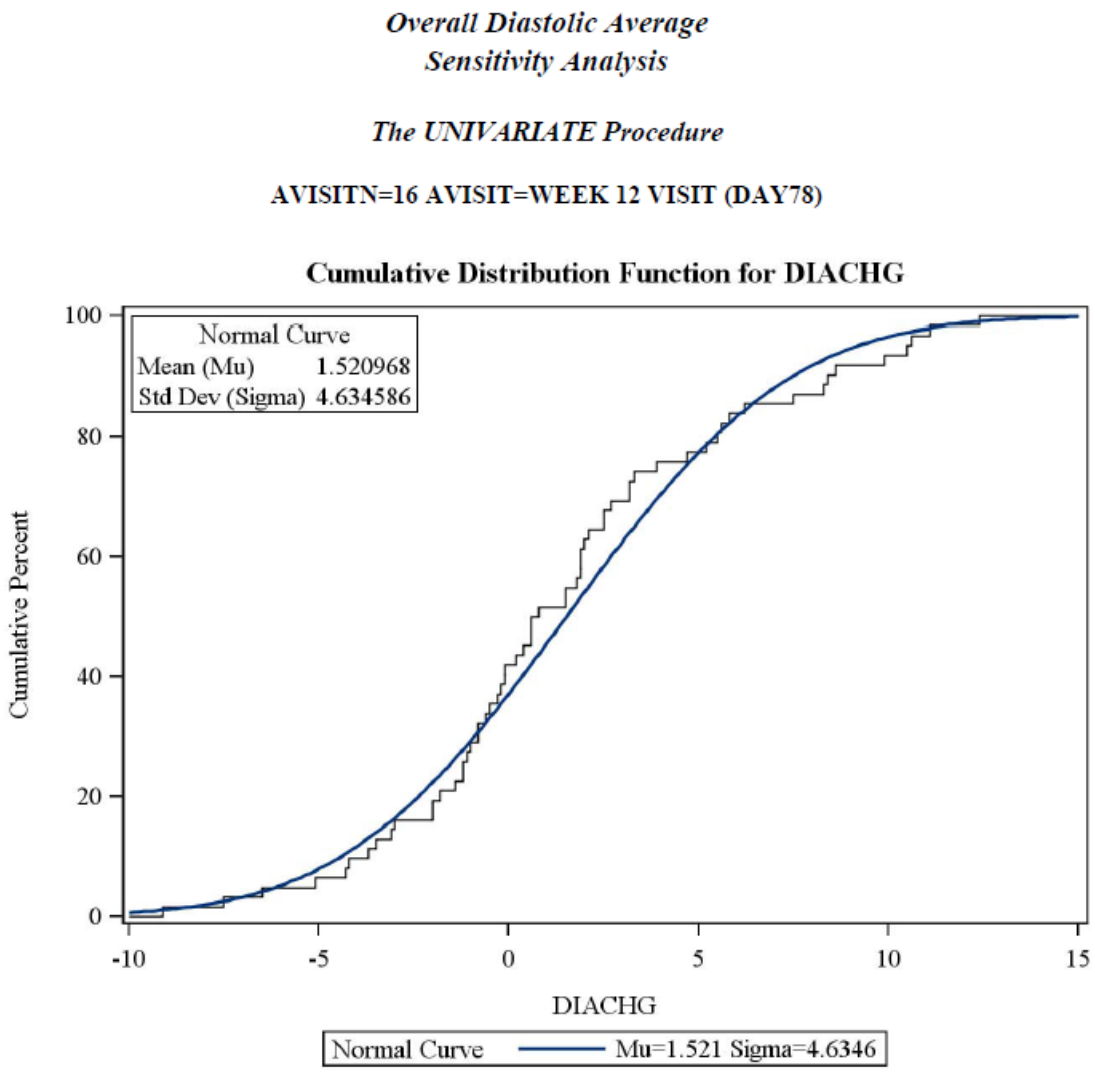
Source: Submission # 0017 Module 5.3.5.1

Figure 7. CDF-SBP Week 6 (Study QST-15-005)-Sensitivity Analysis



Source: Submission # 0017 Module 5.3.5.1

Figure 8. CDF-SBP Week 12 (Study QST-15-005)-Sensitivity Analysis



Source: Submission # 0017 Module 5.3.5.1

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/s/

FORTUNATO F SENATORE
08/01/2017

MARTIN ROSE
08/02/2017

NORMAN L STOCKBRIDGE
08/03/2017

Clinical Inspection Summary

Date	June 6, 2017
From	Roy Blay, Ph.D., Reviewer Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations (OSI)
To	Jeannie Roule, RPM Debuene Chang, Clinical Reviewer Mark Hirsch, Clinical Team Leader Division of Bone, Reproductive, and Urologic Products (DBRUP)
NDA#	209863
Applicant	Antares Pharma, Inc.
Drug	Xyosted (testosterone enanthate)
NME (Yes/No)	No
Therapeutic Classification	Standard Review
Proposed Indication(s)	Testosterone replacement therapy in adults, 18 years or older, males for conditions associated with a deficiency of absence of endogenous testosterone – primary hypogonadism (congenital or acquired) or secondary hypogonadism (congenital or acquired)
Consultation Request Date	February 8, 2017
Summary Goal Date	June 30, 2017
Action Goal Date	October 20, 2017
PDUFA Date	October 20, 2017

1. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The clinical sites of Drs. Kaminetsky, Mook, and Gittelman were inspected in support of this NDA. The inspection of Dr. Gittelman's site revealed that the 24-hour arterial blood pressure measurements (ABPMs) collected at baseline and at Weeks 6 and 12 for seven of 15 subjects had one or more sets of readings determined to be of "Not Good Quality" since they were not obtained in accordance with the investigational plan.

These concerns regarding ABPMs (Not Good Quality) were discussed in a May, 10, 2017, meeting with DBRUP and the Division of Cardiorenal Products (DCRP). After the conclusion of the meeting, the review division sent an information response (IR) letter to the sponsor requesting that a sensitivity analysis be performed on the ABPMs for the subjects in Study QST-15-005 including an analysis of only those subjects with at least 18 measurable readings per 24-hour period. The assessment of the significance of these blood pressure data analyses for the different study populations is left to the review division.

Otherwise, based on the results of these inspections, the studies appear to have been conducted adequately, and the data generated by these sites and submitted by the sponsor appear acceptable in support of the respective indication.

The final classification of the inspections of Dr. Kaminetsky was Voluntary Action Indicated (VAI), while the final classification of the inspections of Drs. Mook and Gittelman was No Action Indicated (NAI).

2. BACKGROUND

The Applicant submitted this NDA to support the use of Xyosted (testosterone enanthate) for testosterone replacement therapy in adult men, 18 years or older, for conditions associated with a deficiency or absence of endogenous testosterone –primary hypogonadism (congenital or acquired) or secondary hypogonadism (congenital or acquired).

Inspections were requested for the following protocols in support of this application:

Protocol QST-13-003, entitled "A double-blind, multiple-dose, 52-week study to evaluate the efficacy and safety of QuickShot™ Testosterone administered subcutaneously once each week to adult males with hypogonadism"

This was a Phase 3, double-blind (to dosage strength), multiple-dose, 52-week study to evaluate the efficacy and safety of QST administered subcutaneously once each week to adult male patients with hypogonadism. The study included a Screening Phase, a Treatment Titration Phase, and an Extended Treatment Phase for evaluation of long-term safety.

The primary objective of this study was to demonstrate the efficacy of QST administered subcutaneously once each week to adult males with hypogonadism.

The primary endpoint for this study was the percentage of patients with a TT average concentration over the 7-day dosing interval (0-168 hours) ($C_{avg168h}$) within the defined range (300 to 1100 ng/dL).

Protocol QST-13-003 was conducted at 30 sites in the U.S. with a total of 150 randomized subjects in the study.

Protocol QST-15-005, entitled "A 6-Month Safety Study of QuickShot™ Testosterone Administered Subcutaneously Once Each Week to Adult Males with Hypogonadism"

This was a Phase 3, multiple-dose, 6-month study to collect safety information on QST administered subcutaneously once each week to adult male patients with subnormal testosterone blood levels. The study included a Screening Period, a Treatment Titration Period, and an Extended Treatment Period for evaluation of long-term safety.

Because this study was designed to investigate the safety of the administered test article, efficacy was not examined. Safety assessments included adverse events, clinical laboratory tests (biochemistry profile, hematology, coagulation, urinalysis, PSA, and endocrine evaluations), 12-lead ECGs, vital signs, 24-hour ABPM, physical examinations, digital rectal exam of the prostate, injection site assessments, and the Assessment of Essential Tasks questionnaire.

Protocol QST-15-005 was conducted at 21 sites in the U.S. with a total of 133 randomized subjects in the study.

Rationale for Site Selection

The clinical sites of Drs. Kaminetsky, Mook, and Gittelman were selected for inspection because of the enrollment of large numbers of study subjects and a high percentage of discontinuations from the study due to AEs.

3. RESULTS (by site):

Site #/ Name of CI/ Address	**Protocol #/ # of Subjects (enrolled)**	**Inspection Dates**	**Classification**
Jed Kaminetsky 215 Lexington Avenue, 21st Floor New York, NY 10016	QST-13-003/ (14 enrolled) and QST-15-005/ (14 enrolled)	22-29 Mar 2017	VAI
Tommy Mook Regional Urology, LLC 255 Bert Kouns Industrial Loop Shreveport, LA 71106	M51810-US003/ (12 enrolled) and QST-15-005/ (18 enrolled)	13-16 March 2017	NAI
Marc Gittelman 21150 Biscayne Boulevard, #300 Aventura, FL 33180	QST-15-005/ (15 enrolled)	28 Mar-4 Apr 2017	NAI

Key to Compliance Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data unreliable.
Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending. Final classification occurs when the post-inspectional letter has been sent to the inspected entity.

General Observations

As mentioned in Section 1, the inspection of Dr. Gittelman's site revealed problems with the 24-hour arterial blood pressure measurements (ABPMs). Specifically, per protocol, 24-hour ambulatory blood pressure monitoring (ABPM) on an hourly basis was to be performed prior to the first study drug administration (Day-1/Baseline) and at Weeks 6 and 12. Overall, these measurements were taken; however, seven of 15 subjects had one or more sets of readings

determined to be of "Not Good Quality" as they did not meet pre-specified criteria. These criteria as stated in the ABPM Staff & User Guide included:

- at least 18 valid measurements over the 24-hour period;
- no more than three consecutive hours with less than one valid BP reading; and
- no more than five total hours of missing data

ABPMs meeting these criteria were determined to be of "Good Quality" while measurements not meeting these criteria were of "Not Good Quality" and were to be repeated. The protocol and related study documents did not adequately describe the repeat measurement process. Of note, the 24-hour ABPM data was uploaded from the device and sent to a vendor. The vendor was supposed to send back, in a timely fashion, the "ABPM Feedback Form," which would indicate whether the data was of "Good Quality" or "Not Good Quality." The "ABPM Feedback Form" did not indicate that "Not Good Quality" measurements needed to be repeated.

Site personnel stated during the inspection that the training provided did not adequately address the need for repeat measurements, that notification of the quality of the measurements via the "ABPM Feedback Form" was not made in real time (making it impossible to do a repeat measurement in a timely manner), that there was no control or assurance that subjects would follow verbal instruction or the quick reference guide given them to take home, and also, that neither the subject nor the site would know if the ABPM device was working properly. This lack of proper training and communication resulted in multiple subjects having readings of "Not Good Quality" that were not repeated.

The nature of the problems with the 24-hour ABPMs at Dr. Gittelman's site raised concerns about the quality of the 24-ABPMs collected from all the sites. These concerns regarding ABPMs were discussed in a meeting held on May, 10, 2017. Attendees included:

- Drs. Debuene Chang and Mark Hirsch (DBRUP)
- Drs. Phillip Kronstein and Roy Blay, Office of Scientific Investigations (OSI)
- Drs. Stephen Grant, Fortunato Senatore, and Martin Rose (DCRP)
- Devi Kozeli, regulatory project manager, (DCRP)

As mentioned above, the meeting concluded with a decision to draft an information response (IR) letter to the sponsor from the review division requesting clarification of the blood pressure data and the manner of its classification and presentation.

1. Jed Kaminetsky, M.D.

For Protocol QST-13-003, 36 subjects were screened, 14 subjects were enrolled, five subjects discontinued the study, and nine subjects completed the study. For Protocol QST-05-015, 38 subjects were screened, 14 were enrolled, four subjects discontinued the study, and ten subjects completed the study.

The consent forms for all enrolled subjects in both studies were reviewed. All subjects signed the consent forms prior to any study-related procedures. Study records for all enrolled subjects in both studies were reviewed. Source documents were compared to data listings. All source documents were in paper and transcribed to electronic Case Report Forms (eCRFs). Records reviewed included, but were not limited to, staff qualifications; enrollment logs; protocol deviations; IRB, sponsor, and monitor communications; IVRS confirmations; adverse events; concomitant medications; sample shipment records; and test article accountability and storage.

A Form FDA 483 was issued at the conclusion of the inspection with two observations: lack of adherence to protocol and inadequate records. Examples of lack of adherence to protocol are the inclusion of four subjects (b) (6) in the study despite exclusionary blood pressure measurements at their initial screening visits. These four subjects completed the study without any problems, and the site was unaware of these deviations until notified by the monitor. Also, Subject (b) (6) was noted as taking dutasteride, a prohibited concomitant medication, throughout the course of the study. This deviation was discovered during a monitoring visit. All of these deviations were reported.

Examples of inadequate records include those for Subject (b) (6) who did not complete a required follow-up visit. The deviation was noted in the source documents but not on the corresponding eCRF.

Dr. Kaminetsky responded to the Form FDA 483 in writing on April 12, 2017. He acknowledged the inappropriate inclusion of study subjects with exclusionary blood pressure readings and of another subject treated with an exclusionary medication. Dr. Kaminetsky determined that the blood pressure values were not clinically significant nor did they compromise subject safety. Dr. Kaminetsky said that secondary checks of inclusion/exclusion criteria had been implemented to prevent future enrollment of ineligible subjects. These deviations were noted in the source documents and the IRB was notified. Dr. Kaminetsky also noted that Subject (b) (6) completed the early termination visit but did not return for the follow up visit. The missed visit was noted in the source documents but not transferred to the relevant eCRF. Dr. Kaminetsky has initiated additional reviews of data entry to detect such instances of missing data.

Notwithstanding the observations noted above, neither safety nor efficacy considerations appear to have been affected. This study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

2. Tommy Mook, M.D.

For Protocol QST-13-003, 19 subjects were screened, 12 subjects were randomized, two subjects discontinued from the study (both moved out-of-state), and ten subjects completed the study. For Protocol QST-15-005, 38 subjects were screened, 18 subjects were randomized, 3 subjects discontinued from the study (one withdrew consent, one had an elevated hematocrit, and one had a serious adverse event), and 15 subjects completed the study.

Study records for all of the randomized subjects for each study were reviewed. These subjects signed and dated the consent forms prior to any study-related procedures. Source documents were compared with the data listings. Records reviewed included but were not limited to sponsor, monitor, and IRB correspondence; financial disclosure; study staff qualification; delegation logs; laboratory evaluations; subject study eligibility; site visit logs; adverse events; protocol deviations; and test article accountability and storage.

Minor deviations from protocol resulting from out-of-window (OOW) visits, including OOW pharmacokinetic sample collections, OOW injection site assessments, and OOW dosing were noted. All these minor deviations were reported to the sponsor and the IRB

Study data were captured on source template documents, then entered into electronic Case Report Forms (eCRFs) and signed by Dr. Mook. Data disks containing case report form data were forwarded to the site by the sponsor for each study.

A Form FDA 483 was not issued at the conclusion of the inspection. This study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

3. Marc Gittelman, M.D.

For Protocol QST-15-005, 25 subjects were screened, 15 subjects enrolled, two subjects either discontinued from the study or were lost to follow up, and 13 subjects completed the study.

Study records for all of the randomized subjects were reviewed. These subjects signed and dated the consent forms after IRB approval and prior to any study related procedures. Records reviewed included but were not limited to sponsor, CRO, IRB, and monitoring correspondence; financial disclosure; staff qualifications; delegation logs; the screening and enrollment log; laboratory measurements; and test article accountability and storage.

Deviations from protocol included conducting ECGs on nine subjects prior to having them rest for 15 minutes. The site submitted protocol deviations for eight of these nine subjects; however, none of these deviations appeared in the data listings. Deviations regarding follow-up testosterone testing were also noted. Testosterone Test 2 was performed out-of-window for the majority of subjects. This testing was to be done seven to nine days after the first test. As a result of a misunderstanding by the site, such follow-up testing was performed two to three days early. All deviations regarding the timing of testosterone testing were reported in the data listings.

As previously mentioned, the ABPMs for seven of 15 subjects were determined to be of "Not Good Quality". This matter was discussed with DBRUP and DCRP. An IR letter was forwarded to the sponsor requesting that sensitivity analyses be performed for the subjects in study QST-15-005 and for the subpopulation having at least 18 measurable blood pressure readings per 24-hour period. The assessment of the significance of these analyses is left to the review division. A Form FDA 483 was not issued at the conclusion of the

inspection. Other than the concerns regarding ABPMs as discussed above, this study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

{See appended electronic signature page}

Roy Blay, Ph.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

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Phillip Kronstein, M.D.
Team Leader
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DBRUP\Division Director\Hylton Joffe
DBRUP\Team Leader\Mark Hirsch
DBRUP\Medical Officer\Debuene Chang
DBRUP\Project Manager\Jeannie Roule
OSI\DCCE\Division Director\Ni Khin
OSI\DCCE\GCPAB\Branch Chief\Kassa Ayalew
OSI\DCCE\GCPAB\Team Leader\Phillip Kronstein
OSI\DCCE\GCPAB\Reviewer\Roy Blay
OSI\DCCE\Program Analysts\Joseph Peacock\Yolanda Patague
OSI\Database Project Manager\Dana Walters

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/s/

ROY A BLAY
06/19/2017

PHILLIP D KRONSTEIN
06/19/2017

KASSA AYALEW
06/19/2017

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: June 19, 2017

TO: Hylton V. Joffe, M.D., M.M.Sc.
Director
Division of Bone, Reproductive, and Urologic Products (DBRUP)
Office of Drug Evaluation III
Office of New Drugs

FROM: Kara A. Scheibner, Ph.D.
Pharmacologist Division of Generic Drug Bioequivalence Evaluation
(DGDBE)
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Sam H. Haidar, Ph.D., R. Ph.
Deputy Director,
Division of Generic Drug Bioequivalence Evaluation
(DGDBE)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: [redacted] covering NDA 209863

Inspection Summary:

At the request of the Division of Bone, Reproductive, and Urologic Products (DBRUP) in the Office of New Drugs (OND), the Office of Study Integrit [redacted] that audited analytical portions of study QST-13-003 submitted as part of NDA 209863. Based upon the results of this inspection, we recommend that analytical data from study QST-13-003 be accepted for agency review.

Study audited during this inspection:

Study Number: QST-13-003 ([redacted] study number 14253; NDA 209863)
Study Title: "A Double-Blind, Multiple-Dose, 52-Week Study to Evaluate the Efficacy and Safety of QuickShot™ Testosterone Administered

Subcutaneously Once Each Week to Adult Males with Hypogonadism"

Analysis Dates: October 27, 2014 through September 12, 2015

OSIS investigator Kara A. Scheibner, Ph.D. conducted the inspection of analytical portions of the study from May 1 through May 5, 2017.

The bioanalytical audit included a thorough review of facilities and equipment, training records, current bioanalytical SOPs, study records and correspondence hod validation records, and interviews and discussions with [redacted] management and staff.

At the conclusion of the inspection, Form FDA-483 (**Attachment 1**) was issued [redacted] The observations, [redacted] response to the observations (**Attachment 2**), and our evaluation follow.

Observation 1:

[redacted]

Specifically:

[redacted]

[redacted] Response:

In their written response, [redacted] acknowledged the observation. Updated method validation reports have been submitted (**Attachments 3 and 4;** [redacted]

[redacted] committed to the review and update of SOPs for method validation and bioanalytical report generat [redacted] d SOP [redacted] respectively) to ensure that " [redacted] is sufficiently and consistently presented in method validation reports." Further, [redacted] committed to the review of method validation reports from the previous five years; corrective actions will be implemented as appropriate.

OSIS Evaluation:
We acknowledge the efforts in corrective actions initiated by (b) (4) in response to Observation 1. However, upon review of the amended reports, we find the response unacceptable.

(b) (4)

(b) (4)

In our opinion, we find the overall (b) (4) methodology to be accurate and precise within t lidated concentration range. However, we suggest that (b) (4) precision and accuracy data should be evaluated carefully in future applications, and OSIS should verify that appropriate corrections have been implemented during the next surveillance inspection.

Observation 2:

(b) (4)

Specifically:

(b) (4)

(b) (4) Response:
In their written response, (b) (4) acknowledged the observation. Stability experiments were repeated to confirm the originally reported stability data in both method vali ions, and amended reports were issued (**Attachments 4 and 5**). (b) (4) committed to review and revise SOPs for method validation and bioanalytical report generation (SOP (b) (4) and SOP (b) (4) respectively) to ensure that stability data are properly reported.

OSIS Evaluation:
We find (b) (4) response to Observation 2 acceptable. Results for (b) (4) stability in method validation (b) (4) and (b) (4) stability in method validation (b) (4) were acceptable, and respective stabilities were adequately demonstrated to be accurate and ise under validated conditions. We also acknowledge (b) (4) commitment to revise relevant SOPs to ensure adequate stability assessments in future method validations.

Observation 3:

[redacted]

[redacted] Response:
In their written response, [redacted] acknowledged the observation. The firm conducted an additional validation study [redacted] (**Attachment 6**). The updated method validation reports include a statement regarding [redacted] results and a reference to report [redacted] also committed to review and revise the SOP for method validation and bioanalytical report generation (SOP [redacted]) to ensure assessment of all potentially interfering molecules in future method validations.

OSIS Evaluation:
We find [redacted] response to Observation 3 acceptable. Results from the interference evaluations in study [redacted] were acceptable, [redacted] We acknowledge [redacted] commitment to revising the method validation SOP, and find this action appropriate to prevent a similar condition in future multi-analyte studies.

Recommendation:

Following review of the EIR [redacted] data for study QST-13-003, FDA-483 observations, and [redacted] responses, we recommend that the analytical portion of study QST-13-003 be accepted for further agency review.

In addition, studies of similar design conducted from [redacted] through [redacted] should be accepted for review by the Agency without an inspection. However, precision and accuracy data should be reviewed carefully in applications from this time period and in future applications. OSIS should verify that appropriate corrections have been implemented during future surveillance inspections.

Kara A. Scheibner, Ph.D.
DGDBE, OSIS

Final Classification:

VAI: [redacted]
(FEI#: [redacted])

CC:
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Draft: KAS 6/12/2017; KAS 6/16/2017
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ECMS: Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good Laboratory Practice Compliance/INSPECTIONS/BE Program/Analytical Sites/[redacted]
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/s/

KARA A SCHEIBNER
06/19/2017

SAM H HAIDAR
06/19/2017

LABEL, LABELING, AND PACKAGING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	May 12, 2017
Requesting Office or Division:	Division of Bone, Reproductive, and Urologic Products
Application Type and Number:	NDA 209863
Product Name and Strength:	Xyosted (testosterone enanthate) injection 100 mg/mL, 150 mg/mL, 200 mg/mL
Total Product Strength:	50 mg/0.5 mL, 75 mg/0.5 mL, 100 mg/0.5 mL
Product Type:	Combination Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Antares Pharma, Inc.
Submission Date:	December 20, 2016
OSE RCM #:	2017-432
DMEPA Primary Reviewer:	Denise V. Baugh, PharmD, BCPS
DMEPA Team Leader:	Lolita White, PharmD

1 REASON FOR REVIEW

The Division of Bone, Reproductive, and Urologic Products (DBRUP) consulted the Division of Medication Error Prevention and Analysis (DMEPA) to evaluate the Xyosted[a] (testosterone enanthate) injection container label, carton labeling, and prescribing information (PI) from a medication error perspective.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C (N/A)
ISMP Newsletters	D (N/A)
FDA Adverse Event Reporting System (FAERS)*	E (N/A)
Other	F (N/A)
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Our review of the proposed Xyosted container labels, carton labeling, and prescribing information (PI) identified the following areas of needed improvement that may lead to medication errors.

a. In the Dosage and Administration section of the Highlights of Prescribing Information (HPI) and in the Full Prescribing Information (FPI), the route of administration (subcutaneous) and the recommended location for injection (abdomen) is not stated. This information is needed to decrease risk of medication error of wrong route and to ensure the use of the correct administration site.

b. On the container label and carton labeling, the established name (testosterone enanthate) lacks prominence commensurate with the proprietary name (Xyosted).

[a] The proposed proprietary name, Xyosted is being reviewed separately and has not been found to be acceptable at the time of this label and labeling review.

This is required according to 21 CFR 201.10(g)(2) to decrease risk of error in product selection.

c. On the container label and carton labeling, the established name (testosterone enanthate) lacks clarity. Specifically, the established name is not separated from the dosage form (injection) to clearly identify this information.

d. For the professional sample carton labeling, we note that there is no space for a prescriber to affix a label to add the patient name and specific instructions for use. The availability of this information may help reinforce prescriber instructions and minimize the opportunity for medication errors.

e. On the container label and carton labeling, the controlled substance symbol appears in the lower left corner on some panels and is non-existent on others. This placement of the controlled substance symbol is not customary and may result in storing the product among non-controlled products.

f. Section 16 (How Supplied/Storage) of the full PI states that this product should be kept in the carton until use to minimize light exposure. However, this warning is not present on the carton labeling.

We provide recommendations regarding these areas below in Section 4.1 and 4.2 in order to help minimize the potential for medication errors to occur with the use of the product.

4 CONCLUSION

We identified areas on the PI, container label and carton labeling where the presentation of drug-identifying information should be added or increased in prominence in order to help ensure the safe use of the product. We provide recommendations in Sections 4.1 and 4.2 to address our concerns. We advise these recommendations are implemented prior to approval of this product.

4.1 RECOMMENDATIONS FOR THE DIVISION

1. Highlights of Prescribing Information (HPI) and Full Prescribing Information (PI)
   a) The Dosage and Administration section of the HPI and FPI do not specify the intended route of administration (e.g. subcutaneous) or site of administration (e.g. abdomen). The lack of this important information may pose a risk of wrong route error or 'drug administered at inappropriate site' errors. We recommend you include the route of administration (subcutaneous) and recommended location of injection (abdomen) in the dosage and administration sections of the PI. This change is intended to provide completeness and to minimize the risk of 'wrong route' and 'wrong injection site' errors.

4.2 RECOMMENDATIONS FOR ANTARES PHARMA INC.

We recommend the following be implemented prior to approval of this NDA:

A. Container Label and Carton Labeling

1. The established name (testosterone enanthate) lacks prominence commensurate with the proprietary name (Xyosted). We are concerned the lack of prominence may pose risk of medication error of product selection. We recommend you increase the prominence of the established name taking into account all pertinent factors, including typography, layout, contrast, and other printing features in accordance with 21 CFR 201.10(g)(2). In addition, we recommend you revise the established name to be at least half the size of the proprietary name in accordance with 21 CFR 201.10(g)(2).

2. The established name (testosterone enanthate) and dosage form (injection) are not clearly separated from the proprietary name which is not in accordance with the Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (April 2013). We are concerned this lack of separation will decrease the readability and pose risk of medication error of product selection. We recommend you clearly separate the established name from the dosage form by use of parenthesis as follows: "(testosterone enanthate) injection, USP." The presentation may appear in either of the following ways:

   TRADENAME (testosterone enanthate) Injection, USP
   or
   TRADENAME (testosterone enanthate)
   Injection, USP

3. As proposed, the controlled substance symbol is not prominently placed. We are concerned the symbol may be overlooked. This will pose risk of the product being inadvertently stored with non-controlled products. We recommend you locate the controlled symbol on all panels of the container label and carton labeling and next to the proprietary name to increase its prominence and visibility.

4. The How Supplied section of your prescribing information states: "Protect from light (keep in carton until time of use)." However, this warning message does not appear on the carton labeling. Given that light exposure could impact the efficacy of this product, we recommend inclusion of the statement: "Keep in carton until ready to use" to reinforce the storage statement in Section 16 of the Prescribing Information. We recommend you locate this statement on the bottom third of the principal display panel of

the carton labeling. Furthermore, consider bolding the statement or increase the prominence of this statement by other means.

B. Carton Labeling (Professional Sample)

1. Your professional sample carton labeling dos not provide a space for the patients name or specific instructions for use. We are concerned this may pose a risk of vulnerability to medication dosing error (i.e. overdose or underdose). If space allows, consider adding sufficient white space on one of the panels for a prescriber to affix a label to write the patient name and specific instructions. The availability of this information may help reinforce prescriber instructions and minimize the opportunity for medication errors.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Xyosted that Antares Pharma Inc. submitted on December 28, 2016.

Table 2. Relevant Product Information for Xyosted	
Initial Approval Date	N/A
Active Ingredient	Testosterone enanthate
Indication	replacement therapy for adult males with a deficiency or absence of endogenous testosterone
Route of Administration	subcutaneous
Dosage Form	injection
Strength	100 mg/mL, 150 mg/mL, 200 mg/mL
Dose and Frequency	50 mg, 75 mg or 100 mg once weekly up to a maximum of 100 mg once weekly
How Supplied	one carton will contain 4 single-use, auto-injector devices
Storage	20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F). Protect from light (keep in carton until time of use)

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On February 10, 2017, we searched the L: drive and AIMS using the terms, “Xyosted” and “209863” to identify reviews previously performed by DMEPA.

B.2 Results

Our search identified no previous reviews relevant to this review.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[b] along with postmarket medication error data, we reviewed the following Xyosted labels and labeling submitted by Antares Pharma, Inc. on December 20, 2016.

- Container label (Trade)
- Carton labeling (Trade)
- Professional Sample Container Label
- Professional Sample Carton Labeling
- Instructions for Use (no image)
- Medication Guide (no image)

G.2 Label and Labeling Images

Container Label (Trade)

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[b] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

DENISE V BAUGH
05/12/2017

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