CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-774

MEDICAL REVIEW(S)

MEMORANDUM

DATE: August 31, 2005

FROM: Director
Division of Neurology Products/HFD-120

TO: File, NDA 21-774

SUBJECT: Action Memo for NDA 21-774, for the use of Ambien CR (zolpidem tartrate extended-release tablets) in patients with insomnia

Sanofi-Synthelabo Inc. submitted NDA 21-774, for the use of Ambien CR (zolpidem tartrate extended-release tablets) in patients with insomnia on June 8, 2004. Ambien immediate release tablets are currently approved for the treatment of insomnia. The application was submitted to HFD-170, the division responsible at that time for sedative/hypnotic drug products. The application consisted of the results of two randomized controlled trials, each of 2 weeks duration. Study 29, in non-elderly adults, compared the effects of a 12.5 mg dose to placebo; Study 30 compared the effects of a 6.25 mg dose to placebo in elderly adults. HFD-170 issued an Approvable letter on April 8, 2005, informing the sponsor that, "The data in this application are inadequate to establish the efficacy of Ambien CR for the treatment of sleep maintenance insomnia.", and asking the sponsor to perform at least one additional study, "...that supports not only an early treatment effect over a reasonable period during the night, but a reasonable degree of durability of that effect as well.".

Presumably, these conclusions were based on the division's view that Study 29 in non-elderly adults did not adequately demonstrate an effect on sleep maintenance after the first two nights of treatment. This conclusion was based on the fact that the protocol-specified outcome, PSG WASO over hours 0-8 on nights 15 and 16, did not reach statistical significance.

Briefly, the protocol-specified primary outcome in this study was PSG WASO from hours 0-8 on nights 1 and 2. By protocol, if this outcome reached statistical significance on an ANOVA (which it did), the same outcome was to be tested on nights 15 and 16. This comparison, however, failed to reach statistical significance. Further analyses of these data revealed that there were highly significant results at nights 15 and 16 from hours 0-6; based on this observation, the protocol-specified outcome in Study 30 was changed to PSG WASO from hours 0-6. In this second study, this outcome did reach statistical significance on nights 1 and 2, and also at nights 15 and 16.

Further, because the results of the WASO on nights 15 and 16 were not significant in Study 29, the protocol prohibited an examination of other secondary outcomes on these nights, including especially measures of sleep latency.

The sponsor responded to this letter with a submission dated 5/31/05. In this submission, they argue that it is more appropriate to rely on ANCOVA for the WASO measurements (utilizing the baseline value of the measurement in question as the covariate because of baseline differences in these measures; such an analysis was included in the protocol to be utilized if there were baseline imbalances, and the prior record suggests that the Agency actually requested an ANCOVA), and further, that it is also appropriate to rely on the contrasts in Study 29 (in non-elderly adults) on WASO hours 0-6, as was done prospectively for Study 30. In addition, they argue that subjective assessments of sleep were in favor (some reaching statistical significance) of Ambien CR on nights 15 and 16.

Examination of the results reveals a number of findings of interest.

Study 30 is unequivocally "positive" on WASO 0-6 hours on nights 1 and 2 and nights 15 and 16. Examination of WASO hour by hour reveals significant differences in favor of drug on hours 2-6 on nights 1 and 2, and in favor of drug on hours 2-4 on nights 15 and 16. On hour 8 on nights 15 and 16, the direction of the effect reverses. Further, analyses of sleep latency on nights 1 and 2 clearly reached statistical significance, as it did on nights 15 and 16.

In Study 29, although the results of the analyses of PSG WASO over hours 0-8 do not reach significance on nights 15 and 16, the study is clearly "positive" on its primary outcome (WASO over hours 0-8 on nights 1 and 2). Analyses of WASO over hours 0-6 (the primary outcome in Study 30) on nights 15 and 16 is also clearly nominally significant ($p<0.0001$ by ANCOVA; similar results on ANOVA). Examination of WASO hour by hour reveals significant differences favoring drug on hours 1-7 on nights 1 and 2, and for hours 2-5 on nights 15 and 16. On hours 7 and 8, the direction of effect reverses on nights 15 and 16. Further, sleep latency is clearly significant on nights 1 and 2 ($p<0.0001$ by ANCOVA; $p=0.04$ by ANOVA) and nights 15 and 16 ($p=0.034$) by ANCOVA, but only on nights 1 and 2 by ANOVA.

In both studies, differences on subjective measures generally favored drug over placebo both on nights 1 and 2 and nights 15 and 16, although not all statistically significantly (see, for example, Dr. Buenconsejo's statistical review, page 45). Mean change in patients' overall global impression reached significance at all time points in both studies.

COMMENTS

Although HFD-170 issued an Approvable letter for this application, they had concluded that Study 29 did not demonstrate the (persistent) effectiveness of Ambien CR in improving sleep maintenance, and, that, therefore, the sponsor needed to perform an additional trial to demonstrate this effect. I have a different view.

The Agency had agreed that examining PSG WASO from hours 0-6 (in Study 30) was a clinically appropriate measure of Ambien CR's ability to improve sleep maintenance. In this study, there were clearly significant findings on nights 1 and 2 as well as on nights 15 and 16.

A post-hoc analysis of this measure in Study 29 showed a highly nominally statistically significant effect favoring drug on this outcome on nights 15 and 16, with a p-value of <0.0001 (recall that this outcome was already clearly positive on nights 1 and 2). Further, an examination of the hour to hour results out to Hour 5 on nights 15 and 16 (analyses we asked the sponsor to perform) yields highly significant treatment differences favoring drug (p-values typically <0.001). Although we would not typically accept as definitive the results of a post hoc analysis, in this case it seems to me to be reasonable to do so. Although the sponsor presumably chose this duration as primary for Study 30 based on the retrospective examination of the Study 29 data, the Agency's acceptance of this time period as being clinically meaningful was clearly independent of the specific findings. That is, the Agency **agreed to accept** hours 0-6 as a clinically meaningful period on which to base a conclusion about Ambien CR's effectiveness as a sleep maintenance drug **not** because of any specific results, but based on an **independent** judgement that this had clinical meaning (for example, had retrospective analyses of Study 29 revealed nominal significance only on Hours 0-2, the Agency would not have accepted this as a primary outcome measure for Study 30, because it would not have been clinically appropriate as a measure of sleep maintenance). Once this point is accepted, the question then becomes whether or not the (retrospective) finding on this measure in Study 29 is acceptable.

I believe it is, despite the fact that it is post hoc, primarily because of the robustness of the finding. Specifically, the p-value for the overall Hours 0-6 contrast is highly significant (p<0.001), and the p-values for the hour by hour analyses are of a similar magnitude. I believe that these highly robust results, on a measure independently considered to be meaningful (and which show similarly, though actually somewhat **less**, robust results in Study 30, in which they were prospectively designated and are considered unequivocally "positive"), support the conclusion that Study 29 has demonstrated an effect on sleep maintenance at nights 15 and 16. Further, examination of the record suggests that the Agency required the sponsor to establish an effect on WASO beyond Hour 3; this was shown in both studies out to nights 15 and 16.

It is true that with increasing duration of treatment, the effect seems to diminish, and at the last hour(s) of the night, the effect reverses. Experts consider the panoply of effects seen here to represent what may be called "consolidation" of sleep, in which effects on sleep are essentially "shifted to the left" (that is, patients fall asleep faster and stay asleep better during the night, with a slight "rebound" in the early morning hour(s), giving rise to better sleep quality for most

of the night). In these studies, as a general matter, patients considered the overall effects on sleep to be superior on drug compared to placebo, even on nights 15 and 16.

Dr. John Feeney, Neurology team leader, concludes that the application should not be approved until the observation of the early morning change in the direction of the WASO findings is better understood.

I agree that the genesis of this finding may not be completely understood at this time, and that the finding is of some concern, but I do not believe that this undermines the conclusion that the treatment is useful. Patients clearly considered the treatment useful overall, including out to nights 15 and 16. In addition, patients did not experience early morning "hangover" or cognitive impairment; it is possible that, had the drug's sleep-inducing effects persisted out to hour 8, patients would have been more likely to suffer early morning negative symptoms. The sponsor also performed additional analyses that demonstrated that early morning wakefulness was correlated with improvements in sleep latency and middle of the night sleep, independent of treatment; because drug induced greater improvements than placebo in these latter measures, drug-treated patients had more wakefulness in the early morning compared to placebo patients. In this sense, there appears to be a "trade-off" of drug effects, a trade-off that, in my view, the data suggest was preferable to patients.

Further, the very short duration of the studies is also of some concern (had the development program been initiated today, we would require longer studies; however, there are many areas of drug development in which similarly evolving standards are not imposed on sponsors whose development under older standards has been largely complete at the time of submission of their application). In any event, I believe that the sponsor has demonstrated effectiveness on sleep latency and maintenance in two studies for up to 2 weeks, and that the specific issues discussed above (short duration of the studies, diminishing of the effects over time, and early morning reversal of effect) can, and should, be clearly described in labeling.

For these reasons, I will issue the attached Approval letter, with appended agreed-upon labeling.

Russell Katz, M.D.

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/s/

Russell Katz
9/9/2005 02:12:59 PM
MEDICAL OFFICER

MEMORANDUM

NDA 21-774 Ambien CR (zolpidem tartrate extended-release tablets)

FROM: John Feeney, M.D.
Neurology Team Leader

SUBJECT: Response to Approvable Letter; July 6, 2005

DATE: August 31, 2005

On April 8, 2005, an Approvable Letter was sent to the sponsor for Ambien CR for the treatment of insomnia. The letter was sent by the Division of Anesthetic and Critical Care Drug Products; subsequently responsibility for the sedative/hypnotic drug group was transferred to the Division of Neurology Products. In the Approvable Letter, the sponsor was asked to perform another clinical study to demonstrate "...not only an early treatment effect (on sleep maintenance) over a reasonable period during the night, but a reasonable degree of durability of that effect as well."

In support of the original application, the sponsor had performed 2 clinical studies. The first included non-elderly adult patients with chronic insomnia. The protocol-specified primary outcome was wake-time after sleep onset (WASO) from 0-8 hours on nights 1,2 post-randomization. Using a stepdown approach, if the outcome at nights 1,2 was statistically significant, the same outcome was to be assessed at nights 15,16.

The WASO 0-8 hours was statistically significant at nights 1,2. However, it was not statistically significant at nights 15,16.

As a post hoc analysis, the sponsor investigated the WASO from 0-6 hours and found the result nominally significant at nights 1,2 and at nights 15,16.

The second clinical study included elderly adult patients with chronic insomnia. Based on the outcome from the non-elderly study described above, the sponsor prospectively defined the primary outcome to be WASO 0-6 hours in this study. Again the timing of the primary outcome assessment was to be nights 1,2. Using a stepdown procedure, if the outcome at nights 1,2 was statistically significant, the same outcome would be assessed at nights 15,16.

The WASO 0-6 hours was statistically significant at both nights 1,2 and nights 15,16.

Subsequent to the Approvable Letter, there was internal discussion about the clinical relevance of a drug product that might improve sleep maintenance for only the first 6 hours of the night. The quote from the Approvable Letter in the above first paragraph suggests that the agency was willing to consider variable periods of time for assessment of the WASO in support of a sleep maintenance claim ("...over a

reasonable period of time during the night..."). From these discussions, a consensus emerged that a 0-6 hour effect was clinically relevant. Given this evolution of thinking within the agency, the sponsor was informed at a June 28, 2005 meeting that, with agreement on labeling, Ambien CR could be approved without the conduct of an additional clinical trial.

The sponsor submitted labeling on July 6, 2005.

Dr. Elizabeth McNeil reviewed the clinical data from the original NDA and has reviewed the new labeling in the context of recent meetings. I should note that this is the first review that I have written about Ambien CR, having only come to the project in the past two months.

Basis for Approval

A. In her current review, Dr. McNeil concludes that Ambien CR should now be approved based on the results of the 2 clinical trials discussed above. In both trials, she argues, the primary protocol-specified outcome measure was statistically significant. In the first trial, this was the WASO 0-8 hours on nights 1,2. In the second trial, this was the WASO 0-6 hours on nights 1,2. Given the new consensus that a 0-6 hour maintenance effect (the primary outcome in the elderly study) was clinically relevant, she believes Ambien CR should be approved.

Because the nights 15,16 outcome was not a primary outcome in either trial, she does not believe the failure of the WASO at nights 15,16 in the non-elderly study should preclude approval. She believes this finding should be described in labeling.

[While not clearly reflected in the previous record for this application, I believe that a failure on the primary outcome at nights 15,16 for a treatment for chronic insomnia would be viewed by others involved in the review of sedative/hypnotics as a critical flaw that should prevent approval.]

B. There is a view of this application different from Dr.McNeil's view and, again, it is one not clearly reflected in the previous record. In my discussions with others who attended recent meetings about this application, I believe the sentiment arose that, once agreement was reached that a 0-6 hour maintenance effect was clinically relevant, it was appropriate to abandon the protocol-specified outcome in the first, non-elderly study (the 0-8 hour WASO) in favor of a more-appropriate 0-6 hour WASO. At first glance, this seems like a reasonable evolution of thinking about this application. While unusual to look at post hoc outcomes, there is agency precedent for doing this when the originally stated primary outcome was viewed as less relevant or less appropriate.

If the 0-6 hour WASO is adopted as the outcome of interest in the non-elderly study, the outcome is statistically significant both at nights 1,2 and nights 15,16. This essentially reproduces the finding on the 0-6 hour WASO in the elderly study at nights 1,2 and

nights 15,16. It is with this body of evidence that the sponsor was told at the June 28, 2005 meeting with the agency that the application could be approved once labeling was negotiated.

C. I believe the review team has identified a stumbling block with this last approach. In their first-cycle reviews, Dr.McNeil and Dr.Joan Buenconsejo, the statistician, discuss the WASO results for each hour of the night. Reproducibly in both studies, wake time is greater for patients treated with Ambien CR in hours 7 and 8 of nights 15,16. The margin of difference is not trivial and approaches the best effect in favor of drug seen at earlier hours in the night.

I do not think that I have a complete enough understanding of the phenomenon at this point in time to recommend an approval action. The traditional teaching is that most people require 8 hours of sleep per night. The pattern of the data in the 2 controlled trials in this NDA suggest that Ambien CR **re-distributes** WASO to the last 2 hours of an 8 hour night. Such a **consolidation** of sleep toward the beginning of the night seems to represent a phenomenon beyond a simple sleep maintenance claim. This phenomenon has not been fully characterized. In particular, given the emergence of this paradoxical effect after 2 weeks of treatment, one has to wonder what will happen after longer periods of treatment.

Miscellaneous Labeling Issue/Pregnancy Category

During the review of the original NDA for Ambien CR, the pharm/tox reviewers considered the pregnancy category for Ambien. Although, previous reviews of the data had resulted in a Category – in labeling, reconsideration resulted in the recommendation that a Category C be implemented. Although not directly discussed in the Approvable Letter, the draft labeling that accompanied the letter included this change. The Supervisory Pharm/Tox Memo in DFS from the first-cycle review period explains in detail the rationale for the change.

In the response to the approvable letter, the sponsor changed the category back to – without further discussion. I contacted the sponsor by phone and explained the background for the recommended change, based on the available Pharm/Tox review. The sponsor has subsequently agreed to the change.

Recommendation

I recommend that an Approval Action be postponed pending further discussion of the above issues. A simple claim for sleep maintenance may be misleading to patients and prescribers given the pattern of WASO data observed in these 2 trials after 2 weeks.

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/s/

John Feeney
8/31/2005 06:01:33 PM
MEDICAL OFFICER

CLINICAL REVIEW

Application Type	NDA 21-774
Submission Number	014
Submission Code	AZ
Letter Date	July 6 2005
Stamp Date	July 6 2005
PDUFA Goal Date	September 6 2005
Reviewer Name	D. Elizabeth McNeil
Review Completion Date	August 09 2005
Established Name	zolpidem tartrate
(Proposed) Trade Name	Ambien CR
Therapeutic Class	sedative/hypnotic
Applicant	sanofi-synthelabo
Priority Designation	S
Formulation	controlled release tablets
Dosing Regimen	Once daily before bed
Indication	Insomnia
Intended Population	Adults

Table of Contents

1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

I recommend an approval action.

The proposed labeling should be revised to add information on morning somnolence and detail the findings from the clinical trials. The pregnancy category rating should be modified from – to C in light of the preclinical data available for zolpidem tartrate. The indication for use should be modified to make it consistent with other recently approved hypnotics. Final labeling will be negotiated with the sponsor.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

No risk management activity is recommended.

1.2.2 Required Phase 4 Commitments

The sponsor will be required, as per PREA, to perform safety and efficacy studies of Ambien CR in the pediatric population.

1.2.3 Other Phase 4 Requests

There are no Phase 4 requests.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Zolpidem tartrate is an imidazopyridine class hypnotic with an affinity for the benzodiazepine (BZ_1) receptor of $GABA_A$. It is currently marketed as an immediate release formulation under the trade name Ambien (NDA 19-908) by Sanofi-synthelabo.

Sanofi-synthelabo now proposes to market a modified release preparation of zolpidem as Ambien CR. The sponsor has developed a bilayer formulation which is intended to produce an immediate as well as a sustained release of zolpidem. This formulation is meant to maintain the same elimination half-life as the immediate release formulation but give slightly higher plasma concentrations during the middle of the night in order to improve sleep maintenance. The sponsor tried to preserve the elimination half-life from the immediate release formulation in order to try to prevent next-day residual effects.

The sponsor has developed a 12.5 mg tablet for use in adults and a 6.25 mg tablet for use in the elderly.

The sponsor proposes that this product, Ambien CR, be used for the — treatment of chronic insomnia, recommending one tablet be taken at bedtime. This medication is for use in the adult population, including the elderly. It has not been studied in pediatric patients.

2.2 Currently Available Treatment for Indication

Currently there are four FDA approved products indicated for the short-term treatment of chronic insomnia: Halcion (triazolam); Prosom (estazolam); Ambien (zolpidem); Sonata (zaleplon).

Lunesta (eszopiclone) and Rozerem (ramelteon) are approved for the treatment of chronic insomnia. The indication sections of their respective labels do not limit them to short term use.

A number of other products are used off-label to treat chronic insomnia e.g. tricyclic antidepressants, anxiolytics, and antihistamines.

2.3 Availability of Proposed Active Ingredient in the United States

Zolpidem tartrate is currently being marketed by Sanofi-synthelabo as Ambien. There have been no major safety concerns or labeling changes for this product.

2.5 Presubmission Regulatory Activity

On April 8 2005, the Agency took an 'approvable' action on the Ambien CR application.

On May 10 2005, the Agency met with the applicant to discuss the approvable letter and clarify the requirements for the application to progress.

On June 28 2005, the applicant and the Agency met to discuss the planned complete response to the approvable letter. At that meeting, the Agency agreed to accept the two previously submitted studies in support of a sleep maintenance indication, with sleep onset as a key secondary endpoint. It was agreed that the complete response would consist of labeling informed by the labeling changes which had been previously suggested as part of the approvable letter dated April 8 2005.

This current submission is a labeling supplement without new clinical data.

2.6 Other Relevant Background Information

When I reviewed the original submission for this product, I recommended an approvable action for this product. The sponsor has made the case that they upheld the letter, if not the spirit, of the original development plan. The primary endpoint in both studies was a decrease in WASO on nights 1 and 2, i.e. objective demonstration of an immediate effect. This criterion was met in both studies submitted so the demonstration of efficacy has been replicated; therefore an approval may be granted.

As I stated originally, I concur that this product has a hypnotic effect and therefore may appropriately be used in the treatment of insomnia. Hypnotic benefits were clearly demonstrated in both studies on nights 1 and 2. The data from nights 15 and 16 were not as convincing. Since we do not have any measure of drug effectiveness at days 7/8, it is fair to say that there are immediate effects on sleep maintenance and latency to persistent sleep though persistence of that effect for 2 weeks has not been clearly demonstrated and the point at which the benefit begins to decline cannot be identified. There are some people who would benefit from the use of Ambien CR, since the immediate increase in sleep maintenance benefit may be expected to last up to 6 (elderly) or 7 hours (adults). The clinical utility of this product when used for a 2 week period is uncertain since the sleep maintenance benefit, after a fortnight of use, decreases to 4 (elderly) or 5 hours (adults).

Since we realize that insomnia may be a chronic condition, it would have been good to have hypnotics demonstrate long-term efficacy but that may be a matter for future hypnotic development plans. In the label for this product, we can assure that the duration of benefit, a key component of a product intended for sleep maintenance, is clearly stated. As other products for sleep maintenance are developed, we shall attempt to make certain that the expected duration of benefit is clearly stated in those labels as well.

6 INTEGRATED REVIEW OF EFFICACY

No Integrated Review of Efficacy is needed as this supplement provides new labeling without additional clinical data beyond what was submitted to the original NDA.

7 INTEGRATED REVIEW OF SAFETY

No Integrated Review of Safety is needed as this supplement provides new labeling without additional clinical data beyond what was submitted to the original NDA.

9 OVERALL ASSESSMENT

9.1 Conclusions

The applicant has submitted labeling for their new product, Ambien CR.

This labeling is submitted as a complete response to the approvable letter that was sent from the Agency on April 8 2005. There is no new clinical data provided with this submission. The support for the labeling claims was previously submitted as part of the original NDA.

The wording in the indication should be modified for clarity and consistency. I would agree that the [redacted] may be removed from this section though the [redacted] should stand.

The clinical trials section should provide details on the findings from the two studies conducted and I have modified the proposed language so that the details will be provided.

The pregnancy rating should be changed from [redacted] C in light of the available data from animal studies.

9.2 Recommendation on Regulatory Action

This reviewer recommends an "approval" action be taken on this submission.

9.3 Recommendation on Postmarketing Actions

No postmarketing actions are recommended.

9.4 Labeling Review

I have provided general comments on the proposed labeling in this section. A line-by-line review, informed by the Agency's comments in the approvable letter for this NDA issued on 8 April 2005, may be found in the Appendix, with my additions to the text underlined.

Description:
I made no changes to the proposed text.

Clinical Pharmacology

Reviewer's note:
While I made no changes to the proposed text, a pharmacokinetics consult was requested to review the figure and accompanying text in this section.

Controlled trials supporting safety and efficacy:
The sponsor proposed the following language:
Adult outpatients (18-64 years) with primary insomnia (N=212) were evaluated in a double-blind, randomized, parallel-group, 3-week trial comparing Ambien CR 12.5 mg and placebo. Ambien CR was superior to placebo on objective measures (polysomnography recordings) of sleep induction (by decreasing latency to persistent sleep [LPS]) , during the first two nights and after two weeks of treatment. Ambien CR 12.5 mg was shown to be superior to placebo on the patient's global impression regarding the aid to sleep

Elderly outpatients (≥ 65 years) with primary insomnia (N=205) were evaluated in a double-blind, randomized, parallel-group, 3-week trial comparing Ambien CR 6.25 mg and placebo. Ambien CR was superior to placebo on objective measures (polysomnography recordings) of sleep induction (by decreasing LPS) during the first two nights and after two weeks of treatment. Ambien CR 6.25 mg was superior to placebo on the patient's global impression regarding the aid to sleep

Reviewer's note:
I modified these two paragraphs to more fully reflect the studies and the study results:

Adult outpatients (18-64 years) with primary insomnia (N=212) were evaluated in a double-blind, randomized, parallel-group, 3-week trial comparing Ambien CR 12.5 mg and placebo.

Ambien CR 12.5 mg was superior to placebo, on objective measures (polysomnography recordings) of sleep induction (by decreasing latency to persistent sleep) during the first 2 nights of treatment. , Ambien CR 12.5 mg was also superior to placebo on the patient's global impression regarding the aid to sleep, after the first two nights and 3 weeks of treatment.

Elderly outpatients (=65 years) with primary insomnia (N=205) were evaluated in a double-blind, randomized, parallel-group, 3-week trial comparing Ambien CR 6.25 mg and placebo.

. Ambien CR 6.25 mg was superior to placebo, on objective measures

(polysomnography recordings) —

— *of sleep induction (by decreasing latency to persistent sleep) during the first 2 nights of treatment and — two weeks on treatment. Ambien CR 6.25 mg was superior to placebo on the patient's global impression regarding the aid to sleep, after the first 2 nights and — 3 weeks of treatment.* —

Studies pertinent to safety concerns for sedative/hypnotic drugs
In the **Next-day residual effects** section, I have added a sentence reporting the incidence of morning somnolence seen during the placebo-controlled trials.

INDICATIONS AND USAGE
The sponsor proposed the following language: "In controlled sleep laboratory studies, Ambien

Reviewer's comments:
I have modified the language of the indication to make it consistent with the wish to provide clear information without use of the — wording. My suggestion reads "Ambien CR (zolpidem tartrate extended-release tablets) is indicated for the treatment of insomnia characterized by difficulties with sleep onset and/or difficulties with sleep maintenance as measured by wake time after sleep onset."

The sponsor deleted the following language:

Reviewer's note:
This language was deleted from a recently approved hypnotic (Rozerem) by the DAARP Division Director because it was felt to be related to the good practice of medicine and was not necessary as part of labeling. This statement does appear in the labeling for Ambien IR and Sonata. Internal discussion within DNDP led to the decision that this statement should be removed from this section and should be incorporated into the warnings section.

CONTRAINDICATIONS
I made no changes to the proposed text.

WARNINGS
Reviewer's comment:
I added information on the reports of visual and auditory hallucinations.

PRECAUTIONS:
I made no changes to the proposed text.

Drug interactions:
I made no changes to the proposed text.

Carcinogenesis, mutagenesis and impairment of fertility
I made no changes to the proposed text.

Pregnancy
In our AE letter from 8 April 2005, we had recommended that Ambien CR be made a Category C drug based on available animal data. The sponsor has made it a category – drug.

Reviewer's note:
I have modified the label to make it consistent with the recommendation in our AE letter.

ADVERSE REACTIONS
Reviewer's note:
I have changed the table found in the section entitled ***Adverse events observed at an incidence of ≥1% in controlled trials of Ambien CR.*** *The sponsor had grouped the two dosages studies and provided a single comparison to placebo. I disagree.*

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22 Page(s) Withheld

____ § 552(b)(4) Trade Secret / Confidential

____ § 552(b)(5) Deliberative Process

✓ § 552(b)(4) Draft Labeling

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/s/

Dawn McNeil
8/24/2005 05:21:00 PM
MEDICAL OFFICER

John Feeney
8/28/2005 05:55:55 PM
MEDICAL OFFICER
See my cover memo. I would not recommend an approval action at this time.

FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANESTHETIC, CRITICAL CARE, AND ADDICTION DRUG PRODUCTS
HFD-170, Room 9B-45, 5600 Fishers Lane, Rockville MD 20857 Tel:(301)827-7410

DIVISION DIRECTOR REVIEW AND BASIS FOR APPROVABLE ACTION

DATE:	April 8, 2005
DRUG:	Ambien CR (zolpidem tartrate extended-release tablets, 6.25 and 12.5 mg)
NDA:	21-774
NDA Code:	Type 3S NDA
SPONSOR:	Sanofi-Synthelabo, Inc.
INDICATION:	for the — treatment of insomnia

Sanofi-Synthelabo, Inc. has submitted NDA 21-774 in support of marketing approval for their extended-release formulation of Ambien, zolpidem tartrate, in doses of 6.25 and 12.5 mg. Ambien CR is a modified-release formulation of zolpidem tartrate, a non-benzodiazapine hypnotic of the imidazopyridine class. The pharmacologic mechanism of action of zolpidem is believed to be mediated by agonist action at an allosteric binding site associated with the GABA-A receptor complex, by selective binding to the receptors containing alpha-1 subunits.

The sponsor has submitted this application to support the approval of a product that they propose will improve sleep maintenance insomnia, in addition to sleep latency insomnia. An immediate-release formulation of Ambien was approved in 1993, and is currently marketed by Sanofi-Synthelabo, Inc. for the short-term treatment of insomnia. The new formulation consists of coated, bilayer tablets that are intended to produce both immediate and sustained release of zolpidem. The sponsor notes that this formulation releases 60% of the dose within 30 minutes of ingestion and the remaining 40% of the dose over the succeeding 4 hours.

Review of the CMC portion of this application was completed by Danae D. Christodoulou, Ph.D. Adam M. Wasserman, Ph.D. provided a review of the pharmacology/toxicology portions of the product label. R. Daniel Mellon, Ph.D.
provided a supervisory memo regarding the Pregnancy section of the product label. Review of the clinical pharmacology and biopharmaceutics data in the application was completed by David Lee, Ph.D. A statistical review and evaluation was completed by Joan Buenconsejo, Ph.D. Consultation on this application was obtained from the Division of Drug Marketing, Advertisement and Communications (DDMAC), the Office of Drug Safety (ODS), and the Controlled Substances Staff. The sponsor has submitted two studies in support of efficacy. A detailed review of these studies and of the safety of the product was performed by D. Elizabeth McNeil, M.D. Rigoberto Roca, M.D. completed a supervisory review of the application. Dr. McNeil's and Dr. Roca's reviews provide a thorough and detailed evaluation of the efficacy and safety data in the application. I will briefly summarize their findings.

Efficacy:

Studies EFC 4529 (29) and EFC 4530 (30)

These were multi-center, randomized, placebo-controlled, double-blind, parallel-group trials that compared Ambien CR to placebo in subjects with a diagnosis of primary insomnia, based on DSM-IV and polysomnographic (PSG) criteria. The study duration was 25 nights per patient, consisting of a 2-day placebo "run-in," 21 days of double-blind treatment, and a 2-day "run-out." Study 29 enrolled healthy adult (18 to 64 years) subjects. Study 30 enrolled healthy subjects aged 65 years and older. The Ambien CR subjects were treated with 12.5 mg in Study 29 and 6.25 mg in Study 30. The 12.5 mg dose was chosen based on the data from a PK study (Study #4054), which compared 8 different modified-release formulations to the marketed Ambien in 36 adults volunteers.
The 6.25 mg dose was chosen empirically, based on the fact that older patients tolerated one-half of the dose of immediate-release Ambien better than the higher, adult dose.

The primary efficacy variable was defined as the mean change on the PSG measure Wake Time After Sleep Onset (WASO). This endpoint was calculated as the mean of the two treated nights minus the mean of the two screening nights. PSG WASO was calculated based on the first 8 hours of the night in Study 29. A one-way analysis of variance (ANOVA) was used to analyze the mean change on PSG WASO for the immediate effect. If the immediate effect (N1/N2) was significant at the 0.05 level, then another one-way ANOVA was used to analyze the mean change of PSG WASO for the persistence of effect (N15/N16) at the 0.05 significance level. An imbalance at baseline in PSG measurement was observed, and an analysis of covariance (ANCOVA), adjusting for baseline PSG, was added post hoc to the pre-specified analysis. The results of this analysis were consistent with the ANOVA analysis for the primary outcome variable.

The sponsor's analysis demonstrated that, while there was a statistically significant treatment effect for the mean of the first two nights, the effect was small and not statistically significant for the mean of N15 and N16.

Study 29: WASO Results

	No. of patients	Mean of the difference (min:sec)	95% CI	p-value
Nights 1 and 2	212	-19:44	[-30:02;-9:25]	0.0002
Nights 15 and 16	199	-2:40	[-14:14; 8:53]	0.6489

Reproduced from Dr. Roca's review, page 4

An exploratory analysis of the data by hour over the night demonstrated statistically significant treatment effects only up to Hour 7 for N1/N2 and Hour 5 for N15/N16.

Results of the ANCOVA of the comparison of the PSG WASO per hour data, Zolpidem-MR 12.5mg versus Placebo – Study EFC4529 (ITT Population)

	Number of patients	Adjusted mean - Placebo	Adjusted mean - Zolpidem-MR 12.5 mg	Adjusted mean of the difference	Adjusted 95% - Confidence Interval	df	p-value
WASO H1/Nights 1, 2	212	0:01	-0:45	-0:46	[-1:32 ;-0:00]	(1,209)	0.0488 *
WASO H1/Nights 15, 16	199	0:22	-0:20	-0:42	[-1:31 ; 0:08]	(1,196)	0.1002
WASO H2/Nights 1, 2	212	-1:59	-5:42	-3:43	[-5:06 ;-2:20]	(1,209)	<0.0001 *
WASO H2/Nights 15, 16	199	-1:36	-4:51	-3:15	[-4:48 ;-1:41]	(1,196)	<0.0001 *
WASO H3/Nights 1, 2	212	-2:26	-6:34	-4:09	[-5:49 ;-2:29]	(1,209)	<0.0001 *
WASO H3/Nights 15, 16	199	-2:37	-6:46	-4:09	[-5:50 ;-2:27]	(1,195)	<0.0001 *
WASO H4/Nights 1, 2	212	-1:55	-7:46	-5:51	[-7:53 ;-3:49]	(1,208)	<0.0001 *
WASO H4/Nights 15, 16	199	-2:57	-8:08	-5:10	[-7:17 ;-3:04]	(1,196)	<0.0001 *
WASO H5/Nights 1, 2	212	-0:54	-7:26	-6:32	[-9:12 ;-3:51]	(1,209)	<0.0001 *
WASO H5/Nights 15, 16	199	-2:07	-7:12	-5:05	[-7:47 ;-2:23]	(1,196)	0.0003 *
WASO H6/Nights 1, 2	212	-2:35	-6:24	-3:49	[-6:40 ;-0:58]	(1,209)	0.0089 *
WASO H6/Nights 15, 16	199	-3:51	-3:42	0:10	[-2:44 ; 3:03]	(1,195)	0.9132
WASO H7/Nights 1, 2	212	-1:11	-4:07	-2:56	[-5:45 ;-0:08]	(1,209)	0.0405 *
WASO H7/Nights 15, 16	199	-1:56	0:56	2:52	[-0:40 ; 6:24]	(1,196)	0.1103
WASO H8/Nights 1, 2	212	-2:16	-3:50	-1:34	[-5:15 ; 2:08]	(1,209)	0.4054
WASO H8/Nights 15, 16	199	-1:37	2:36	4:14	[-0:16 ; 8:44]	(1,196)	0.0653

-ref=PGM= SLS0075023/EFC4529/CSR/BS/PGM_RPT/t1111psg.sas OUT= OUTPUT/t1111psg_6.gcd (25NOV2003 - 17:09)

*: p<0.05

source: CSR-BDY_EFC4529_EN-E01 Table (11.1.1.2.2)

Based on this finding, the sponsor amended the protocol for Study 30 (with the Division's concurrence) to restrict their analysis to the first 6 hours of the night. The analysis of the primary outcome variable in Study 30 was, otherwise, comparable to the analysis in Study 29.

Study 30: WASO Results

	No. of patients	Mean of the difference (min:sec)	95% CI	p-value
Nights 1 and 2	203	-25:42	[-32:19;-19:05]	<0.0001
Nights 15 and 16	199	-11:27	[-19:14; -3:39]	0.0042

Reproduced from Dr. Roca's review, page 8

The sponsor also looked at the primary outcome variable by hour over the night in Study 30. This analysis failed to find a statistically significant treatment effect beyond Hour 6 for the mean of N1 and N2, and beyond Hour 4 for the mean of N15 and N16.

Results of the ANCOVA of the comparison of the PSG WASO per hour data, Zolpidem-MR 6.25 mg versus Placebo – Study EFC4530 (ITT Population)

Parameter	Time	Number of patients	Adjusted mean - Placebo	Adjusted mean - Zolpidem-MR 6.25 mg	Adjusted mean of the difference	Adjusted 95% - Confidence Interval	df	p-value
WASO H1	Nights 1, 2	203	0:03	-0:37	-0:39	[-1:32 ; 0:13]	(1,200)	0.1434
	Nights 15, 16	199	0:21	-0:13	-0:34	[-1:29 ; 0:20]	(1,196)	0.2148
WASO H2	Nights 1, 2	203	-1:07	-5:30	-4:24	[-5:57 ;-2:50]	(1,200)	<.0001 *
	Nights 15, 16	199	-1:23	-4:01	-2:38	[-4:34 ;-0:42]	(1,196)	0.0080 *
WASO H3	Nights 1, 2	203	-0:35	-6:45	-6:09	[-8:14 ;-4:05]	(1,200)	<.0001 *
	Nights 15, 16	199	-0:38	-4:46	-4:09	[-6:13 ;-2:04]	(1,196)	0.0001 *
WASO H4	Nights 1, 2	203	-2:05	-7:47	-5:42	[-8:06 ;-3:18]	(1,200)	<.0001 *
	Nights 15, 16	199	-2:31	-6:48	-4:17	[-6:45 ;-1:50]	(1,196)	0.0007 *
WASO H5	Nights 1, 2	203	-2:03	-7:08	-5:05	[-7:38 ;-2:32]	(1,200)	0.0001 *
	Nights 15, 16	199	-1:58	-2:00	-0:02	[-3:25 ; 3:20]	(1,196)	0.9815
WASO H6	Nights 1, 2	203	-0:51	-5:16	-4:25	[-7:37 ;-1:13]	(1,200)	0.0070 *
	Nights 15, 16	199	-0:16	-1:08	-0:52	[-4:40 ; 2:56]	(1,196)	0.6547
WASO H7	Nights 1, 2	203	0:12	-0:22	-0:34	[-4:25 ; 3:17]	(1,199)	0.7730
	Nights 15, 16	199	-0:37	0:28	1:05	[-2:26 ; 4:36]	(1,196)	0.5428
WASO H8	Nights 1, 2	203	-0:00	-0:18	-0:17	[-4:02 ; 3:27]	(1,200)	0.8782
	Nights 15, 16	199	-0:32	3:14	3:46	[-0:24 ; 7:56]	(1,196)	0.0758

<ref>PGM= SLS007523:EFC4530:CSR:BS:PGM_RPT:t111psg.sas OUT= OUTPUT:t111psg_4 ged (25NOV2003 - 13:29)

*: p<0.05

source: CSR-BDY_EFC4530_EN-E01 Table (11.1.1.2.2)

Secondary efficacy measures included:

- Sleep efficiency measured by PSG
- Latency to persistent sleep by PSG
- Quality of sleep
- Patient's global impression (PGI) of the treatment as an aid to sleep
- Refreshing quality of sleep

- Subjective WASO
- Subjective Total Sleep Time (TST)
- Subjective Sleep Onset Latency
- Number of awakenings after sleep onset (NAASO) by PSG
- Subjective number of awakenings
- Difficulty in activities due to sleep problems
- WASO per hour
- WASO during intervals during the night (Hours 1-3, Hours 4-6, Hours 7-8)
- PGI of latency to sleep, total sleep time, and the appropriateness of the medication in terms of strength
- Sleep architecture

A statistically significant treatment effect was found for Latency to Persistent Sleep for N1/N2 in both studies, and for N15/N16 only for Study 30. Statistically significant treatment effects were not demonstrated for Subjective Sleep Latency for N15/N16 in either study.

The results for Sleep Efficiency, Subjective WASO, and Subjective TST were consistent with the results for WASO. While statistically significant effects were found for both Quality of Sleep and Refreshing Quality of Sleep for N1/N2, this was not demonstrated for N15/N16. For Patient's Global Impression of the treatment as an aid to sleep, statistically significant treatment effects were found for N1/N2 and for N15/N16. For Difficulty in Activities Due to Sleep Problems, statistically significant treatment effects were not demonstrated for either period. Statistically significant treatment effects were found for NAASO on N1/N2, and for Subjective Number of Awakenings for both periods, but only for NAASO on N15/N16 in Study 29.

Clinical Safety:

The adverse event profile was similar to that seen with immediate-release Ambien. The sponsor did attempt to assess withdrawal effects, rebound effects, and next-day residual effects. Dr. Roca summarizes those evaluations on page 10 of his review:

> Additional evaluations were performed in several of the pharmacokinetic/pharmacodynamic studies to assess for withdrawal effects after abrupt discontinuation, rebound effects, and next-day residual effects. Withdrawal symptoms were reported in a minority of patients after 21 days of use, which tended to be short-lived and perhaps dose-related, since they were less apparent in the elderly subjects (who had received a lower dose). Rebound effects on sleep were also seen on the first night after discontinuation, which were also short-lived. There was a relatively high incidence of morning somnolence reported, but there did not appear to be any next-day residual effects on attention or vigilance.

Biopharmaceutics:

The sponsor submitted clinical pharmacology and biopharmaceutics studies of dose selection, absolute bioavailability, bioavailability relative to Ambien, effect of food, and bioequivalence of the commercial and clinical trial formations. These studies were found to be acceptable, and the data generated from the studies supported the sponsor's dosing choices for the Phase 3 trials.

Nonclinical Safety:

No new nonclinical safety data was submitted. However, upon review of the label, Drs. Wasserman and Mellon determined that this product, and therefore immediate-release Ambien, should have a pregnancy C categorization. It is not clear why immediate-release Ambien was approved with a B categorization. The Segment II reproductive toxicology studies in rabbits documented an increase in post-implantation loss in the high dose dams. This study also noted sedation and weight loss in the dams. However, Dr. Mellon concludes in his supervisory memo:

> I believe that an increase in post-implantation losses alone, regardless of the mechanism of the effect (i.e. directly on the embryo or indirectly through maternal toxicity), should be considered an embryocidal effect.

Chemistry, Manufacturing and Controls:

There were no outstanding concerns from the CMC review team by the end of the review cycle.

Nomenclature:

The trade name, Ambien CR, was cleared for safety concerns by the Division of Medical Errors and Technical Support in ODS, and for promotional concerns by DDMAC. The current established name (zolpidem tartrate extended-release tablets) was cleared by the Labeling and Nomenclature Committee after the sponsor agreed to change it from their original request for zolpidem tartrate — tablets.

Discussion:

Study 30 demonstrates a statistically significant treatment effect on the protocol-specified primary outcome variable, polysomnographically determined WASO at 6 hours. However, this primary endpoint was chosen based on the lack of efficacy noted at the protocol-specified endpoint time of 8 hours in the earlier Study 29. Thus, the sponsor has not provided replicated data to support their contention that Ambien CR will treat not only sleep onset insomnia, but sleep maintenance insomnia as well. It is important to note that the statistically significant treatment effect in Study 29 was not maintained through to the second set of measured time points, Nights 15 and 16.

Additional concern regarding these results has been raised by the sponsor's post hoc analyses of the effects by hour over the night in each of these studies. In Study 29, the treatment effect appeared to persist only until Hour 7 for the first two nights, and until Hour 5 for Nights 15 and 16. In the older subjects in Study 30, the treatment effect appeared to persist only until Hour 6 for the first two nights, and until Hour 4 for Nights 15 and 16. Most patients with primary insomnia have chronic or chronic-intermittent symptoms, and require treatment over more than just a few nights. Without clear evidence of durability of effect, both over the night, and over a reasonably extended treatment period, the product could not purport to be a treatment for sleep maintenance insomnia. These concerns appear to have been confirmed by the sponsor's secondary assessments of patient-reported outcomes (Quality of Sleep, etc.) that demonstrated loss of efficacy by Nights 15 and 16.

Ambien CR's effect on maintaining sleep appears to be limited to 7 hours or less at best, and it has not been clearly established that there is a reasonable degree of durability to that effect over more than the first two days of treatment. Inclusion in the label of any clinical experience that purportedly demonstrates treatment of sleep maintenance insomnia will require that the sponsor submit at least one more adequate and well-controlled study that supports not only an early treatment effect over a reasonable period during the night, but a reasonable degree of durability of that effect as well.

Action: Approvable

Bob A. Rappaport, M.D.
Director
Division of Anesthetic, Critical Care and Addiction Drug Products
Office of Drug Evaluation II, CDER, FDA

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/s/

Bob Rappaport
4/8/05 06:14:20 PM
MEDICAL OFFICER

FDA Center for drug evaluation and research
Division of Anesthetic, Critical Care, and Addiction Drug Products
HFD-170, Room 9B-45, 5600 Fishers Lane, Rockville MD 20857 (301)827-7410

Medical Officer Team Leader Memorandum

Date: April 8, 2005

To: File, NDA 21-774/S00

From: Rigoberto Roca, M.D.
Deputy Director
Division of Anesthetic, Critical Care and Addiction Drug Products

Re: NDA 21-774
Ambien CR® (zolpidem tartrate controlled release tablets)
12 mg and 6.25 mg tablets
Sanofi-Synthelabo

Background

Ambien CR[1] is a modified release formulation of zolpidem tartrate, a non-benzodiazepine hypnotic of the imidazopyridine class. The pharmacological effect of zolpidem is believed to be mediated by agonist action at an allosteric binding site associated with the GABA-A receptor complex, selectively binding to the receptors containing alpha-1 subunits.

An immediate-release formulation of zolpidem was approved in 1993, and is currently marketed by Sanofi-Synthelabo under the trade name Ambien ® (NDA 19-908) for the short-treatment of insomnia. The language in the Indications section of the label also adds the following : "Ambien has been shown to decrease sleep latency and increase the duration of sleep for up to 35 days in controlled clinical studies (see Clinical Pharmacology:Controlled trials supporting safety and efficacy). Hypnotics should generally be limited to 7 to 10 days of use, and reevaluation of the patient is recommended if they are to be taken for more than 2 to 3 weeks. Ambien should not be prescribed in quantities exceeding a 1-month supply (see Warnings)."

The new formulation consists of coated bilayer tablets intended to produce an immediate and a sustained release of zolpidem, specifically 60% of the dose within 30 minutes of

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[1] Also referred to as zolpidem MR in this memorandum.

ingestion, and the remaining 40% over the succeeding 4 hours. The applicant conducted a phase 1 study to evaluate the pharmacokinetic and pharmacodynamic effects of 8 different formulations (varying combinations of immediate release and delayed release components). The applicant's goal was to identify a formulation that would achieve comparable initial plasma concentrations as the currently marketed immediate release formulation, maintain plasma concentrations during the middle of the night, and have low potential for next-day residual effects.

The proposed formulation, identified as "formulation E" by the applicant, contains 12.5 mg total dose of zolpidem; 7.5 mg to be released within the first 30 minutes, and the remaining 5 mg released after the first 30 minutes and before the first 4 hours.

Regulatory History
An End-of-Phase 2 meeting was held in January 2002, at which time several key issues were discussed with the sponsor, including:

- The number of phase III studies that would be sufficient;
- The patient population;
- The proposed primary endpoint;
- The potential role of secondary endpoints to support additional claims;
- The data required to support additional labeling claims —
- The type of safety data that would be required;
- The recommendation from the CSS staff for classification of the product as a Schedule IV controlled substance.

Additional communications occurred with the applicant during October 2002, September 2003, October 2003, and December 2003, addressing additional questions about data required for certain types of labeling claims, the statistical analysis plan, the SAS code to be used for the ANCOVA model for one of the studies, and technical aspects of the NDA submission. No face-to-face pre-NDA meeting was held.

It is noteworthy that the September 2003 communications from the Agency were in response to a submission to the applicant's related IND (IND 25,361/Serial #238), asking for concurrence on a modification to the proposed primary endpoint and primary analysis. Specifically, preliminary analysis of Study EFC 4529 had shown increased variability during the last part of the night (hours 7 and 8), and subsequently the applicant proposed to restrict their analysis to the first 6 hours of the night. The applicant proposed to incorporate the new primary analysis into the other pivotal study (Study EFC 4530). The Agency's response was to note that although it was acceptable to use the first 6 hours of sleep instead of 8 hours, a labeling claim —
would not be obtainable with data which covered only the initial 6 hours.

Clinical Studies
The applicant's pivotal studies in support of this application consisted of two phase III studies: Study EFC 4529 in adult patients, and Study EFC 4530 in elderly patients. Additional clinical data were submitted in the form eight PK/PD studies in healthy

volunteers (two of these studies were in healthy elderly volunteers). Study EFC 4529 used 12.5 mg of the modified formulation of zolpidem as the study dose in the adult patients, and Study EFC 4530 used 6.25 mg of the modified formulation as the study dose in the elderly patients.

Study EFC 4529: Comparison of efficacy and safety of zolpidem-MR 12.5 mg and placebo in patients with primary insomnia. A double-blind, randomized, placebo-controlled, parallel group study.

This was an international study involving 40 centers (29 in the U.S., 5 in Canada, and 6 in Australia) and 212 patients diagnosed with primary insomnia as per DSM-IV and PSG criteria. The primary objectives of the study were:

- Evaluation of the hypnotic efficacy of a 12.5 mg dose of modified-released zolpidem (zolpidem-MR)compared to placebo, using polysomnography and patient sleep questionnaires
- Evaluation of the residual effects that may be associated with zolpidem-MR as compared with placebo
- Comparison of the effect on sleep, between zolpidem-MR and placebo, following abrupt discontinuation after 21 days of treatment
- Evaluation of the clinical safety and tolerability of zolpidem-MR compared to placebo
- Assessment of the residual plasma concentration of zolpidem

The inclusion and exclusion criteria are detailed in Dr. McNeil's review, and are notable for the following: patients were to be between the ages of 18 and 64, and have primary insomnia for at least one month preceding the study visit with clinically significant distress or impairment in social, occupational, or other important areas of functioning. The primary insomnia was defined as difficulty in initiating sleep, difficulty in maintaining sleep, or non-restorative sleep, and patients had to have at least one hour of wakefulness after sleep onset for at least 3 nights per week over the preceding month.

Several conditions would make a patient ineligible for the study, including the more commonly cited reasons: clinically significant comorbid conditions, pregnancy or lactation, hypersensitivity to zolpidem or its excipients, or participation in other clinical trials in the preceding 2 months. Notable exclusion criteria peculiar to this study were night shift workers, persons who took a nap 3 or more times per week in the preceding month, and sleep disorders due to other etiologies.

The demographics of the study population are summarized in the table below.

	Placebo N = 110 (%)	**Zolpidem-MR 12.5 mg N = 102 (%)**
Gender		
Male	52 (46)	38 (37)
Female	59 (54)	64 (63)
Ethnicity		

	Placebo N = 110 (%)	Zolpidem-MR 12.5 mg N = 102 (%)
White	101 (92)	90 (88)
Black	8 (7)	10 (10)
Asian	0	1 (1)
Other	1 (1)	1 (1)
Age (years)		
Mean (± SD)	45.1 (± 12.5)	43.6 (± 13.5)
Range	18 - 64	18 – 64

Fifty-two patients were excluded from the per-protocol population secondary to not meeting the exclusion/inclusion criteria, or not being compliant with the protocol.

The following polysomnographic sleep parameters were assessed:

1. Wake time after sleep onset (WASO), measured from sleep onset to lights-on
    a. calculated as the number of wake epochs from sleep onset to lights-on divided by two.
2. Latency to persistent sleep (LPS), measured from lights-out to the first epoch of 20 consecutive non-wake epochs (sleep onset)
    a. calculated as the number of epochs from lights-out to the first epoch of 20 consecutive non-wake epochs (sleep onset) divided by two
3. Total sleep time (TST), defined as the duration of REM plus non-REM sleep from lights-out to lights-on
    a. calculated as the number of REM plus non-REM epochs from lights-out to lights-on divided by two
4. Number of awakenings
    a. calculated as the number of times after sleep onset where there is a wake entry on the PSG recording of at least one minute duration or 2 consecutive wake epochs. Pairs of awakenings had to be separated by Stage 2 or Stage 3/4 sleep. Wake entries separated by Stage 1 sleep were considered a single awakening.

The applicant performed a one-way ANOVA comparison of the polysomnographic WASO results from nights 1 and 2 (N1/N2), which demonstrated a significant difference in the means between zolpidem and placebo. However, a similar analysis for the results of nights 15 and 16 failed to demonstrate a significant difference between the means. These results are summarized in the table below:

	No. of patients	Mean of the difference (min:sec)	95% CI	p-value
Nights 1 and 2	212	-19:44	[-30:02;-9:25]	0.0002
Nights 15 and 16	199	-2:40	[-14:14; 8:53]	0.6489

The applicant noted that although the two treatment groups were comparable with respect to the demographic characteristics, they were unbalanced at baseline with respect to the

following PSG parameters: TST, WASO, WASO during hours 1 – 3, and WASO during hours 4 – 6. The applicant performed an ANCOVA analysis which used the baseline PSG parameters in an attempt to account for the heterogeneity, but the results were comparable: a significant decrease was seen in objective WASO for the active group compared to placebo for the first two nights, but the effect was not persistent to nights 15 and 16.

An exploratory ANCOVA analysis of the effect of study drug throughout the night was performed by the applicant on the ITT population. These results of these analyses are summarized in the table below, reproduced from the applicant's submission (p. 62 of *CS_BDY-EFC4529-EN-E01*). The treatment effect appears to persist only until Hour 7 for the first two nights and until Hour 5 on Nights 15 and 16.

placebo - ITT population

	Number of patients	Adjusted mean - Placebo	Adjusted mean - Zolpidem-MR 12.5 mg	Adjusted mean of the difference	Adjusted 95% - Confidence Interval	df	p-value
WASO H1/Nights 1, 2	212	0:01	-0:45	-0:46	[-1:32 ;-0:00]	(1,209)	0.0488 *
WASO H1/Nights 15, 16	199	0:22	-0:20	-0:42	[-1:31 ; 0:08]	(1,196)	0.1002
WASO H2/Nights 1, 2	212	-1:59	-5:42	-3:43	[-5:06 ;-2:20]	(1,209)	<0.0001 *
WASO H2/Nights 15, 16	199	-1:36	-4:51	-3:15	[-4:48 ;-1:41]	(1,196)	<0.0001 *
WASO H3/Nights 1, 2	212	-2:26	-6:34	-4:09	[-5:49 ;-2:29]	(1,209)	<0.0001 *
WASO H3/Nights 15, 16	199	-2:37	-6:46	-4:09	[-5:50 ;-2:27]	(1,195)	<0.0001 *
WASO H4/Nights 1, 2	212	-1:55	-7:46	-5:51	[-7:53 ;-3:49]	(1,208)	<0.0001 *
WASO H4/Nights 15, 16	199	-2:57	-8:08	-5:10	[-7:17 ;-3:04]	(1,196)	<0.0001 *
WASO H5/Nights 1, 2	212	-0:54	-7:26	-6:32	[-9:12 ;-3:51]	(1,209)	<0.0001 *
WASO H5/Nights 15, 16	199	-2:07	-7:12	-5:05	[-7:47 ;-2:23]	(1,196)	0.0003 *
WASO H6/Nights 1, 2	212	-2:35	-6:24	-3:49	[-6:40 ;-0:58]	(1,209)	0.0089 *
WASO H6/Nights 15, 16	199	-3:51	-3:42	0:10	[-2:44 ; 3:03]	(1,195)	0.9132
WASO H7/Nights 1, 2	212	-1:11	-4:07	-2:56	[-5:45 ;-0:08]	(1,209)	0.0405 *
WASO H7/Nights 15, 16	199	-1:56	0:56	2:52	[-0:40 ; 6:24]	(1,196)	0.1103
WASO H8/Nights 1, 2	212	-2:16	-3:50	-1:34	[-5:15 ; 2:08]	(1,209)	0.4054
WASO H8/Nights 15, 16	199	-1:37	2:36	4:14	[-0:16 ; 8:44]	(1,196)	0.0653

<ref>PGM= SLS0075023/EFC4529/CSR/BS/PGM_RPT/t1111psg.sas OUT= OUTPUT/t1111psg_6.ged (25NOV2003 - 17:09)

*: p<0.05

Secondary Endpoints

The applicant had several pre-specified secondary endpoints. The following table is a summary of the results of these endpoints, adapted from Dr. McNeil's review.

Endpoint	Result
Sleep efficiency (SE, measured by PSG)	The sponsor's ANOVA analysis showed a statistically significant effect for the active drug on N1/N2 (p=0.0002) but not N15/N16 (p=0.4401). The sponsor's ANCOVA analysis showed an effect on N1/N2, with 13% vs. 5.5% increases in sleep duration (active compared with placebo, p<0.0001). That effect persisted on N15/N16, with 9.4 % vs. 6.4 % increases in sleep duration (active compared with placebo, p<0.0172).
Latency to persistent sleep (LPS, measured by PSG)	The sponsor's ANOVA analysis showed a statistically significant effect for the active drug on N1/N2 (p=0.0411) but not N15/N16 (p=0.2704). The sponsor's ANCOVA analysis showed an effect for the

Endpoint	Result
	active drug on N1/N2, with decreases of 23:48 min vs. 13:30 min (active compared with placebo, p<0.0001). That effect persisted on N15/N16, with decreases of 21:20 min vs. 13:47 min (active compared with placebo, p=0.0338).
Quality of sleep	The sponsor's ANOVA analysis showed an immediate positive effect for the active drug on N1/N2 though this effect was not demonstrated on N15/N16.
Patient's global impression (PGI) item 1 (aid to sleep)	The sponsor's analysis showed an immediate effect on N1/N2 which persisted on N15/N16 when 82% of the active group responded favorably as opposed to 37% of the placebo group.
Refreshing quality of sleep	The sponsor's ANOVA analysis showed an immediate positive effect for the active drug on N1/N2 though not on N15/N16.
Subjective WASO	The sponsor's ANOVA analysis showed a statistically significant effect for the active drug on N1/N2 (p=0.0006) but not N15/N16 (p=0.2427). The sponsor's ANCOVA analysis showed an effect on N1/N2, with decreases of 35:49 min vs. 7:46 min (active compared with placebo, p=0.0006).
Subjective TST	The sponsor's ANOVA analysis showed a statistically significant effect for the active drug on N1/N2 (p<0.0001) but not N15/N16 (p=0.2301). The sponsor's ANCOVA analysis showed an effect on N1/N2, with increases of 67:43 min vs. 27:51 min (active compared with placebo, p<0.0001). That effect persisted on N15/N16, with 9.4 % vs. 6.4 % increases in sleep duration (active compared with placebo, p<0.0172).
Subjective sleep onset latency	The sponsor's ANOVA analysis showed a statistically significant effect for the active drug on N1/N2 (p=0.0024) but not N15/N16 (p=0.1344). The sponsor's ANCOVA analysis showed an effect on N1/N2, with decreases of 29:39 min vs. 11:23 min (active compared with placebo, p=0.0024).
Number of awakenings after sleep onset (NAASO, measured by PSG)	The sponsor's ANOVA analysis showed a statistically significant effect for both N1/N2 and N15/N16. The sponsor's ANCOVA analysis showed an effect on N1/N2, with decreases of 3 vs. 0.9 (active compared with placebo, p<0.0001). That effect persisted on N15/N16, with decreases of 2.7 vs. 0.8 (active compared with placebo, p<0.0001).
Subjective number of awakenings	The sponsor's ANOVA analysis showed a statistically significant effect for active drug on both N1/N2 and N15/N16.

Endpoint	Result
	The sponsor's ANCOVA analysis showed an effect on N1/N2, with decreases of 2.7 vs. 1.0 (active compared with placebo, p=0.0001). That effect persisted on N15/N16, with decreases of 2.2 vs. 1.1 (active compared with placebo, p=0.0298).
Difficulty in activities due to sleep problems	The sponsor's ANOVA analysis did not show a statistically significant effect for active drug on either N1/N2 (p=0.0790) or N15/N16 (p=0.0706).

Study EFC 4530: Comparison of efficacy and safety of zolpidem-MR 6.25 mg and placebo in elderly patients with primary insomnia. A double-blind, randomized, placebo-controlled, parallel group study.

This was also an international study involving 41 centers and 205 patients diagnosed with primary insomnia as per the previously described criteria. Half of the patients came from the United States, as noted in the table below.

Country	No. of Centers	No. of patients enrolled
United States	16	103
Canada	7	49
Germany	6	28
Argentina	5	13
France	4	7
Mexico	2	5

The primary objectives were comparable to Study EFC 4529, with the major difference being that the dose studied was 6.25 mg instead of 12.5 mg. The inclusion/exclusion criteria were also comparable, with the exception of the age group (patients had to be 65 years of age or older), and the lack of pregnancy or lactation as an exclusion criterion.

The demographics of the study population are summarized in the table below.

	Placebo N = 106 (%)	Zolpidem-MR 6.25 mg N = 99 (%)
Gender		
Male	49 (46)	39 (39)
Female	57 (54)	60 (61)
Ethnicity		
White	101 (95)	94 (95)
Black	3 (3)	4 (4)

	Placebo N = 106 (%)	Zolpidem-MR 6.25 mg N = 99 (%)
Asian	2 (2)	1 (1)
Age (years)		
Mean (± SD)	70.1 (± 4.2)	70.3 (± 4.8)
Range	65 – 83	64 – 87

The two treatment groups were balanced at baseline for the subjective sleep parameters, and most of the objective sleep parameters (there was an imbalance in the number of awakenings and in the quality of sleep.

As noted previously, the applicant had requested concurrence to change the primary analysis for this study to restrict their analysis to the first 6 hours of the night (submission Serial #238 to IND 25,361). Otherwise, the primary variables, secondary variables, and analyses were comparable to Study EFC 4529.

The results of the primary analysis, a one-way ANCOVA comparison of the mean difference in the PSG WASO for nights 1 and 2 (N1/N2) and on nights 15 and 16 (N15/N16) demonstrated statistical significance for both timepoints. This is summarized in the table below.

	No. of patients	Mean of the difference (min:sec)	95% CI	p-value
Nights 1 and 2	203	-25:42	[-32:19;-19:05]	<0.0001
Nights 15 and 16	199	-11:27	[-19:14; -3:39]	0.0042

As with Study EFC 4529, the applicant also analyzed the effect of study drug throughout the night. These results of these analyses on the ITT population are summarized in the table below, in a table reproduced from the applicant's submission (p. 57 of *CDS_BDY-EFC4530-EN-E01*). The treatment effect appears to persist only until Hour 6 during the first two nights, and only until Hour 4 for Nights 15 and 16.

Parameter	Time	Number of patients	Adjusted mean - Placebo	Adjusted mean - Zolpidem-MR 6.25 mg	Adjusted mean of the difference	Adjusted 95% - Confidence Interval	df	p-value
WASO H1	Nights 1, 2	203	0:03	-0:37	-0:39	[-1:32 ; 0:13]	(1,200)	0.1434
	Nights 15, 16	199	0:21	-0:13	-0:34	[-1:29 ; 0:20]	(1,196)	0.2148
WASO H2	Nights 1, 2	203	-1:07	-5:30	-4:24	[-5:57 ; -2:50]	(1,200)	<.0001 *
	Nights 15, 16	199	-1:23	-4:01	-2:38	[-4:34 ; -0:42]	(1,196)	0.0080 *
WASO H3	Nights 1, 2	203	-0:35	-6:45	-6:09	[-8:14 ; -4:05]	(1,200)	<.0001 *
	Nights 15, 16	199	-0:38	-4:46	-4:09	[-6:13 ; -2:04]	(1,196)	0.0001 *
WASO H4	Nights 1, 2	203	-2:05	-7:47	-5:42	[-8:06 ; -3:18]	(1,200)	<.0001 *
	Nights 15, 16	199	-2:31	-6:48	-4:17	[-6:45 ; -1:50]	(1,196)	0.0007 *
WASO H5	Nights 1, 2	203	-2:03	-7:08	-5:05	[-7:38 ; -2:32]	(1,200)	0.0001 *
	Nights 15, 16	199	-1:58	-2:00	-0:02	[-3:25 ; 3:20]	(1,196)	0.9815
WASO H6	Nights 1, 2	203	-0:51	-5:16	-4:25	[-7:37 ; -1:13]	(1,200)	0.0070 *
	Nights 15, 16	199	-0:16	-1:08	-0:52	[-4:40 ; 2:56]	(1,196)	0.6547
WASO H7	Nights 1, 2	203	0:12	-0:22	-0:34	[-4:25 ; 3:17]	(1,199)	0.7730
	Nights 15, 16	199	-0:37	0:28	1:05	[-2:26 ; 4:36]	(1,196)	0.5428
WASO H8	Nights 1, 2	203	-0:00	-0:18	-0:17	[-4:02 ; 3:27]	(1,200)	0.8782
	Nights 15, 16	199	-0:32	3:14	3:46	[-0:24 ; 7:56]	(1,196)	0.0758

"ref=PGM= SLS0075023-EFC4530 CSR/BS/PGM_RPT rTTTpsg.sas" OUT= OUTPUT rTTTpsg_4.qcd 25NOV2005 - 13:29:0

*: p<0.05

Secondary Endpoints

As for Study EFC 4529, the applicant had identified several endpoints that were classified as "secondary." The following table is a summary of the results of these endpoints, adapted from Dr. McNeil's review.

Endpoint	Result
Sleep efficiency (SE, measured by PSG)	The sponsor's ANCOVA analysis showed a statistically significant effect for the active drug on N1/N2 ($p<0.0001$) but not N15/N16 ($p=0.4509$).
Latency to persistent sleep (LPS, measured by PSG)	The sponsor's ANCOVA analysis showed an effect for the active drug on N1/N2, with decreases of 17:10 min vs. 6:55 min (active compared with placebo, $p=0.0001$). That effect persisted on N15/N16, with decreases of 14:18 min vs. 8:30 min (active compared with placebo, $p=0.0255$).
Quality of sleep	The treatment groups were not equal for this characteristic at baseline. The sponsor's ANCOVA analysis showed an immediate positive effect for the active drug on N1/N2 though this effect was not demonstrated on N15/N16.
Patient's global impression (PGI) item 1 (aid to sleep)	The sponsor's analysis showed an immediate effect which persisted on N15/N16 when 66% of the active group responded favorably as opposed to 49% of the placebo group.
Refreshing quality of sleep	The sponsor's ANOVA analysis showed an immediate positive effect for the active drug on N1/N2 ($p=0.0014$) though not on N15/N16 ($p=0.1081$).
Subjective WASO	The sponsor's analysis showed a statistically significant effect for the active drug on N1/N2 ($p=0.0101$) but not N15/N16 ($p=0.1620$).
Subjective TST	The sponsor's analysis showed a statistically significant effect for the active drug on N1/N2 ($p=0.0006$) but not N15/N16 ($p=0.2143$).
Subjective sleep onset latency	The sponsor's analysis showed a statistically significant effect for the active drug on N1/N2 ($p=0.0421$) but not N15/N16 ($p=0.8636$).
Number of awakenings after sleep onset (NAASO, measured by PSG)	The sponsor's analysis showed an effect on N1/N2. That effect was not seen on N15/N16.
Subjective number of awakenings	The sponsor's analysis showed a statistically significant effect for active drug on both N1/N2 and N15/N16.
Difficulty in activities due to sleep problems	The sponsor's analysis did not show a statistically significant effect for active drug on either N1/N2 or N15/N16.

Safety

The safety database submitted with the application appears to indicate that the modified formulation of zolpidem has a similar adverse event profile as the immediate release formulation that is currently being marketed. There were more adverse events reported in the zolpidem treatment group than the placebo treatment group, and these were predominantly neuropsychiatric in nature: headache, dizziness, somnolence, and visual disturbance. These were generally mild to moderate in severity and seemed to be dose-related, as would be expected from the clinical experience with the immediate-release formulation.

Additional evaluations were performed in several of the pharmacokinetic/pharmacodynamic studies to assess for withdrawal effects after abrupt discontinuation, rebound effects, and next-day residual effects. Withdrawal symptoms were reported in a minority of patients after 21 days of use, which tended to be short-lived and perhaps dose-related, since they were less apparent in the elderly subjects (who had received a lower dose). Rebound effects on sleep were also seen on the first night after discontinuation, which were also short-lived. There was a relatively high incidence of morning somnolence reported, but there did not appear to be any next-day residual effects on attention or vigilance.

Additional considerations

There are several issues that need to be considered when assessing the approvability of this application. Some are regulatory in nature, and while others revolve around the results of the pivotal trial.

Regulatory

1. Selection of primary analysis for a pivotal study based on post-hoc analysis

In the time period between the End-of-Phase 2 meeting and the submission of the NDA, the applicant requested, and received concurrence, to change the primary endpoint analysis. Although data would still be collected for the original time period, the analysis of the measurement of total WASO would be reduced to the first six hours of the night, rather than the first 8 hours of the night, as originally proposed. The applicant was informed that a labeling claim for [redacted] would not be possible using only 6-hour data.

Although it is generally expected that primary endpoints and analyses are pre-specified for the pivotal trials, that does not necessarily mean that an endpoint or analysis that is identified in the course of post-hoc evaluation is not clinically relevant. It does bring into question, however, whether it will be necessary to require the applicant to perform another trial to replicate the results. It is important to ascertain as best as possible that the results are valid, and not a spurious finding that was secondary to "data mining." However, the ability, and need, to request another study will be dependent on the indication and the patient population being studied, and potentially the strength of the result observed in the initial trial.

2. Maintenance indication
It is apparent from the communications from the applicant that a "maintenance" indication was one of their goals. It also appears that the Agency's previous position regarding a maintenance claim required data over the initial 8 hour time period, for that was felt to represent a clinically significant time period.

At this point in time it is not clear whether that position is an absolutism, i.e., whether a reduction in oWASO over the initial 6 hour time period could also represent a potentially clinically meaningful result, and therefore warrant the claim of "sleep maintenance."

3. Comparable therapies/comparable data requirements
Since the time of zolpidem's initial approval, eszopiclone (Lunesta®) was approved for the treatment of insomnia, specifically stating in the Indications section that when administered at bedtime eszopiclone "...decreased sleep latency and improved sleep maintenance."

Results from Pivotal Trials
1. Consistency of results
Although Study EFC 4529 demonstrated an improvement over 8 hours for nights 1 and 2, it failed to demonstrate a persistent drug effect for nights 15 and 16. When the data were analyzed for the initial 6 hours, Study EFC 4529 maintained its effect for both timepoints, but Study EFC 4530 failed to maintain it for nights 15 and 16.

One of the secondary goals was to decrease sleep latency. Both studies demonstrated an immediate improvement (N1/N2), but only the study in the elderly demonstrated a persistent effect. It is unclear what contributed to these findings, whether it reflected the patient population being studied, the dose being used, or other factors. However, it would be important to address these findings, perhaps in the context of another study.

Recommendations
If the decision is that in order to be clinically significant a drug needs to have an effect over the first 8 hours, then the applicant has failed to demonstrate that their drug is effective. The applicant has successfully demonstrated that it can effectively reduce oWASO for the first hours (what was deemed to be the primary endpoint after consultation with the Agency), which could be argued to represent a clinically meaningful result. However, there is only one trial where this primary endpoint was pre-specified, therefore, the applicant does not have two studies that replicate the results.

Therefore, my recommendation is that the applicant be advised that this application is approvable, pending the submission of another study that replicates the findings from this submission.

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/s/

Rigoberto Roca
4/8/05 06:09:33 PM
MEDICAL OFFICER

CLINICAL REVIEW

Application Type	NDA
Submission Number	000
Submission Code	N
Letter Date	June 08 2004
Stamp Date	June 08 2004
PDUFA Goal Date	April 08 2005
Reviewer Name	D. Elizabeth McNeil, MD
Review Completion Date	March 15 2005
Established Name	zolpidem tartrate controlled release tablets
(Proposed) Trade Name	Ambien CR
Therapeutic Class	Hypnotic
Applicant	sanofi-synthelabo
Priority Designation	S
Formulation	Controlled release tablets
Dosing Regimen	One po QHS
Indication	Insomnia
Intended Population	Adults with primary insomnia

Table of Contents

1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

I recommend an approvable action for this product.

The sponsor proposed the following indication for this product: "Ambien CR is indicated for the [redacted] treatment of insomnia. [redacted]

The sponsor's primary goal was to demonstrate that this controlled release product improved sleep maintenance by decreasing wake time after sleep onset, WASO. While adequately demonstrating an initial improvement over 8 hours on Nights 1/2, the Phase III trial done in adults, EFC 4529, failed to demonstrate a persistent drug effect since by Nights 15/N16, the improvement was no longer statistically significant. When an exploratory analysis was done to evaluate sleep maintenance over the first 6 hours of the night in study EFC 4529, zolpidem-MR was shown to have statistically significant immediate and persistent positive effects on sleep maintenance. The study done in the elderly, EFC 4530, demonstrated an immediate and persistent positive drug effect on sleep maintenance over the 6 hours studied.

One of the sponsor's secondary goals was to demonstrate that this controlled release product decreased sleep latency (LPS). Both studies demonstrated immediate improvement in decreasing sleep latency. The study done in the elderly, EFC 4530, demonstrated a persistent drug effect though this was not seen in the study done in adults, EFC 4529.

An additional secondary goal was to demonstrate that this controlled release product improved sleep duration. Sleep duration reflects the total sleep time. Total sleep time is influenced by both the amount of time that it takes to fall asleep (sleep latency, LPS) and the amount of time that is spent awake after sleep onset (wake time after sleep onset, WASO). While both studies showed improvement in sleep efficiency on nights 1 and 2, only the study in the elderly demonstrated improvement on nights 15 and 16. This result is consistent with the WASO and LPS results described in the preceding two paragraphs. I would argue that it is not an additional benefit and

I can concur that this product has a hypnotic effect and therefore may appropriately be used in the [redacted] treatment of insomnia. The current label for the approved product notes that hypnotics should not be used for more than 7-10 days. Hypnotic benefits were clearly demonstrated in both studies on nights 1 and 2. The data from nights 15 and 16 were not as convincing. Since we do not have any measure of drug effectiveness at days 7/8, it is fair to say that there are immediate effects on sleep maintenance and latency to persistent sleep though

persistence of that effect for 2 weeks has not been clearly demonstrated and the point at which the benefit begins to decline cannot be identified.

While the common feeling is that a good night's sleep ranges from 7-9 hours, I am unable to find a consensus on the minimal amount of sleep that is needed. I would think that formal study would show a great deal of inter-individual variability. There are some people who would benefit from the short-term (7-10 days) use of Ambien CR, since the immediate increase in sleep maintenance benefit may be expected to last up to 6 (elderly) or 7 hours (adults). The clinical utility of this product when used for a 2 week period is uncertain since the sleep maintenance benefit, after a fortnight of use, decreases to 4 (elderly) or 5 hours (adults). —

— in the label would be appropriate.

I am recommending an approvable action for this product based on the policy that sponsors must replicate efficacy findings in adequate and well-controlled trials. The sponsor has not yet met this standard as they failed on the primary endpoint in study EFC4529. It may seem to be a bit stringent to request a second trial in adults using PSG measured WASO over 6 hours as the primary endpoint thereby holding the sponsor to the letter of this regulation when one could point to the data from EFC 4529. I think it is important to honor the spirit of the policy and not accept *posthoc* and/or secondary analyses as primary support for drug approval. Ideally studies should be statistically powered to support the primary endpoint. We would run the risk of accepting results from improperly powered studies by granting approval based upon acceptance of secondary and exploratory endpoints from studies that failed on the primary endpoint, which I feel would set a bad precedent. I would also note that other hypnotic products have been studied for sleep maintenance over eight hours. The fact that this product was studied for six hours reflects past agency thought. The request for a second study using 6 hours of PSG recording is consistent with our previous requirements for the Ambien CR development program though not necessarily reflective of current Agency thinking on trials designed to demonstrate sleep maintenance.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

There is no recommended risk management activity for this product.

1.2.2 Required Phase 4 Commitments

There are no required Phase 4 commitments for this product.

1.2.3 Other Phase 4 Requests

There are no optional or recommended Phase 4 requests for this product

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Zolpidem tartrate is an imidazopyridine class hypnotic currently marketed as an immediate release formulation under the trade name Ambien (NDA 19-908) by Sanofi-synthelabo.

The current NDA is for zolpidem-MR (Ambien CR), a bilayer formulation which is intended to produce immediate as well as sustained release of zolpidem. This formulation is meant to maintain the same elimination half-life as the immediate release formulation but give slightly higher plasma concentrations during the middle of the night to improve sleep maintenance.

The sponsor submitted two Phase III studies, EFC 4529 and EFC 4530, which were double-blind, randomized, placebo-controlled, parallel group studies comparing the efficacy and safety of zolpidem-MR to placebo in patients with primary insomnia. The former study used zolpidem-MR 12.5 mg as the study dose in adult patients. The latter study used zolpidem-MR 6.25 mg as the study dose in elderly patients.

1.3.2 Efficacy

While adequately demonstrating an initial decrease in objectively measured WASO (oWASO) over 8 hours, EFC4529 failed to demonstrate a persistent drug effect since by N15/N16, the decrease in mean total change in oWASO over 8 hours was no longer statistically significant. This study failed to meet the pre-defined primary endpoint when evaluated by the pre-specified ANOVA analysis as well as when evaluated *posthoc* with an ANCOVA analysis. However, when an analysis was done to evaluate sleep maintenance over the first 6 hours of the night in study 4529, zolpidem-MR was shown to have statistically significant immediate and persistent positive effects on decreasing the oWASO.

With Agency concurrence, the sponsor used the mean change oWASO over 6 hours as the primary efficacy endpoint for study EFC 4530. An immediate and persistent positive drug effect was demonstrated.

1.3.3 Safety

The safety profile for zolpidem-MR is almost identical to that of the currently marketed Ambien.

There were no deaths reported during this clinical development program. While there were no serious adverse events (SAE) reported during the Phase I studies, there were two SAE reported during the Phase 3 studies: epigastric tenderness; angina pectoris.

The most frequently reported treatment emergent adverse events (TEAE) during this development program were headache, somnolence, nausea and dizziness. These TEAE were consistent with what is reported in the Ambien label.

No statistically significant next-day residual effects on objective measures or on subjective measures were seen. While a rebound effect was seen on the first night after abrupt drug discontinuation, that effect did not persist and was gone by the second night after drug discontinuation.

1.3.4 Dosing Regimen and Administration

The proposed dose of Ambien-MR is based upon the known pharmacokinetic/pharmacodynamic activity of zolpidem as well as the data from study PDY 4054. Study PDY 4054 was a double-blind, placebo-controlled, 10-way crossover phase I study which compared the pharmacodynamic effects of eight formulations of zolpidem-MR to the currently marketed immediate release form of zolpidem. Formulation E (12.5 mg) was chosen since it reduced the number of awakenings for up to 5 hours post-dose without statistically significant evidence of next-day residual effects. Elderly patients are known, from experience with Ambien, to be sensitive to lower doses of zolpidem. The sponsor decided to use a half-dose (6.25 mg) in the elderly. Oral administration of this product once daily is an appropriate dosing regimen.

1.3.5 Drug-Drug Interactions

The sponsor assessed drug-drug interactions between zolpidem–MR and concomitantly used cytochrome 450 inhibitors during the two Phase 3 studies. While in the adult study, the numbers were too small to assess, in the elderly study there were no significant pharmacodynamic effects seen.

The current Ambien label addresses interactions seen with CNS-active drugs as well as cimetidine, ranitidine, and digoxin. That language would be appropriate for inclusion in the label for this product as well.

1.3.6 Special Populations

Gender
The percentage of adult females (59.4%) who reported adverse events was similar to the percentage reported by adult males (52.6%). The percentage of elderly females (38.3%) who reported adverse events was similar to the percentage reported by elderly males (38.5%).

Age
Overall, the percentage of elderly patients who reported adverse events was lower than the percentage of adult patients who reported adverse events.

Ethnicity
The number of non-Caucasian participants was too small to make any comments on possible interactions of drug and ethnicity.

Although not assessed during this development program, the approved labeling for Ambien notes that this product should be used with caution in patients with compromised respiratory function.

The label also states that no dosage adjustment is needed in patients with renal compromise while patients with hepatic impairment should be given a reduced dose and should be monitored closely.

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ON ORIGINAL

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ON ORIGINAL

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Zolpidem tartrate is an imidazopyridine class hypnotic with an affinity for the benzodiazepine (BZ_1) receptor of $GABA_A$. It is currently marketed as an immediate release formulation under the trade name Ambien (NDA 19-908) by Sanofi-synthelabo.

The current NDA is for a modified release preparation of zolpidem tartrate to be marketed by Sanofi-synthelabo as Ambien CR. The sponsor has developed a bilayer formulation which is intended to produce an immediate as well as a sustained release of zolpidem. This formulation is meant to maintain the same elimination half-life as the immediate release formulation but give slightly higher plasma concentrations during the middle of the night in order to improve sleep maintenance. The sponsor tried to preserve the elimination half-life from the immediate release formulation in order to try to prevent next-day residual effects.

Ambien is currently indicated for "the short-term treatment of insomnia. Ambien has been shown to decrease sleep latency and increase the duration of sleep for up to 35 days in controlled clinical studies."

The sponsor proposes that this product, Ambien CR, be used for the — treatment of chronic insomnia, recommending one tablet be taken at bedtime. This medication is for use in the adult population, including the elderly. It has not been studied in pediatric patients.

2.2 Currently Available Treatment for Indication

Currently there are four FDA approved products indicated for the short-term treatment of chronic insomnia: Halcion (triazolam); Prosom (estazolam); Ambien (zolpidem); Sonata (zaleplon). Lunesta (eszopiclone) is approved for the treatment of chronic insomnia but its indication does not limit it to short term use.

A number of other products are used off-label to treat chronic insomnia e.g. tricyclic antidepressants, anxiolytics, and antihistamines.

2.3 Availability of Proposed Active Ingredient in the United States

Zolpidem tartrate is currently being marketed by Sanofi-synthelabo as Ambien. There have been no major safety concerns or labeling changes for this product.

2.4 Important Issues With Pharmacologically Related Products

There have been no labeling changes in association with the approved hypnotics due to safety or effectiveness concerns. While most of the approved hypnotic products contain language stating that the product is meant for short-term treatment of insomnia, that language was removed from the eszopiclone label on the basis of studies submitted in support of that NDA.

The safety concerns associated with the hypnotics include next-day residual effects as well as neuropsychiatric adverse events such as confusion, amnesia, hallucinations, and worsening of psychiatric disorders, especially when the medications are not taken immediately before bedtime.

The next-day residual effects on attention and vigilance are evaluated during the development plan for drugs in the sedative/hypnotic group. Some sponsors are beginning to develop methods to specifically evaluate next-day driving ability.

The known neuropsychiatric adverse events are predominantly handled through labeling. These labels for these drugs all specify that the drug is to be taken at bedtime. When people do not take the drug immediately before bed, they may experience confusion as well as lacunar amnesia for their actions between ingestion of the pill and actually falling asleep.

Ambien has been reported (http://www.erowid.org/pharms/zolpidem/zolpidem.shtml) to provide the following sensations when used at a time other than right before going to sleep: a transient sense of "social togetherness", loss of inhibition, thinking difficulties, balance difficulties, loss of motor control, amnesia, heightened sense of relaxation, dissociation, distorted depth perception and visual/auditory hallucinations. [*Reviewer's note: These reports are spontaneous accounts of off-label use.]*

2.5 Presubmission Regulatory Activity

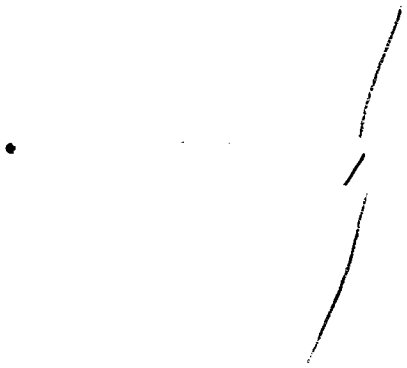
January 31 2002
EOP2 Meeting
(Key points presented below with sponsor's questions followed by FDA response)

1. "Does the Agency agree that the two proposed Phase III studies (EFC 4529 and EFC 4930) with zolpidem-MR, in combination with the extensive human experience of the marketed product [Ambien] will provide substantial evidence for the effectiveness of zolpidem-MR for — treatment of insomnia?"
   - "FDA stated that measuring WASO (wake time after sleep onset) as a primary outcome to support a maintenance claim is appropriate. However, we asked [the sponsor] to do additional analyses to show that the effect on WASO is distributed through the night and not just for the first 3 hours. In essence we were raising the question of what would be the advantage of MR over existing IR if the effect were not persistent throughout the night."
2. "Does the Agency agree that the primary endpoint, the mean change from baseline for WASO, measured by digital polysomnography recordings during the first two nights of

treatment is an accurate measure of sleep maintenance and is appropriate to support the labeling of zolpidem of zolpidem-MR on sleep maintenance?"

- "FDA agree[d] with the sponsor that looking at the first two nights will be acceptable for the primary endpoint , however, FDA noted that the results would also have to be positive at nights 15/16 to support a 2 week claim. "

3. "Given the proven effects of Ambien, does the agency agree that the secondary endpoints



4. "Does the agency agree that the patient population selected for the Phase III studies (patients suffering from primary insomnia with sleep maintenance difficulties) will adequately reflect the use of zolpidem-MR in treating patients with primary insomnia and is appropriate for the desired indication? "
   - "FDA inquired if there is a subpopulation of patients complaining of sleep maintenance only, and the sponsor clarified that the study although requiring a maintenance component will likely include the general population of patients with both latency and maintenance problems."
5. "Does the agency agree that the Phase III trials along with the two clinical pharmacology studies in healthy subjects will support additional labeling

   - "FDA generally agreed that this program should be able to address these issues, however, we noted that information pertinent to will likely not be included in labeling since the clinical significance is unknown. "
6. The agency also agreed to the following:
   - There was no need to assess specific laboratory test or EKG measurements for the proposed trials
   - No long term safety study was needed.
   - The proposed safety database was adequate since the Agency has safety information derived from the original clinical development program as well as post-marketing data.
   - No additional abuse and liability studies were needed as CSS will recommend classification as a Schedule IV controlled substance.

October 10 2002

The Agency held a meeting with the sponsor to discuss the Phase IIIb development plan for this product. The background, as stated in the meeting minutes, for this meeting was Sanofi-synthelabo's wish to make the advertising claim

July 16 2003

The sponsor submitted supplement # 238 to IND 25,361. At the time of this submission, the sponsor wrote that EFC 4529 (the study in adults) had been completed. The final statistical analysis plan (SAP) had been submitted to the Agency and agreed upon prior to locking of the database on April 07 2003.

EFC 4530 (the study in the elderly) was nearing completion with a database lock forecast for early September 2003. "The purpose of this submission [was] to request the Agency's agreement with the expanded SAP for EFC 4530 as provided in attachment 1. The primary endpoint and primary analysis has been prospectively modified from that of the recently completed EFC4529 as described in attachment 2 (text taken from submission cover letter)."

The proposed prospective changes were as follows (text taken from attachment 2 from sN238):

- Modification of primary endpoint

"Based on the available information from EFC 4529, the analysis of WASO per hour in EFC 4529 showed an increased variability during the last part of the night (hours 7 and 8) in comparison to the first 6 hours of the night...Therefore Sanofi-synthelabo proposes to prospectively modify the primary endpoint analysis by restricting the measurement of total WASO during the first 6 hours of the night (instead of 8 hours). This modification is proposed in order to have more stable and consistent estimates and to more accurately reflect the expected hypnotic effect of Zolpidem MR during the first and middle parts of the night. This proposed change in the SAP is still in accordance with the request of the agency to show that the maintenance of sleep persists appropriately beyond the first 3 hours."

- Primary analysis

In the EFC 4529 study, heterogeneity was observed at baseline on the PSG parameters, between the two randomized groups. Consequently, an adjustment to the baseline level was performed to obtain more precise estimates and to take into account this unbalance in the analysis. No significant slope heterogeneity was observed. To be homogenous between the two studies and make the results more comparable, the ANCOVA is proposed to become the

primary analysis for the EFC4530 study. ANCOVA was already planned as the primary analysis in case of heterogeneity at baseline in the original protocol. Therefore in EFC 4530, Sanofi-synthelabo proposes to replace the ANOVA planned as the primary analysis by an ANCOVA taking into account the baseline PSG measurement as covariate. In case of significant slope heterogeneity (significance level =0.1), the ANCOVA will be replaced by an ANOVA for the primary analysis and a subgroup analysis will be performed to illustrate this heterogeneity."

September 23 2003

The sponsor was notified that submission # 238 to IND 25,361 had been reviewed. The Agency, gave the following comments (reproduced verbatim from the text of the email sent to the sponsor):

- We find it acceptable to use the first 6 hours of the night instead of 8 hours, however a labeling claim — would not be attainable using only a 6 hours measuring time.
- We find it acceptable to use baseline PSG values as a covariate in the proposed ANCOVA model
- We note that you intend to use the proc mixed procedure for the ANCOVA model as the primary efficacy analysis. Please provide a detailed description of the mathematical model for the efficacy analyses.
- We ask that you propose a test and its criteria for determining whether or not the normal assumption is met. An alternative statistical method for the primary efficacy analysis should also be proposed in the event that the normal assumption is significantly deviated.
- Please note that analysis of observed cases for nights 15 and 16 will pose difficulty in interpreting the results if missing values become an issue.
- You specified that secondary efficacy parameters will be tested as in the prioritized list, using a step-down procedure stopping as soon as nights 1 and 2 for an endpoint are not statistically significant. However, it is not clear whether or not treatment differences will be tested for Nights 15 and 16 as well. If so the procedure needs to be clarified in the scenario that an endpoint is significant as nights 1 and 2 but not significant at nights 15 and 16.

[*Reviewer's note: I discussed this e-mail communication with Drs. Katz, Andreason, Bastings and Feeney of HFD-120 via telecon on February 24 2005. In September 2003, the Agency regarded sleep latency as the primary variable of clinical interest for this short acting hypnotic. Sleep maintenance was seen as a beneficial drug effect but was not necessary for approval if sleep latency alone was improved. The claim for sleep maintenance could be made if it were demonstrated that WASO was improved when measured for 8 hours. If the duration of action was less than 8-hours,*

September 29 2003

The Agency gave the following statistical comments on submission # 238 (reproduced from the text of the email):

- We are concerned about the interpretation of the efficacy analysis using a mixed model. We recommend that you use ANCOVA for the primary efficacy analysis [for EFC 4530]...the mathematical model provided is not a mixed model.
- We agree that the test of normality is not necessary, provided that the data do not deviate from the normal distribution significantly. In the event of significant deviation from the normal assumption, we would apply non-parametric Wilcoxon method to examine the robustness of the results to ensure the proper interpretation of the results.
- The proposed stopping rule is different from the close testing procedure we normally apply. You could use the standard gate-keeping procedure that stops the testing at the first non-significant result or prove that the type I error is well protected under the current proposed stopping rule.

October 01 2003

The sponsor provided information concerning the SAS code to be used for the ANCOVA model in EFC 4530. The Agency statisticians commented that the mathematical model was acceptable.

November 18 2003

The sponsor sent in a pre-NDA meeting briefing package (sN 250) which contained four questions related to technical aspects of the NDA submission to be answered by the Agency:

1) Does the Division agree with the proposal for the zolpidem-MR package insert to
2) Does the division agree that the organization of the Table of Contents and mapping of the CTD into the electronic submission is acceptable?
3) Does the Division agree that the databases to be provided (as represented in the mock eSub provided with this meeting briefing document) are acceptable and that patient profiles are not necessary?
4) Does the Division agree that the CTD summary is acceptable to satisfy requirements for integrated efficacy and safety summaries?

December 10 2003

The Agency faxed the following responses to the sponsor.

- Response to question 1: the proposal appears acceptable on the surface. Further comments will be based on review of the label in the NDA submission.
- Response to question 2: Module 2 is intended for summary information. In particular section 2.7 is for executive summaries for each section. Module 5.3.5.3 is the appropriate section for what was previously known as the Integrated Summary of Efficacy and the Integrated Summary of Safety.
- Response to question 3: In section 6.2 it is noted that a total of 9 CRFs will be submitted for presenting patients who withdrew due to adverse events. It is also noted that there were no deaths. If there were any serious adverse events, CRFs should be provided for those patients.

An ISS will need to be constructed from all studies involving zolpidem-MR. This information will need to be subsequently integrated with the data from the original zolpidem studies.

- Response to question 4: A CTD summary is not sufficient to satisfy requirements for the ISE and ISS. It is noted that the smaller number of studies contributing to this development plan will result in less material to integrate and fewer groupings for comparison. Note comments on Module 2 and Module 5 in question 3.2.

The sponsor accepted the responses that were given and no face-to-face pre-NDA meeting was held.

2.6 Other Relevant Background Information

There is no other relevant background information for this application.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

A CMC review is being performed by Dr. Danae Christodoulou. The following comments are based upon her preliminary conclusions. The interested reader is referred to her final review for a detailed review of the CMC of this product.

As of February 25, 2005, there were no major problems noted of clinical import. Dr. Christodoulou did note that the proposed

Dr. Dionne Price of the Office of Biostatistics has performed a statistical analysis of the stability data. She found that the — data are within specifications and additionally support extrapolation to 18 months, though not the — expiry period requested by the sponsor.

3.2 Animal Pharmacology/Toxicology

Dr. Adam Wasserman was the pharmacology/toxicology reviewer who reviewed the preclinical data included in the proposed label to make certain that it conformed to the previously approved labeling. There was no new pharmacology/toxicology information submitted with this NDA.

The following material is taken directly from the approved Ambien labeling:

> Zolpidem did not have mutagenic activity in several tests including the Ames test, genotoxicity in mouse lymphoma cells in vitro, chromosomal aberrations in cultured

human lymphocytes, unscheduled DNA synthesis in rat hepatocytes in vitro, and the micronucleus test in mice.

In a rat reproduction study, the high dose (100 mg base/kg) of zolpidem resulted in irregular estrus cycles and prolonged precoital intervals, but there was no effect on male or female fertility after daily oral doses of 4 to 100 mg base/kg or 5 to 130 times the recommended human dose in mg/m^2. No effects on any other fertility parameters were noted.

Dr. Wasserman will provide updated safety margins to reflect the increase in the recommended dose from 10 mg (Ambien) to 12.5 mg (Ambien CR) and add the Segment III reproductive toxicology study results to the label.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The primary source for clinical data was the material submitted by the sponsor in support of this application. Additional data was derived from two sponsor-supplied annual report of adverse events as well as post-marketing data from the AERS database.

4.2 Tables of Clinical Studies

Table1: Clinical studies

	Study population	PK/PD data	Efficacy data	Safety data
ALI 5057	Healthy adults	X		X
BDR 5477	Healthy adults	X		X
BDR 5478	Healthy adults	X		X
GAR 4624	Healthy adults	X		X
PDY 4054	Healthy adults	X		X
PDY 5035	Healthy elderly	X		X
PDY 5036	Healthy adults	X		X
POP 4055	Healthy elderly	X		X
EFC 4529	Adult patients		X	X
EFC 4530	Elderly patients		X	X

4.3 Review Strategy

The sponsor's submission was emphasized in this review, with particular emphasis paid to the two efficacy trials: EFC4529 and EFC4530. All trials were included in the analysis of safety.

I, Dr. D. Elizabeth McNeil, was responsible for the synthesis and documentation of the overall conclusions of this application.

The formal biometrics analyses of the efficacy data were performed by Dr. Joan Buenconsejo, of the Office of Biostatistics.

The analysis of the stability data was performed by Dr. Dionne Price, of the Office of Biostatistics.

Dr. Danae Christodoulou, of the Office of New Drug Chemistry, performed the CMC review.

Dr. David Lee, of the Office of Clinical Pharmacology and Biopharmaceutics, reviewed the pharmacokinetics data.

Dr Adam Wasserman was the pharmacology/toxicology reviewer who reviewed the preclinical data included in the label. There was no new pharmacology/toxicology information submitted with this NDA.

4.4 Data Quality and Integrity

We selected the following sites for inspection:

Study EFC4529

Barbara Harris, PhD	Psypharma Clinical Research Scottsdale AZ

Study EFC4530

Barbara Harris, PhD	Psypharma Clinical Research Scottsdale AZ
Eric Sheldon, MD	Miami Research Associates, Miami FL

The sponsor reported that the screening polysomnogram readings were performed and interpreted at the study site. These screening readings later underwent secondary review at a central reading site.

The polysomnography readings done during the actual trials were performed on site. The raw data was then sent directly to the central reader who tallied the wake/sleep time data prior to sending it to Sanofi for analysis. The PSG efficacy scores were determined by Sanofi's Data Management Group based on the data provided by the central reader. The primary study sites had no further interaction with the data after performing the studies.

DSI obtained the epoch scores from the clinical sites selected for inspection. These scores, which were obtained from the central reader as hard-copy printouts, were compared with the hard copy printouts of mean WASOs reported by Sanofi.

As an additional quality check, the epoch scores, as provided by the central reader, from a small randomly selected subset of patients were requested for tertiary review at the Agency.

4.5 Compliance with Good Clinical Practices

The sponsor reported that 4 patients were omitted from the per protocol population in EFC 4529 as they all came from site center 840127 (United Sleep Medicine LLC where Dr Christopher Phillips was the PI), which was identified as non-compliant to GCP. The Agency's division of scientific investigation (DSI) determined that Mr. Phillips appears to have falsified some of his educational credentials. Additionally, he appears to have performed his studies without appropriate medical supervision. HFD-120 communicated with Dr. Khin of DSI on May 29 2003. Dr Khin reported that a site inspection was conducted and the report was pending. By report, the supervisory IRB was notified and the site was closed.

The other sites appear to have been in compliance with good clinical practices (GCP).

4.6 Financial Disclosures

We obtained financial disclosure information from the principal and sub- investigators for studies EFC 4529 and EFC 4530.

Sanofi-Synthelabo submitted certification of the absence of disclosable interests (form 3454) for the majority of the Principal Investigators and their sub-investigators.

Sanofi-Synthelabo disclosed financial agreements with the following investigators (form 3455):

- Dr. [redacted] Principal investigator) at the [redacted]. She received a research grant for an epidemiological study. Her site enrolled [redacted] 2%) of the randomized patients in study [redacted]
- Dr. [redacted] (Principal investigator) at the [redacted] e received a total of $65,000 (US) for research funding and equipment from 2001-2002. His site enrolled (1%) of the randomized patients in study
- Dr. [redacted] sub-investigator) at [redacted] He serves as part of the speakers [redacted] and as a paid consultant to the sponsor. This site enrolled [redacted] 2%) of the randomized patients in study [redacted] Additionally this site did all of the central PSG readings for both studies.

Reviewer's summary
The submitted financial information is complete.

The payments made to Drs. [redacted] were unlikely to have influenced study outcome. In both instances the data from their sites were consistent with the results from the other sites.

The payments made to Dr. [redacted] were unlikely to have influenced the results of Study [redacted] which failed on its primary endpoint.

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

A pharmacokinetic review is being performed by Dr. David Lee. The interested reader is referred to his final review for a detailed review of the pharmacokinetics of this product. His preliminary conclusions, which were available at the time of my review, concurred with the information found in the currently marketed Ambien.

Zolpidem is metabolized, primarily, by CYP3A and CYP2C9. CYP1A2, 2D6 and 2C19 are other potential contributors to the metabolism of this product.

When a single 12.5 dose was administered to healthy adult males, Ambien CR was found to have the following pharmacokinetic parameters: C_{max} was 134 ng/ml (range: 68.9 to 197 ng/ml) ; T_{max}, 1.5 hours; mean AUC, 740 ng·hr/mL (range: 295 to 1359 ng·hr/mL); mean zolpidem elimination half-life, 2.8 hours (range: 1.62 to 4.05 hr).

When a single 6.25 dose was administered to healthy elderly patients, Ambien CR was found to have the following pharmacokinetic parameters: C_{max} was 70.6 ng/ml (range: 35 to 161 ng/ml) ; T_{max}, 2.0 hours; mean AUC, 413 ng·hr/mL (range: 124 to 1190 ng·hr/mL); mean zolpidem elimination half-life, 2.9 hours (range: 1.59 to 5.50 hrs).

A food effect study revealed that when Ambien was taken with food, the mean AUC was decreased by 23%, the C_{max} was decreased by 30% with an increase in median T_{max} from 2 to 4 hours. The mean half-life was not changed.

In adult and elderly patients who were treated with Ambien CR, zolpidem plasma concentrations were measured on day 1 and day 15 approximately 9 hours post dose. Zolpidem concentrations remained stable. There was no evidence of drug accumulation after up to 15 days of use.

5.2 Pharmacodynamics

A pharmacodynamics review is being performed by Dr. David Lee. The interested reader is referred to his final review for a detailed review of the pharmacodynamics of this product.

Zolpidem, though not a benzodiazepine, shares some of the pharmacological properties of the benzodiazepines. It interacts with the GABA-BZ receptor complex, preferentially binding the (ω1) receptor. This receptor is present in the substantia nigra (pars reticulata), ventral thalamic complex, pons, and globus pallidus, among other places.

5.3 Exposure-Response Relationships

The sponsor performed study PDY 4054, a double-blind, placebo-controlled, 10-way crossover phase I study comparing the pharmacodynamic effects of eight galenic formulations of zolpidem-MR versus the currently marketed immediate release form of zolpidem in healthy adults (n=36).

The primary objective was to evaluate the effect on sleep maintenance using PSG to measure the number of arousals, the total number of arousals during the 8 hours in bed and the total number of arousals during the last four hours. The secondary criteria included psychomotor and cognitive tests, Leeds sleep evaluation questionnaire, wrist actigraphy and PSG variables such as number of awakenings, SOL, sleep continuity, sleep architecture (assessed for the whole night and hourly).

The plasma concentrations (ng/ml) were determined by evaluation of bloods drawn during the training session (baseline) and 8.5 hours post-dose.

The pertinent results are summarized in the following table:

Table 2: Studied formulations with dose and plasma concentration

Formulation	Total dose (mg)	Mean [plasma] with SEM
A	/	19.3 (2.7)
B		24.8 (3.8)
C	12.5	26.6 (4.0)
D	—	28.9 (4.3)
E	12.5	31.0 (4.6)
F	—	43.6 (6.1)
G	12.5	33.7 (4.5)
H	~	39.7 (5.6)
Stilnox[a]	10	23.0 (3.7)
Placebo	0	BLQ

[a]Ambien is marketed as Stilnox in Europe
[b]BLQ=below level of quantification

Formulation E was found to be statistically different from both Stilnox (p=0.01) and placebo (p=0.02) in terms of reducing number of post-dose arousals.

While all formulations reduced the number of awakenings for the first 3 hours post-dosing when compared to placebo, only formulations E, G and H continued to do so by 5 hours post-dose. These three formulations also showed a decrease in the duration of awakenings. When the next-day residual effects were assessed, impairment was evident 8-9 hours after ingestion of Formulations G and H.

Formulation E (12.5 mg) was chosen as the study dose for the Phase III adult trial since it was one of the three formulations that reduced the number of awakenings up to 5 hours post-dose and it was the only one to show no statistically significant evidence of residual effects. Elderly patients are known, from experience with Ambien, to be sensitive to lower doses of zolpidem. The sponsor decided to use a half-dose for the Phase III study in the elderly.

At the EOP2 meeting held with the sponsor on 31 January 2002, the sponsor asked if the agency agreed that the single-dose level of zolpidem-MR proposed for the phase III studies was acceptable based upon the known pharmacokinetic/pharmacodynamic activity of zolpidem as well as well as the data from study PDY 4054. The agency replied that there was no objection to the doses chosen for the two studies (12.5-mg for study EFC 4529 and 6.25-mg for study EFC 4530).

[*Reviewer's note: I note that only three of the formulations studied decreased WASO up to five hours post dosing and one of those was the formulation chosen for Phase III trials. These final results showing that the effect on oWASO was expected to be about 5 hours were not available at the time the Phase III protocols were written. The study was completed on 14 May 2001 but the initial report date was 26 July 2002.*]

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

The sponsor proposes the following indication for this product:
"Ambien CR is indicated for the → reatment of insomnia.

6.1.1 Methods

[*Reviewer's note: The interested reader is referred to the review by Dr. Joan Buenconsejo of the Office of Biostatistics for detailed discussion of the statistical analysis.*]

EFC 4529
The primary efficacy analysis for EFC4529 used the intent to treat (ITT) population which was defined as all patients who were randomized, took at least one dose of double-blind study medication and provided at least one post baseline efficacy notation. The pre-specified primary efficacy variable was the mean change on wake time after sleep onset (WASO) during Hours 1-8. The sponsor planned to use ANOVA to gauge the immediate effect, as seen on Nights 1 and 2 (N1/N2). If the immediate effect result was significant at the 0.05 level, another ANOVA would be done on the observed cases data for Nights 15 and 16 to determine persistence of effect. The sponsor performed an ANOVA analysis of the secondary endpoints, which had been prioritized for analysis in a step-down procedure, with the instruction to stop the analysis as soon as N1/N2 for an endpoint was not statistically significant at the 0.05 level.

The Per-Protocol (PP) population excluded patients from the ITT population who met one of the listed criteria (NB: patients were not limited to a single deviation):

- Positive qualitative drug screen (2 patients, both of whom used benzodiazepines)
- Medication which could have interfered with the study results (9 patients)
- Study site not in compliance with GCP (4 patients)
- Failure to fall within certain sleep parameters on screening (27 patients)
    - Mean PSG WASO on screening night (SN) 1 and SN2 $\geq$ 40 min and
    - No SN with PSG WASO < 30 min and
    - TST between 3 and 7 hours nightly

EFC 4530

The primary efficacy analysis for EFC4530 used the intent to treat (ITT) population which was defined as all patients who were randomized, took at least one dose of double-blind study medication and provided at least one post-baseline efficacy notation. The analysis plan for this study was different from that of EFC 4529, a change made with Agency concurrence. The pre-specified primary efficacy variable was the mean change on WASO during Hours 1-6. The sponsor planned to use ANCOVA including the baseline variables as a covariate. The sponsor planned to gauge the immediate effect, as seen on Nights 1 and 2 (N1/N2). If the immediate effect result was significant at the 0.05 level, another analysis would be done on the observed cases data for Nights 15 and 16 to determine persistence of effect. The secondary endpoints, which had been prioritized in a step-down procedure, were analyzed using a Bonferroni Hommel procedure. The primary endpoint was tested first, if both time points were significant at the 0.05 level or one was significant at the 0.025 level the secondary endpoints would be evaluated in the pre-specified order.

The Per-Protocol (PP) population excluded patients from the ITT population who met one of the listed criteria (NB: patients were not limited to a single deviation):

- Positive drug screen (3 patients: 2 had used opiates, 1 had used amphetamines)
- OTC or sleep medication within 2 weeks or 5 half lives prior to screening (3 patients)
- Substances with properties known to affect sleep/wake within 1 week or 5 half-lives prior to screening (7 patients)
- Medication which could have interfered with the study results (7 patients)
- Poor compliance (2 patients)
- PK abnormalities (3 patients)
- Missing or non-scoreable PSG at baseline or PSG not just after double-blind drug intake (2 patients)
- Failure to fall within certain sleep parameters on screening (5 patients)
    - Mean PSG WASO on screening night (SN) 1 and SN2 $\geq$ 40 min and
    - No SN with PSG WASO < 30 min and
    - TST between 3 and 7 hours nightly

6.1.2 General Discussion of Endpoints

The sponsor used the following definitions for the polysomnographic sleep parameters.

1. Wake time after sleep onset (WASO) was
   - measured from sleep onset to lights-on
   - calculated as the number of wake epochs from sleep onset to lights-on divided by 2
2. Latency to persistent sleep (LPS) was
   - measured from lights-out to the first epoch of 20 consecutive non-wake epochs (sleep onset).
   - calculated as the number of epochs from lights-out to the first epoch of 20 consecutive non-wake epochs (sleep onset) divided by 2
3. Total sleep time (TST) was
   - defined as the duration of REM plus non-REM sleep from lights-out to lights-on.
   - calculated as the number of REM plus non-REM epochs from lights-out to lights-on divided by 2
4. Number of awakenings
   - calculated as the number of times after sleep onset where there is a wake entry on the PSG recording of at least one minute duration or 2 consecutive wake epochs. Pairs of awakenings had to be separated by stage 2 or stage 3/4 sleep. Wake entries separated by stage 1 sleep were considered a single awakening.

The sponsor provided a reasonable rationale for the choice of WASO as the primary efficacy variable to assess sleep maintenance in a chronic insomnia population:

> "The increase of sleep efficiency (SE) and TST is only an indirect measure of sleep maintenance since TST may be increased by a decrease in sleep latency. The two sleep parameters directly measuring sleep maintenance are the number of awakenings and the WASO. The number of awakenings is a parameter more appropriate to transient insomnia where the awakenings are usually short and frequent. WASO is more appropriate to chronic insomnia where the awakenings are fewer but prolonged. Therefore, WASO was selected as an accurate and valid measure of sleep maintenance in patients with primary insomnia. (text taken from p. 30 of the study report for EFC4530)"

[*Reviewer's note: I concur with both the sponsor's rationale and the choice of PSG measured WASO as the primary direct measure of sleep maintenance in the chronic insomniac population.*]

6.1.3 Study Design

Both studies EFC 4529 and EFC 4530 were double-blind, randomized, placebo-controlled, parallel group studies which compared the efficacy and safety of zolpidem-MR to placebo in patients with primary insomnia. The former study used zolpidem-MR 12.5 mg as the study dose in adult patients. The latter study used zolpidem-MR 6.25 mg as the study dose in elderly patients.

The primary efficacy variable for study EFC 4529 was the mean change on polysomnogram (PSG) measured wake after sleep onset (WASO) from Hour 1 to Hour 8. The primary efficacy variable for study EFC 4530 was the mean change on PSG measured WASO from Hour 1 to Hour 6.

In order to determine immediate drug effect, the sponsor calculated the mean of the first two treated nights (N1 and N2) minus the mean of the two screening nights (SN1 and SN2). In order to determine persistence of drug effect-the sponsor calculated the mean of nights (N15 and N16) minus the mean of the two screening nights (SN1 and SN2).

6.1.4 Efficacy Findings

Study EFC4529

[Reviewer's note: The results presented below represent analyses of the ITT population. The results from analyses of the PP population were very similar. Since the latter results do not effect the final conclusions, the analyses of the PP population are not presented here.]

The sponsor did a one-way ANOVA comparison of the PSG WASO results at baseline and found that the mean of the difference was -11:51 min:sec (p-value of 0.0346). When the sponsor performed a one-way ANOVA comparison of the PSG WASO results on N1/N2 to baseline, the mean of the difference was -19:44 min:sec (p-value of 0.0002). When the sponsor performed the same type analysis of the results on N15/N16, the mean of the difference was -2.40 min: sec (p-value of 0.6489).

Table 3: ANOVA results of PSG WASO data

	# of pts	Mean of the difference	95% C.I.	df	p-value
Nights 1,2	212	-19.44	[-30.02; -9.25]	(1,210)	0.0002
Nights 15,16	199	-2.40	[-14.14; 8.53]	(1,197)	0.6489

(modification of study report table 11.1.1.1.3)

The sponsor noted that while the two treatment groups were matched for demographics, the treatment groups were unbalanced at baseline for the following PSG parameters: TST, WASO, WASO H1-H3, WASO H4-H6.

An ANCOVA analysis which used PSG baseline measurement was done by the sponsor in an attempt to account for that heterogeneity.

The sponsor's ANCOVA analysis of the primary endpoint, change in mean total WASO from hour 1-8, showed an immediate effect but that that effect did not persist. A significant decrease in mean total change in oWASO was seen in the active group (-40:25 min) as compared to the placebo group (-14:56 min) on the first two treatment nights (N1 and N2), $p<0.0001$. The study failed to demonstrate a persistent effect since by N15/N16, the decrease in mean total change in

oWASO was no longer statistically significant (-25:23 min vs. -18:17 min for active and placebo respectively, p=0.1913).

Table 4: ANCOVA results of PSG WASO data

	Number of patients	Adjusted mean - Placebo	Adjusted mean - Zolpidem-MR 12.5 mg	Adjusted mean of the difference	Adjusted 95% - Confidence Interval	df	p-value
Nights 1, 2	212	-14:56	-40:25	-25:29	[-34:25 ; -16:33]	(1,209)	<0.0001 *
Nights 15, 16	199	-18:17	-25:23	-7:06	[-17:47 ; 3:35]	(1,196)	0.1913

(study report table 11.1.1.1.4)

The statistical plan included an exploratory analysis of the effect of study drug over different parts of the night. The night was divided into three unequal parts: the first part was comprised of H1+H2+H3; the middle part was comprised of H4+H5+H6; the last part was comprised of H7 +H8. While both groups improved from baseline during the first part of the night, a statistically significant treatment group difference in favor of study drug was seen on N1/N2 and N15/N16 (p<0.0001 in both instances).

Table 5: ANCOVA for the first part of the night H1+H2+H3

	Number of patients	Adjusted mean - Placebo	Adjusted mean - Zolpidem-MR 12.5 mg	Adjusted mean of the difference	Adjusted 95% - Confidence Interval	df	p-value
Nights 1, 2	212	-4:35	-12:48	-8:13	[-10:53 ;-5:32]	(1,209)	<0.0001 *
Nights 15, 16	199	-3:47	-11:42	-7:55	[-10:53 ;-4:57]	(1,196)	<0.0001 *

(study report table 11.1.1.2.1.2)

During the middle part of the night, improvement was noted in both groups with a statistically significant treatment group difference in favor of study drug on N1/N2 (p<0.0001) and N15/N16 (p=0.0016).

Table 6: ANCOVA for the second part of the night H4+H5+H6

	Number of patients	Adjusted mean - Placebo	Adjusted mean - Zolpidem-MR 12.5 mg	Adjusted mean of the difference	Adjusted 95% - Confidence Interval	df	p-value
Nights 1, 2	212	-5:36	-21:16	-15:40	[-21:28 ;-9:53]	(1,209)	<0.0001 *
Nights 15, 16	199	-9:31	-18:57	-9:26	[-15:15 ;-3:37]	(1,196)	0.0016 *

(study report table 11.1.1.2.1.3)

During the last part of the night, both groups improved from baseline but there was no statistical difference demonstrated on N1/N2. On N15/N16, the placebo group improved from baseline while the active group worsened from baseline. The treatment difference reached statistical significance, p=0.0471.

Table 7: ANCOVA for the third part of the night H7+H8

	Number of patients	Adjusted mean - Placebo	Adjusted mean - Zolpidem-MR 12.5 mg	Adjusted Mean of the difference	Adjusted 95% - Confidence Interval	df	p-value
Nights 1, 2	212	-3:29	-7:55	-4:26	[-9:54 : 1:01]	(1,209)	0.1105
Nights 15, 16	199	-3:33	3:33	7:06	[0:05 :14:06]	(1,196)	0.0471 *

(study report table 11.1.1.2.1.4)

Table 8: ANCOVA of the PSG WASO data by hour of study:

Table (11.1.1.2.2) 1 - Results of the ANCOVA of the comparison of the PSG WASO per hour data, zolpidem-MR 12.5 mg versus placebo - ITT population

	Number of patients	Adjusted mean - Placebo	Adjusted mean - Zolpidem-MR 12.5 mg	Adjusted mean of the difference	Adjusted 95% - Confidence Interval	df	p-value
WASO H1/Nights 1, 2	212	0:01	-0:45	-0:46	[-1:32 ;-0:00]	(1,209)	0.0488 *
WASO H1/Nights 15, 16	199	0:22	-0:20	-0:42	[-1:31 ; 0:08]	(1,196)	0.1002
WASO H2/Nights 1, 2	212	-1:59	-5:42	-3:43	[-5:06 ;-2:20]	(1,209)	<0.0001 *
WASO H2/Nights 15, 16	199	-1:36	-4:51	-3:15	[-4:48 ;-1:41]	(1,196)	<0.0001 *
WASO H3/Nights 1, 2	212	-2:26	-6:34	-4:09	[-5:49 ;-2:29]	(1,209)	<0.0001 *
WASO H3/Nights 15, 16	199	-2:37	-6:46	-4:09	[-5:50 ;-2:27]	(1,195)	<0.0001 *
WASO H4/Nights 1, 2	212	-1:55	-7:46	-5:51	[-7:53 ;-3:49]	(1,208)	<0.0001 *
WASO H4/Nights 15, 16	199	-2:57	-8:08	-5:10	[-7:17 ;-3:04]	(1,196)	<0.0001 *
WASO H5/Nights 1, 2	212	-0:54	-7:26	-6:32	[-9:12 ;-3:51]	(1,209)	<0.0001 *
WASO H5/Nights 15, 16	199	-2:07	-7:12	-5:05	[-7:47 ;-2:23]	(1,196)	0.0003 *
WASO H6/Nights 1, 2	212	-2:35	-6:24	-3:49	[-6:40 ;-0:58]	(1,209)	0.0089 *
WASO H6/Nights 15, 16	199	-3:51	-3:42	0:10	[-2:44 ; 3:03]	(1,195)	0.9132
WASO H7/Nights 1, 2	212	-1:11	-4:07	-2:56	[-5:45 ;-0:08]	(1,209)	0.0405 *
WASO H7/Nights 15, 16	199	-1:56	0:56	2:52	[-0:40 ; 6:24]	(1,196)	0.1103
WASO H8/Nights 1, 2	212	-2:16	-3:50	-1:34	[-5:15 ; 2:08]	(1,209)	0.4054
WASO H8/Nights 15, 16	199	-1:37	2:36	4:14	[-0:16 ; 8:44]	(1,196)	0.0653

<ref>PGM= SLS0075023/EFC4529/CSR/BS/PGM_RPT/t1111psg.sas OUT= OUTPUT/t1111psg_6.ged (25NOV2003 - 17:09)

*: p<0.05

(study report table 11.1.1.2.2.1)

EFC 4530

[Reviewer's note: The results presented below represent analyses of the ITT population. The results from analyses of the PP population were very similar. Since the latter results do not effect the final conclusions, the analyses of the PP population are not presented here.]

When the sponsor performed a one-way ANCOVA comparison of the PSG WASO results on N1/N2, and on nights 15/16, the results achieved statistical significance at both timepoints.

Table 9: ANCOVA results of PSG WASO data

	Number of patients	Adjusted mean - Placebo	Adjusted mean - Zolpidem-MR 6.25 mg	Adjusted mean of the difference	Adjusted 95% - Confidence Interval	df	p-value
Nights 1, 2	203	-6:59	-32:41	-25:42	[-32:19 ; -19:05]	(1,200)	<.0001*
Nights 15, 16	199	-6:56	-18:22	-11:27	[-19:14 ;-3:39]	(1,196)	0.0042*

<ref>PGM= SLS0075023/EFC4530/CSR/BS/PGM_RPT/t1111psg.sas OUT= OUTPUT/t1111psg_2.ged (25NOV2003 - 13:28)

(Table 11.1.1.1.2 from the study report)

As in study EFC 4529, the statistical plan included an analysis of the effect of study drug over different parts of the night.

While both groups improved from baseline during the first part of the night, a statistically significant treatment group difference in favor of study drug was seen on N1/N2 and N15/N16 ($p \leq 0.0001$ in both instances).

Table10: ANCOVA for the first part of the night H1+H2+H3

	Number of patients	Adjusted mean - Placebo	Adjusted mean - Zolpidem-MR 6.25 mg	Adjusted mean of the difference	Adjusted 95% - Confidence Interval	df	p-value
Nights 1, 2	203	-1:46	-12:50	-11:04	[-14:20 ;-7:47]	(1,199)	<.0001*
Nights 15, 16	199	-1:40	-8:59	-7:20	[-11:04 ;-3:35]	(1,196)	0.0001*

<ref>PGM= SL80075023/EFC4530/CSR/BS/PGM_RPT/il111psg.sas OUT= OUTPUT/il111psg_14.ged (25NOV2003 - 13:30)
(study report table 11.1.1.2.1.2)

During the middle part of the night, improvement was noted in both groups with a statistically significant treatment group difference in favor of study drug on N1/N2 (p<0.0001) but not on N15/N16 (p=0.2020).

Table 11: ANCOVA for the second part of the night H4+H5+H6

	Number of patients	Adjusted mean - Placebo	Adjusted mean - Zolpidem-MR 6.25 mg	Adjusted mean of the difference	Adjusted 95% - Confidence Interval	df	p-value
Nights 1, 2	203	-5:09	-20:00	-14:51	[-20:25 ;-9:16]	(1,200)	<.0001*
Nights 15, 16	199	-4:57	-9:29	-4:32	[-11:32 ; 2:27]	(1,195)	0.2020

<ref>PGM= SL80075023/EFC4530/CSR/BS/PGM_RPT/il111psg.sas OUT= OUTPUT/il111psg_16.ged (25NOV2003 - 13:30)
(study report table 11.1.1.2.1.3)

During the last part of the night, there were no statistically significant differences demonstrated. On N1/N2, the two groups did not differ (p=0.7147). On N15/N16, the placebo group improved from baseline while the active group worsened from baseline. The treatment difference did not reach statistical significance, p=0.1201.

Table 12: ANCOVA for the third part of the night H7+H8

	Number of patients	Adjusted mean - Placebo	Adjusted mean - Zolpidem-MR 6.25 mg	Adjusted mean of the difference	Adjusted 95% - Confidence Interval	df	p-value
Nights 1, 2	203	0:11	-0:56	-1:07	[-7:09 ; 4:54]	(1,199)	0.7147
Nights 15, 16	199	-1:00	3:32	4:32	[-2:12 ;10:16]	(1,196)	0.1201

<ref>PGM= SL80075023/EFC4530/CSR/BS/PGM_RPT/il111psg.sas OUT= OUTPUT/il111psg_18.ged (25NOV2003 - 13:30)
(study report table 11.1.1.2.1.4)

Table 13: ANCOVA analysis of the PSG WASO data by hour of study

Parameter	Time	Number of patients	Adjusted mean - Placebo	Adjusted mean - Zolpidem-MR 6.25 mg	Adjusted mean of the difference	Adjusted 95% - Confidence Interval	df	p-value
WASO H1	Nights 1, 2	203	0:03	-0:37	-0:39	[-1:32 : 0:13]	(1,200)	0.1434
	Nights 15, 16	199	0:21	-0:13	-0:34	[-1:29 : 0:20]	(1,196)	0.2148
WASO H2	Nights 1, 2	203	-1:07	-5:30	-4:24	[-5:57 ;-2:50]	(1,200)	<.0001 *
	Nights 15, 16	199	-1:23	-4:01	-2:38	[-4:34 ;-0:42]	(1,196)	0.0080 *
WASO H3	Nights 1, 2	203	-0:35	-6:45	-6:09	[-8:14 ;-4:05]	(1,200)	<.0001 *
	Nights 15, 16	199	-0:38	-4:46	-4:09	[-6:13 ;-2:04]	(1,196)	0.0001 *
WASO H4	Nights 1, 2	203	-2:05	-7:47	-5:42	[-8:06 ;-3:18]	(1,200)	<.0001 *
	Nights 15, 16	199	-2:31	-6:48	-4:17	[-6:45 ;-1:50]	(1,196)	0.0007 *
WASO H5	Nights 1, 2	203	-2:03	-7:08	-5:05	[-7:38 ;-2:32]	(1,200)	0.0001 *
	Nights 15, 16	199	-1:58	-2:00	-0:02	[-3:25 : 3:20]	(1,196)	0.9815
WASO H6	Nights 1, 2	203	-0:51	-5:16	-4:25	[-7:37 ;-1:13]	(1,200)	0.0070 *
	Nights 15, 16	199	-0:16	-1:08	-0:52	[-4:40 : 2:56]	(1,196)	0.6547
WASO H7	Nights 1, 2	203	0:12	-0:22	-0:34	[-4:25 : 3:17]	(1,199)	0.7730
	Nights 15, 16	199	-0:37	0:28	1:05	[-2:26 : 4:36]	(1,196)	0.5428
WASO H8	Nights 1, 2	203	-0:09	-0:18	-0:17	[-4:02 : 3:27]	(1,200)	0.8782
	Nights 15, 16	199	-0:32	3:14	3:46	[-0:24 : 7:56]	(1,196)	0.0758

<ref>PGM= SL80075023/EFC4530/CSR/BS/PGM_RPT/il111psg.sas OUT= OUTPUT/il111psg_4.ged (25NOV2003 - 13:29)

[*Reviewer's comment:*
I was interested in determining whether the apparent lack of efficacy in maintaining sleep maintenance over 8 hours might be related to the study population. I asked Dr. Buenconsejo to do an exploratory analysis on the subgroup of patients in each study who could be considered to have difficulty with sleep maintenance but not sleep initiation. We started with the ITT population and separated out those patients who had WASO at screening of ≥ 40 minutes but had sleep latency at screening of 20 minutes or less, i.e. those patients who initiated sleep relatively easily but had problems staying asleep. The number of patients who met this criteria was small in both studies. The findings from this exploratory posthoc analysis are presented in the table below.

The numbers in the study group columns represent the change from baseline in min:sec, therefore a higher number is a better result. The effect shows a consistent numerical difference in favor of zolpidem-MR on nights 1 /2 but the result is only statistically significant in Study 4530. By nights 15/16, there is no longer even a numerical difference in favor of zolpidem-MR except in study EFC 4530. In that instance the difference is not statistically significant.

Table 14: *posthoc* exploratory analysis of subgroup with "pure" sleep maintenance difficulty

Endpoint, Analysis	**Study**	**N**	**Study group**		**p-value**
			Placebo	**Active**	
WASO H1-H8, ANOVA					
	4529				
	Nights 1,2	31	-33:09	-34:53	0.9071
	Nights 15,16	26	-51:27	-2:31	0.0341
WASO H1-H8, ANCOVA					
	4529				
	Nights 1,2	31	-26:09	-40:39	0.2890
	Nights 15,16	26	-43:52	-8:05	0.1040
	4530				
	Nights 1,2	49	-7:38	-31:24	0.0070
	Nights 15,16	48	-15:32	-14:18	0.9063
WASO H1-H6, ANCOVA					
	4529				
	Nights 1,2	31	-19:33	-39:09	0.1197
	Nights 15,16	26	-34:01	-30:34	0.8034
	4530				
	Nights 1,2	49	-13:32	-34:42	0.0070
	Nights 15,16	48	-10:14	-20:25	0.2157

I was also interested in determining whether patients had more frequent awakenings or longer duration of awakening at the end of the trial since either could contribute to a perceived decline in sleep quality.

As may be seen in the table below, in both studies, the number of awakenings appeared to increase only slightly when Nights 15/16 were compared to Nights 1/2 but the time spent awake increased in the group treated with active drug.

Table 15: descriptive summary of WASO/Number of awakenings

Study		Placebo		Active	
		WASO (min:sec)	# awakenings	WASO	# awakenings
EFC 4529					
*measured over 480 minutes	**Nights 1/2**				
	n	110	110	102	102
	Mean (SD)	75:37 (44:56)	9:1 (4.3)	44:02 (30:29)	6:4 (3.7)
	Min				
	Max				
	Nights 15/16				
	n	103	103	96	96
	Mean (SD)	70:50 (44:10)	9:2 (4.4)	57:46 (43:55)	6:6 (3.6)
	Min				
	Max				
EFC 4530					
*measured over 360 minutes	**Nights 1/2**				
	n	104	104	99	99
	Mean (SD)	62:31 (30:41)	11.4 (3.7)	35:23 (26:41)	9.5 (3.6)
	Min				
	Max				
	Nights 15/16				
	n	103	103	96	96
	Mean (SD)	62:45 (31:28)	11.1 (3.7)	41:53 (36:21)	10.8 (4.3)
	Min				
	Max				

(Data taken from EFC 4529 study report tables 11.1.1.1.1 and 15.2.7 and EFC 4530 study report tables 11.1.1.1.1 and 15.2.5)

6.1.5 Clinical Microbiology

This section is not applicable to this new drug application.

6.1.6 Efficacy Conclusions

Comments from the statistical review by Dr. Joan Buenconsejo of the Office of Biostatistics:

- Immediate hypnotic effects (Nights 1/2)
  - Zolpidem-MR 6.25 and 12.5 mg are effective in providing immediate sleep maintenance effects during the first 6 and 8 hours respectively
  - There is strong evidence that zolpidem-MR improved sleep induction (LPS), sleep duration (SE) and quality of sleep during nights 1 and 2

- Persistent hypnotic effects(Nights 15/16)
    - Dr. Buenconsejo performed secondary analyses assessing the efficacy in relation to other sleep variables and concluded that while there is evidence that both Zolpidem 12.5 and 6.25 mg are effective in providing persistent sleep maintenance effects during the first 6 hours, this evidence is not conclusive enough to warrant a claim.
- Next-day residual effects of Ambien MR use (partial review)
    - There was no objective or subjective evidence of next-day residual effects.
- Rebound effects of Ambien MR use (partial review)
    - Rebound effects on WASO, SE and LPS were seen on the first night after abrupt drug discontinuation but not on the second night after discontinuation

Clinical reviewer's comments:
While adequately demonstrating an initial decrease in objectively measured WASO (oWASO) over 8 hours, EFC4529 failed to demonstrate a persistent drug effect since by N15/N16, the decrease in mean total change in oWASO over 8 hours was no longer statistically significant (-25:23 min vs. -18:17 min for active and placebo groups respectively, p=0.1913) even when baseline differences were accounted for using ANCOVA analysis. This study failed to meet the pre-defined primary endpoint when evaluated by the pre-specified ANOVA analysis as well as when evaluated *posthoc* with an ANCOVA analysis. However, when an analysis was done to evaluate sleep maintenance over the first 6 hours of the night in study 4529, zolpidem-MR was shown to have statistically significant immediate and persistent positive effects on decreasing the oWASO. The exploratory hourly WASO analysis shows that the immediate effect on WASO may last up to 7 hours while the persistent effect lasts up until 5 hours.

As agreed upon with the agency, the primary efficacy endpoint for study EFC 4530 was the mean change in objectively measured WASO over 6 hours. An immediate and persistent positive drug effect was demonstrated. The hourly WASO analysis shows that the immediate effect on WASO may last up to 6 hours while the persistent effect lasts up until 4 hours in the elderly.

While it is clear that this product does diminish oWASO for up to 7 hours as an immediate effect in adults and up to 5 hours as a persistent effect in adults, with shorter effect durations in the elderly, it is not clear that this is a benefit that has clinical utility in a group of patients who may be expected to take this medication for a month or longer (off-label). The elderly population represents a large proportion of the persons suffering from chronic insomnia. Our analysis indicates a correlation between more frequent awakenings and the patients' perception of diminished sleep quality. I would note that, in both studies, the number of awakenings appeared to increase only slightly when Nights 15/16 were compared to Nights 1/2 but the time spent awake increased in the group treated with active drug.

While we might speculate that a higher dose might produce a plasma concentration that would support decreased WASO during the last part of the night, the results from study PDY4054 indicate that the — , of zolpidem-MR as represented by formulation H was associated with statistically significant residual effects 8-9 hours after dosing though it did have a positive effect

on WASO for up to 5 hours. This could be an artifact of the formulation since one of the other 12.5 formulations also had statistically significant residual effects 8-9 hours after dosing. The sponsor might be able to reduce the next day residual effects by making alterations in the formulation used for the higher dose and presumably achieving higher plasma concentrations.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

7.1.1 Deaths

There were no deaths during the studies done in support of this application.

7.1.2 Other Serious Adverse Events (SAE)

[*Reviewer's note: The data used for this section consists of the sponsor's narrative summaries, line listings and case report forms. The relevant AE are highlighted with bold font.*]

Study EFC 4529
A 56-year old woman (# 36102002), whose past medical history was significant for angina pectoris, reported **mild abdominal tenderness** 12 days after her first ingestion of zolpidem-MR 12.5 mg. This condition did not remit and she was hospitalized for further evaluation on Study day 23, 2 days after the last ingestion of zolpidem-MR 12.5. Her evaluation revealed a mild antral gastritis which was not felt to be sufficient explanation for her symptoms.

Although the double-blind treatment phase was over, the patient was removed from the study due to the hospitalization during the placebo run-out period. The investigator proposed esophageal or biliary spasm as the cause of her moderate intensity symptoms and excluded a relationship to study drug. While there is not a clear causal connection, it is not possible to completely rule out an association with study drug since abdominal pain and esophageal spasm have been reported in association with Ambien use. Both adverse events are included in the currently approved label.

Study EFC 4530
An 81-year old man (# 840231019), whose past medical history was significant for angina pectoris coronary artery bypass graft, aortic valve disease and hypertension, was hospitalized with severe **angina** on study day 3. He was receiving placebo study medication. During his hospitalization he was found to have atrial fibrillation with a rapid ventricular response. He was treated with dilitazem, digoxin, heparin and glyceryl trinitrite. The investigator excluded a relationship to study drug and the patient completed the study. This adverse event was probably not related to study drug.

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts from studies EFC4529 and EFC 4530[a]

Table 16: Reasons for discontinuation

Reason	Placebo (n=216)	Zolpidem-MR 12.5 mg (n=212)	Zolpidem-MR 6.25 mg (n=99)
Total	13 (6%)	9(4%)	5(5%)
Disease progression /lack of efficacy	1(8%)	0	1 (20%)
Adverse event	2 (15%)	6 (66%)	1 (20%)
Poor compliance	2 (15%)	0	0
Investigator/subject request	5 (38%)	0	3 (60%)
Lost to follow-up	1 (8%)	0	0
Other	2 (15%)	3 (33%)	0

[a]The percentages in the rows other than the total row reflects the percentage of dropouts who discontinued for a given reason

7.1.3.2 Adverse events associated with dropouts from clinical studies

[*Reviewer's note: The relevant AE are highlighted with bold font.*]

Zolpidem 12.5 mg treatment arm

- A 60-year old woman (# 36107008) with a past medical history significant for persistent ophthalmic migraine, breast cancer, osteoarthritis, sinus congestion and sinusitis, began to experience **moderate fatigue** and **mild nausea** 5 days after the first ingestion of zolpidem-MR 12.5 mg. Twelve days later, she had **severe dizziness**. While the nausea and dizziness spontaneously resolved, the fatigue persisted. While there is not a clear causal connection, it is not possible to completely rule out an association with study drug since these symptoms have been reported in association with Ambien use. These adverse events are included in the currently approved label. [Study EFC4529]
- A 46-year old woman (# 124103002) began to experience **severe labyrinthitis** 17 days after the first ingestion of zolpidem-MR 12.5 mg. The symptom did not spontaneously resolve. While there is not a clear causal connection, it is not possible to completely rule out an association with study drug. [Study EFC4529]
- A 47-year old woman (# 840103002) with a past medical history significant for environmental allergies, lower back pain, tinnitus, began to experience **severe depersonalization and somnolence** 4 days after the first ingestion of zolpidem-MR 12.5 mg. The symptoms spontaneously resolved. These adverse events were probably associated with the use of study drug. [Study EFC4529]
- A 28-year old man, (# 840129005) began to experience **moderate somnolence** 8 days after the first ingestion of zolpidem-MR 12.5 mg. His symptom spontaneously resolved

shortly after stopping use of study drug. This adverse event was probably associated with the use of study drug. [Study EFC4529]

- A 51-year old woman (# 840131025) began to experience **severe headache, mild hypoaesthesia, mild hallucinations and mild binge eating** 7 and 8 days after the first ingestion of zolpidem-MR 12.5 mg. Her symptoms spontaneously resolved shortly after stopping use of study drug. These adverse events were probably associated with the use of study drug. [Study EFC4529]
- A 71-year old woman (# 124205010) with a past medical history significant for environmental allergies, lower back pain, tinnitus, began to experience **moderate dizziness and attention disturbance** 12 days after the first ingestion of zolpidem-MR 12.5 mg. The symptoms spontaneously resolved 4 days after she discontinued the study. These adverse events were probably associated with the use of study drug. [Study EFC4530]
- A 23 year old female (# 84100050) had **mild vomiting** two minutes after intake of a single dose of zolpidem, this resolved without corrective action. While there is not a clear causal connection, it is not possible to completely rule out an association with study drug. [Study ALI5057]
- A subject (# 840110013) discontinued due to severe **confusion, fall, ataxia, and somnolence** experienced after the second ingestion of Ambien 12.5 mg. The subject recovered within 24 hours.

Zolpidem at doses other than 6.25mg or 12.5 mg

- A 21 year old male (# 5770007) had **depressed mood** that occurred two day after intake of zolpidem-MR [redacted] (formulation A). While there is not a clear causal connection, it is not possible to completely rule out an association with study drug. [Study PDY4054]
- A 34 year old female (# 5770011) had **agitation, depressed mood, and abnormal thinking** all of which were noted after ingestion of zolpidem-MR 12.5 mg (formulation C). The subject decided to continue the study despite the persistence of these psychiatric adverse events and went on to take formulation F ([redacted] mg) and formulation D ([redacted] mg). Approximately one day after taking the latter, the subject began to experience **insomnia and tremor**. These adverse events were probably associated with the use of study drug. [Study PDY4054]
- A subject (# 840001001) discontinued due to **hypertension** experienced 6 days after ingestion of Ambien 10 mg. Initially the recorded systolic blood pressure was 143 mm Hg, with a diastolic blood pressure of 92 mm HG and a heart rate of 100 bpm. Fifteen minutes later the recorded systolic blood pressure was 136 mm Hg, with a diastolic blood pressure of 86 mm HG and a heart rate of 88 bpm. No treatment was given. This adverse event was probably not related to study drug.[Study PKD 5070]

Placebo treatment arm

- A 39-year old man (#124103003) began to experience **moderate dizziness and mild attention disturbance** 2.5 hours before the first intake of study drug. [Study EFC4529]
- A 48-year old man (# 840132003) began to experience **back and extremity pain** 16 days after the first intake of study drug. [Study EFC4529]

- A subject who had been treated with placebo (# 840001017) discontinued due to **urticaria** attributed to ingestion of a peanut. Diphenhydramine was given as treatment. This adverse event was probably not related to study drug. [Study PKD 5070]

7.1.3.3 Other significant adverse events

The Phase 3 studies for this product evaluated the patients after abrupt drug discontinuation to assess for evidence of drug withdrawal after 21 days of nightly use. In both studies, the AE occurred mainly on night 22, the first night after discontinuation. The incidence of reported AE on night 22 was higher in the 12.5 mg group (18.1 %) than in the placebo group. This was not the case for the 6.25 mg group (5.3 %) when compared to the placebo group (7.7 %).

[*Reviewer's note: I have reproduced part of the table from the sponsor's clinical summary, as may be seen below. The part which I have reproduced shows the incidence of neuropsychiatric effects, which are perhaps the most clinically significant effects after product discontinuation.*]

Table 17: A selection of adverse events seen after abrupt drug discontinuation

Table (2.7.4.7) 19 - Summary of adverse events by organ class and preferred term during run-out period in Phase 3 studies

	EFC4529						EFC4530					
	Placebo (N=99)			Zolpidem-MR 12.5 mg (N=94)			Placebo (N=104)			Zolpidem-MR 6.25 mg (N=94)		
Organ class - Pref. term n (%)	N22	N23	Total	N22	N23	Total	N22	N23	Total	N22	N23	Total
Any class - any event	4(4.0%)	5(5.1%)	8(8.1%)	17(18.1%)	1(1.1%)	17(18.1%)	8(7.7%)	1(1.0%)	9(8.7%)	5(5.3%)	1(1.1%)	6(6.4%)
Infections and infestations												
Any event	0(0.0%)	0(0.0%)	0(0.0%)	2(2.1%)	0(0.0%)	2(2.1%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)
Influenza	0(0.0%)	0(0.0%)	0(0.0%)	1(1.1%)	0(0.0%)	1(1.1%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)
Nasopharyngitis	0(0.0%)	0(0.0%)	0(0.0%)	1(1.1%)	0(0.0%)	1(1.1%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)
Blood and lymphatic system disorders												
Any event	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	1(1.0%)	1(1.0%)	0(0.0%)	1(1.1%)	1(1.1%)
Lymphadenopathy	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	1(1.0%)	1(1.0%)	0(0.0%)	1(1.1%)	1(1.1%)
Psychiatric disorders												
Any event	0(0.0%)	0(0.0%)	0(0.0%)	5(5.3%)	0(0.0%)	5(5.3%)	1(1.0%)	0(0.0%)	1(1.0%)	1(1.1%)	0(0.0%)	1(1.1%)
Nightmare	0(0.0%)	0(0.0%)	0(0.0%)	2(2.1%)	0(0.0%)	2(2.1%)	0(0.0%)	0(0.0%)	0(0.0%)	1(1.1%)	0(0.0%)	1(1.1%)
Abnormal dreams	0(0.0%)	0(0.0%)	0(0.0%)	2(2.1%)	0(0.0%)	2(2.1%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)
Anxiety	0(0.0%)	0(0.0%)	0(0.0%)	2(2.1%)	0(0.0%)	2(2.1%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)
Agitation	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	1(1.0%)	0(0.0%)	1(1.0%)	0(0.0%)	0(0.0%)	0(0.0%)
Nervous system disorders												
Any event	1(1.0%)	1(1.0%)	2(2.0%)	4(4.3%)	0(0.0%)	4(4.3%)	3(2.9%)	0(0.0%)	3(2.9%)	3(3.2%)	0(0.0%)	3(3.2%)
Headache	1(1.0%)	1(1.0%)	2(2.0%)	2(2.1%)	0(0.0%)	2(2.1%)	2(1.9%)	0(0.0%)	2(1.9%)	2(2.1%)	0(0.0%)	2(2.1%)
Dizziness	0(0.0%)	0(0.0%)	0(0.0%)	1(1.1%)	0(0.0%)	1(1.1%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)
Somnolence	0(0.0%)	0(0.0%)	0(0.0%)	1(1.1%)	0(0.0%)	1(1.1%)	1(1.0%)	0(0.0%)	1(1.0%)	0(0.0%)	0(0.0%)	0(0.0%)
Tremor	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	1(1.1%)	0(0.0%)	1(1.1%)

While neuropsychiatric events such as anxiety and depressed mood were infrequently described by patients during the development program, these events are all known to occur in association with zolpidem use. These events did not occur at a higher incidence during the development plan for zolpidem-MR than would be expected from the pre- and post-marketing data from the currently marketed Ambien.

7.1.4 Other Search Strategies

There were no other search strategies used in the review of this product.

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

Phase I trials
During the Phase I single dose trials, subjects were assessed at screening and during the course of the trial for adverse events.

Phase III trials
Spontaneously reported or investigator observed adverse events were recorded for participants in both EFC 4529 and EFC 4530 at the initial screening, on screening nights 1 & 2, on screening day 1 & 2, on treatment days 1, 2, 15, 16, 22 and 23. Adverse events which were present prior to the first intake of study medication and worsening after were to be reported in the CRF with a new onset date at the date of the worsening.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

Phase I trials
Treatment emergent adverse events (TEAE) were defined as events which occurred or worsened during study treatment, defined as the time between the first intake and up to 24 hours after the last study drug intake for the Phase I trials.

Phase III trials
Treatment emergent adverse events (TEAE) were defined as events which occurred or worsened during study treatment, defined as the time between the first intake and up to 12 hours after the last study drug intake for the Phase III trials.

The clinical study reports used different dictionaries for coding of adverse events.

- Studies GAR 4624 and PDY 4054: WHO-ART
- Study ALI5057: MedDRA (version 5.1)
- Studies PDY 5035, PDY 5036, EFC 4529 and EFC 4530: MedDRA (version 6.0)
- Studies BDR5477 and BDR 5478: MedDRA (version 6.1)
- No adverse events were reported during study POP4055.

In order to facilitate pooling of the safety information, the sponsor subsequently recoded all the information using MedDRA (version 6.1). The adverse event categorization and preferred terms used were appropriate.

7.1.5.3 Incidence of common adverse events

Phase I studies
Adults
The adverse event reported with the highest incidence overall during the Phase I single-dose trials done with adult volunteers was headache (3.6% in the 12.5mg treatment arm). In the

controlled trial, somnolence (3.8% in the 12.5mg treatment arm, 1.9% in the placebo treatment arm), ear pain, myalgia and memory impairment (1.9% in the 12.5mg treatment arm, none in the placebo treatment arm for each individual AE) were also reported.

Elderly

The adverse event reported with the highest incidence overall during the Phase I single-dose trials done with elderly volunteers were headache (7.2% in the 6.25mg treatment arm), and somnolence (6.0% in the 6.25mg treatment arm). In the controlled trial somnolence (5/23 subjects in the 6.25 mg treatment arm, 6/23 subjects in the placebo treatment arm), insomnia (3/23 subjects in the 6.25mg treatment arm, 7/23 subjects in the placebo treatment arm), and headache, (3/23 patients in both treatment arms) were also reported.

Phase III studies

The adverse events reported with the highest incidence during the Phase III placebo-controlled trials were headache (18.6% in the 12.5mg treatment arm, 14.1% in the 6.25mg treatment arm), somnolence (14.7% in the 12.5mg treatment arm, 6% in the 6.25mg treatment arm), dizziness (11.8% in the 12.5mg treatment arm, 8.1% in the 6.25mg treatment arm), and nausea (6.9% in the 12.5mg treatment arm, 6.1% in the 6.25mg treatment arm).

- Headache

Most of the reported cases in the 12.5 mg were mild or moderate though one case was severe enough to lead to study discontinuation. All of the cases in the 6.25 mg group were mild or moderate and none led to study discontinuation.

- Dizziness

Most of the reported cases in the 12.5 mg were mild or moderate and lasted less than one day though one case was severe enough to lead to study discontinuation. All of the cases in the 6.25 mg group were mild or moderate, one case led to study discontinuation.

- Somnolence

Most of the reported cases were mild or moderate and lasted less than one day. This AE led to study discontinuation in two cases (one moderate and one severe, both in the 12.5 mg group). Most of the complaints of somnolence reflected morning sleepiness, an indirect report of next day residual effect. The sponsor did attempt to detect next day sleepiness through administering questionnaires during the study visits. Patients were asked to rate their morning sleepiness, using a visual analog scale, and their ability to concentrate in the morning, using a categorical rating. The statistical analysis of these subjective ratings did not show evidence of a drug effect.

- Nausea

Most of the reported cases were mild or moderate though one case (12.5 mg group) was severe enough to lead to study discontinuation.

7.1.5.4 Common adverse event tables

Table 18: Common adverse events seen in the Phase III studies

Table (2.7.4.2.1) 3 - Summary of TEAEs present in at least two patients in one of the zolpidem-MR groups by organ class and preferred term

	EFC4529		EFC4530	
Organ class - Pref. term n (%)	**Placebo (N=110)**	**Zolpidem-MR 12.5 mg (N=102)**	**Placebo (N=106)**	**Zolpidem-MR 6.25 mg (N=99)**
Any class - any event	57 (51.8 %)	58 (56.9 %)	42 (39.6 %)	38 (38.4 %)
Infections and infestations				
Any event	7 (6.4 %)	4 (3.9 %)	6 (5.7 %)	10 (10.1 %)
Nasopharyngitis	4 (3.6 %)	1 (1.0 %)	4 (3.8 %)	6 (6.1 %)
Influenza	0 (0.0 %)	3 (2.9 %)	1 (0.9 %)	1 (1.0 %)
Psychiatric disorders				
Any event	11 (10.0 %)	18 (17.6 %)	7 (6.6 %)	7 (7.1 %)
Anxiety	0 (0.0 %)	2 (2.0 %)	2 (1.9 %)	3 (3.0 %)
Psychomotor retardation	0 (0.0 %)	2 (2.0 %)	0 (0.0 %)	2 (2.0 %)
Disorientation	2 (1.8 %)	3 (2.9 %)	0 (0.0 %)	0 (0.0 %)
Depression	0 (0.0 %)	2 (2.0 %)	0 (0.0 %)	0 (0.0 %)
Hallucination	0 (0.0 %)	2 (2.0 %)	1 (0.9 %)	0 (0.0 %)
Nervous system disorders				
Any event	24 (21.8 %)	41 (40.2 %)	21 (19.8 %)	25 (25.3 %)
Headache	18 (16.4 %)	19 (18.6 %)	12 (11.3 %)	14 (14.1 %)
Somnolence	2 (1.8 %)	15 (14.7 %)	5 (4.7 %)	6 (6.1 %)
Dizziness	6 (5.5 %)	12 (11.8 %)	3 (2.8 %)	8 (8.1 %)
Disturbance in attention	0 (0.0 %)	2 (2.0 %)	2 (1.9 %)	1 (1.0 %)
Balance disorder	0 (0.0 %)	2 (2.0 %)	0 (0.0 %)	0 (0.0 %)
Hypoaesthesia	1 (0.9 %)	2 (2.0 %)	1 (0.9 %)	0 (0.0 %)
Memory impairment	0 (0.0 %)	2 (2.0 %)	0 (0.0 %)	0 (0.0 %)
Sinus headache	2 (1.8 %)	2 (2.0 %)	1 (0.9 %)	0 (0.0 %)
Eye disorders				
Any event	2 (1.8 %)	8 (7.8 %)	1 (0.9 %)	0 (0.0 %)
Visual disturbance	0 (0.0 %)	3 (2.9 %)	0 (0.0 %)	0 (0.0 %)
Eye redness	0 (0.0 %)	2 (2.0 %)	0 (0.0 %)	0 (0.0 %)
Vision blurred	1 (0.9 %)	2 (2.0 %)	0 (0.0 %)	0 (0.0 %)
Ear and labyrinth disorders				
Any event	0 (0.0 %)	3 (2.9 %)	1 (0.9 %)	0 (0.0 %)
Vertigo	0 (0.0 %)	2 (2.0 %)	0 (0.0 %)	0 (0.0 %)
Cardiac disorders				
Any event	3 (2.7 %)	0 (0.0 %)	6 (5.7 %)	2 (2.0 %)
Palpitations	1 (0.9 %)	0 (0.0 %)	0 (0.0 %)	2 (2.0 %)
Gastrointestinal disorders				
Any event	14 (12.7 %)	12 (11.8 %)	13 (12.3 %)	9 (9.1 %)
Nausea	4 (3.6 %)	7 (6.9 %)	6 (5.7 %)	6 (6.1 %)
Constipation	0 (0.0 %)	2 (2.0 %)	2 (1.9 %)	2 (2.0 %)
Abdominal pain upper	1 (0.9 %)	1 (1.0 %)	3 (2.8 %)	2 (2.0 %)
Skin and subcutaneous tissue disorders				
Any event	3 (2.7 %)	4 (3.9 %)	4 (3.8 %)	4 (4.0 %)
Pruritus	1 (0.9 %)	0 (0.0 %)	2 (1.9 %)	2 (2.0 %)

Table 18: Common adverse events seen in the Phase III studies (continued)

Organ class - Pref. term n (%)	EFC4529 Placebo (N=110)	EFC4529 Zolpidem-MR 12.5 mg (N=102)	EFC4530 Placebo (N=106)	EFC4530 Zolpidem-MR 6.25 mg (N=99)
Musculoskeletal and connective tissue disorders				
Any event	7 (6.4 %)	11 (10.8 %)	7 (6.6 %)	7 (7.1 %)
Back pain	3 (2.7 %)	4 (3.9 %)	3 (2.8 %)	2 (2.0 %)
Myalgia	0 (0.0 %)	4 (3.9 %)	0 (0.0 %)	0 (0.0 %)
Muscle cramp	1 (0.9 %)	1 (1.0 %)	1 (0.9 %)	2 (2.0 %)
Neck pain	0 (0.0 %)	1 (1.0 %)	0 (0.0 %)	2 (2.0 %)
Arthralgia	1 (0.9 %)	0 (0.0 %)	0 (0.0 %)	2 (2.0 %)
General disorders and administration site conditions				
Any event	7 (6.4 %)	6 (5.9 %)	7 (6.6 %)	6 (6.1 %)
Fatigue	2 (1.8 %)	3 (2.9 %)	3 (2.8 %)	3 (3.0 %)

<ref>PGM= SL80075023/OVERALL/NDA0087/BS/PGM_RPT/2742ae_p.sas OUT= OUTPUT/2742ae_p_4.ged (19MAR2004 - 15:30)

N = number of patients exposed; n (%) = number and percent of patients with at least one TEAE.

7.1.5.5 Identifying common and drug-related adverse events

The following adverse events, as may be seen in the table above, showed a consistent difference from control across doses and across study populations:

- Psychomotor retardation
- Somnolence (with possible dose/response effects)
- Dizziness
- Nausea

The following adverse events, as may be seen in the table above, showed a consistent difference from control at the 12.5 mg dose though not at the 6.25 mg dose:

- Memory impairment
- Visual disturbance
- Blurred vision
- Vertigo

7.1.5.6 Additional analyses and explorations

No additional analyses or explorations were done since the adverse events listed in 7.1.5.5 are well described in the literature on zolpidem.

7.1.6 Less Common Adverse Events

Though a consistent difference from control across doses and across study populations was not seen in the phase I or III trials, hallucinations (visual and auditory) have been described as an

associated adverse event with this product. It would appear that there may be a dose response relationship but that cannot be definitively stated from the available evidence.

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

Phase I trials
The protocols for the Phase I studies required laboratory testing as a baseline and at the termination visit. No clinically significant findings were noted.

Phase III trials
The protocols for the Phase III studies, EFC 4529 and EFC 4530, required laboratory testing during screening in order to determine eligibility. There was no follow up testing, therefore no comparisons can be made between pre- and post-treatment values. [*Reviewer's note: The sponsor had discussed their plan not to do routine labs during these studies during the EOP2 meeting-the Agency agreed that these studies would not be necessary.*]

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

This section is not relevant for this review [*see explanation in section 7.1.7.1*].

7.1.7.3 Standard analyses and explorations of laboratory data

This section is not relevant for this review [*see explanation in section 7.1.7.1*].

7.1.7.4 Additional analyses and explorations

This section is not relevant for this review [*see explanation in section 7.1.7.1*].

7.1.7.5 Special assessments

This section is not relevant for this review [*see explanation in section 7.1.7.1*].

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

Phase I trials
In most of the Phase I studies vital signs were examined on the day following the single-dose of study drug and at the termination visit. In study GAR4624 vital signs were performed 12 hours after IV administration and 16 hours after each oral administration while in study PDY4054,

vital signs were only performed at the end of the study. No clinically significant findings were noted in the 318 Phase I study participants (234 adults, 84 elderly).

Phase III trials
In the Phase III studies vital signs were examined 1 day, 2 days, 15 days and 16 days after the first ingestion of study drug and during the run-out period, study days 22 and 23..

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

The Phase III studies were chosen for analysis since they provided information about patients who used the product as it might be expected to be used in the real world.

Pooling was not done since the studies used different dose levels and different populations.

7.1.8.3 Standard analyses and explorations of vital signs data

Mean changes from baseline
As may be seen in the table below, the mean changes from baseline were not clinically significant during the Phase III studies.

Table 19: Mean changes in vital signs

Table (2.7.4.4) 2 - Vital signs mean changes from baseline in Phase 3 studies

Parameter			EFC4529 Placebo (N=110)	EFC4529 Zolpidem-MR 12.5 mg (N=102)	EFC4530 Placebo (N=106)	EFC4530 Zolpidem-MR 6.25 mg (N=99)
Sitting HR	Baseline	Mean (SD)	66.8 (9.1)	67.7 (10.0)	69.7 (8.9)	70.4 (10.0)
	End of treatment	Mean (SD)	67.5 (9.6)	68.4 (9.5)	69.0 (8.0)	69.8 (8.5)
	End of treatment - baseline	Mean (SD)	0.7 (9.3)	0.7 (9.4)	-0.7 (7.4)	-0.6 (8.7)
Sitting SBP	Baseline	Mean (SD)	118.7 (14.4)	119.8 (13.8)	130.9 (16.4)	131.4 (19.4)
	End of treatment	Mean (SD)	116.6 (13.4)	117.5 (14.1)	129.2 (14.5)	130.1 (18.3)
	End of treatment - baseline	Mean (SD)	-2.1 (11.7)	-2.2 (10.3)	-1.7 (13.7)	-1.4 (16.9)
Sitting DBP	Baseline	Mean (SD)	76.6 (8.8)	76.5 (9.8)	78.7 (11.0)	78.3 (9.4)
	End of treatment	Mean (SD)	75.3 (9.7)	75.7 (9.3)	77.0 (9.8)	76.3 (9.2)
	End of treatment - baseline	Mean (SD)	-1.3 (7.5)	-0.8 (8.8)	-1.7 (9.6)	-2.0 (10.3)

PGM= SLS0975023/OVERALL/NDA0087/BSTPGM RPT:2744vital.sas OUT= OUTPUT:2744vital_2.ged (22OCT2003 - 9:47)
HR = heart rate; SBP = systolic blood pressure; DBP = diastolic blood pressure; SD = standard deviation.

Reproduction of table from the sponsor's clinical summary, p.136

The sponsor provided a summary of the potentially clinically significant adverse events during the Phase III studies, as may be seen in the table below.

The involved patients in the active treatment arm:

- Patient 250210003 had a decrease in SBP to 90 mmHg on N1/D1, which resolved the next day (6.25 mg)
- Patient 124201003 had an increase in SBP to 184 mmHg on N16/D16, and to 190 mmHg on N23/D23 from her baseline SBP of 130 mmHg. At screening, she had been noted to have a SBP of 190 mm Hg. Her SBP at SN1 was 182 mmHg. (6.25 mg)

- Patient 840225025 had a decrease in DBP to 48 mmHg on N16/D16. On N22/D22 her DBP was 70 mmHg. At baseline, she had been noted to have a DBP of 90 mm Hg. (6.25 mg)
- Patient 840204016 had an increase in DBP to 113 mmHg on N15/D15. His DBP was 63 mmHg. His baseline SBP was 94 mmHg. (6.25 mg)
- Patient 840115006 had a decrease in heart rate to 36 bpm on N2/D2. At the time her blood pressure was 106/76. Her baseline heart rate was 76 bpm. (12.5 mg)
- Patient 840111011 had a decrease in SBP to 90 mmHg on N15/D15 which resolved to a SBP of 110 the next day. At baseline, she had been noted to have a SBP of 116mm Hg. (12.5 mg)

Table 20: Summary of potentially clinically significant changes in vital signs

Table (2.7.4.4) 1 - Summary of vital signs PCSAs in Phase 3 studies

Parameter		EFC4529 Placebo (N=110)	EFC4529 Zolpidem-MR 12.5 mg (N=102)	EFC4530 Placebo (N=106)	EFC4530 Zolpidem-MR 6.25 mg (N=99)
Sitting HR	≤50 bpm and decrease ≥15 bpm	2/110 (1.8%)	1/102 (1.0%)	1/106 (0.9%)	0/99 (0.0%)
	≥120 bpm and increase ≥15 bpm	0/110 (0.0%)	0/102 (0.0%)	0/106 (0.0%)	0/99 (0.0%)
Sitting SBP	≤90 mmHg and decrease ≥20 mmHg	1/110 (0.9%)	1/102 (1.0%)	0/106 (0.0%)	1/99 (1.0%)
	≥180 mmHg and increase ≥20 mmHg	0/110 (0.0%)	0/102 (0.0%)	1/106 (0.9%)	1/99 (1.0%)
Sitting DBP	≤50 mmHg and decrease ≥15 mmHg	0/110 (0.0%)	0/102 (0.0%)	2/106 (1.9%)	1/99 (1.0%)
	≥105 mmHg and increase ≥15 mmHg	0/110 (0.0%)	0/102 (0.0%)	1/106 (0.9%)	1/99 (1.0%)

PGM= SI.80\75023\OVERALL\NDA\087\BS\PGM_RPT\2744vital.sas OUT= OUTPUT\2744vital_1.gsd (22OCT2003 - 9:45)

HR = heart rate; bpm = beats per minute; SBP = systolic blood pressure; DBP = diastolic blood pressure; mmHg = millimeters of mercury.

Reproduction of table from the sponsor's clinical summary, p.136

The changes seen were not persistent therefore it is not possible to definitively attribute the changes to study drug or to definitively declare that the changes were unrelated to study drug use.

7.1.8.4 Additional analyses and explorations

No additional analyses or explorations were performed.

7.1.9 Electrocardiograms (ECGs)

7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results

Phase I trials

The protocols for the Phase I studies required ECGs at the termination visit. No clinically significant findings were noted in the 318 Phase I study participants (234 adults, 84 elderly).

Phase III trials

The protocols for the Phase III studies, EFC 4529 and EFC 4530, required electrocardiograms during screening in order to determine eligibility. There was no follow-up testing, therefore no comparisons can be made between pre- and post-treatment studies. [*Reviewer's note: The sponsor had discussed their plan not to do ECGs during these studies during the EOP2 meeting- the Agency agreed that these studies would not be necessary.*]

7.1.9.2 Selection of studies and analyses for overall drug-control comparisons

This section is not relevant for this review [*see explanation in section 7.1.9.1*].

7.1.9.3 Standard analyses and explorations of ECG data

This section is not relevant for this review [*see explanation in section 7.1.9.1*].

7.1.9.4 Additional analyses and explorations

This section is not relevant for this review [*see explanation in section 7.1.9.1*].

7.1.10 Immunogenicity

There was no immunogenicity data provided to assess the impact of immunogenicity on safety, efficacy, clinical pharmacokinetics or pharmacology.

7.1.11 Human Carcinogenicity

The following text is taken directly from the currently approved label for Ambien:

> "Zolpidem was administered to rats and mice for 2 years at dietary dosages of 4, 18, and 80 mg/kg/day. In mice, these doses are 26 to 520 times or 2 to 35 times the maximum 10-mg human dose on a mg/kg or mg/m^2 basis, respectively. In rats these doses are 43 to 876 times or 6 to 115 times the maximum 10-mg human dose on a mg/kg or mg/m2 basis, respectively.
>
> No evidence of carcinogenic potential was observed in mice.
>
> Renal liposarcomas were seen in 4/100 rats (3 males, 1 female) receiving 80 mg/kg/day and a renal lipoma was observed in one male rat at the 18 mg/kg/ day dose. Incidence rates of lipoma and liposarcoma for zolpidem were comparable to those seen in historical controls and the tumor findings are thought to be a spontaneous occurrence."

7.1.12 Special Safety Studies

7.1.12.1 Assessment of residual drug (next-day) effects

Phase I studies

Three pharmacodynamic studies were done to assess potential residual effects of zolpidem-MR. These studies used a battery of tests to assess psychomotor and cognitive functioning after ingestion of zolpidem MR. Flurazepam 30 mg was used as a positive control in studies PDY 5035 and PDY 5036. The sponsor did not detect residual effects at the recommended doses. When elderly subjects were given double the recommended dose, residual effects were still not seen. [*Reviewer's note: Brief summaries of these studies may be found in appendix 10.*]

Table 21: Phase I studies done to assess residual effects

	Healthy Young Subjects	Healthy Elderly Subjects	8 hours Postdosing	9 hours Postdosing	Zolpidem-MR 12.5 mg	Zolpidem-MR 6.25 mg
PDY4054	X		X	X	X	
PDY5035		X	X		X	X
PDY5036	X		X		X	

table 2.7.4.5.9.1.1 from the sponsor's clinical summary

Table 22: Summary of residual effects from Phase I studies

Table (2.7.4.5.9.1) 3 - Summary of residual effects in Phase I studies: difference versus placebo

	Difference Estimate versus Placebo [95% CI] and p-value						
Study	PDY4054		PDY5036		PDY5035		
Population	Healthy Young subjects		Healthy Young subjects		Healthy Elderly subjects		
Study Drugs	zolpidem-MR 12.5mg (E) (N=34)	zolpidem-MR 12.5mg (E) (N=34)	zolpidem-MR 12.5mg (E) (N=18)	Flurazepam 30mg (N=18)	zolpidem-MR 6.25mg (N=23)	zolpidem-MR 12.5mg (E) (N=23)	Flurazepam 30mg (N=23)
Time of evaluation	8 hours	9 hours	8 hours	8 hours	8 hours	8 hours	8 hours
CFF	-0.28 [-0.86 ; 0.29] 0.3337	-0.20 [-0.74 ; 0.34] 0.4658	-0.15 [-0.77 ; 0.48] 0.6375	-0.90 [-1.52 ; -0.27] **- 0.0066**	0.20 [-0.38 ; 0.77] 0.4970	-0.44 [-1.02 ; 0.14] 0.1312	-1.01 [-1.59 ; -0.42] **- 0.0011**
CRT Recognition Reaction Time	2.27 [-21.23 ; 25.76] 0.8496	-6.69 [-23.72 ; 10.34] 0.4398	5.22 [-8.56 ; 19.01] 0.4458	21.66 [7.87 ; 35.44] **- 0.0031**	-10.60 [-36.75 ; 15.56] 0.4212	11.18 [-14.97 ; 37.33] 0.3962	24.05 [-2.10 ; 50.20] 0.0709
CRT Motor Reaction Time	9.68 [-5.81 ; 25.16] 0.2197	-1.97 [-15.89 ; 11.96] 0.7812	10.87 [-6.01 ; 27.76] 0.1989	21.04 [5.06 ; 38.83] **- 0.0125**	9.16 [-12.51 ; 30.82] 0.4015	-2.22 [-23.89 ; 19.44] 0.8383	25.03 [3.26 ; 46.69] **- 0.0243**
CRT Total Reaction Time	11.81 [-19.02 ; 42.65] 0.4513	-8.69 [-31.56 ; 14.17] 0.4550	16.10 [-8.03 ; 40.23] 0.1837	43.60 [19.47 ; 67.73] **- 0.0009**	-1.44 [-35.13 ; 32.26] 0.9322	8.96 [-24.74 ; 42.65] 0.5972	49.07 [15.38 ; 82.77] **- 0.0050**
CTT Mean deviation	-0.06 [-4.53 ; 4.41] 0.9801	0.73 [-1.23 ; 2.70] 0.4649	1.55 [-0.14 ; 3.24] 0.0713	2.79 [1.10 ; 4.48] **- 0.0020**	-2.55 [-10.53 ; 5.43] 0.5260	4.20 [-3.78 ; 12.18] 0.2974	7.28 [-0.70 ; 15.26] 0.0732
CTT Mean response time	13.39 [-41.48 ; 68.27] 0.6313	19.78 [-10.48 ; 50.04] 0.1993	49.56 [12.43 ; 86.68] **- 0.0105**	95.89 [58.77 ; 133.01] **- 0.0001**	-19.59 [-113.56 ; 74.39] 0.6785	43.80 [-50.17 ; 137.78] 0.3552	112.46 [18.49 ; 206.43] **- 0.0198**
DSST	1.05 [-2.21 ; 4.31] 0.5276	-2.26 [-5.24 ; 0.72] 0.1368	0.06 [-4.39 ; 4.50] 0.9798	-3.94 [-8.39 ; 0.50] 0.0801	0.68 [-1.24 ; 2.61] 0.4817	0.73 [-1.20 ; 2.65] 0.4519	-1.90 [-3.83 ; 0.02] 0.0526

(continued)

Table 22: (Continued)

Table (2.7.4.5.9.1) 3 - Summary of residual effects in Phase I studies: difference versus placebo (continued)

Study	Difference Estimate versus Placebo [95% CI] and p-value						
	PDY4054		PDY5036		PDY5035		
Population	Healthy Young subjects		Healthy Young subjects		Healthy Elderly subjects		
Study Drugs	zolpidem-MR 12.5mg (E) (N=34)	zolpidem-MR 12.5mg (E) (N=34)	zolpidem-MR 12.5mg (E) (N=18)	Flurazepam 30mg (N=18)	zolpidem-MR 6.25mg (N=23)	zolpidem-MR 12.5mg (E) (N=23)	Flurazepam 30mg (N=23)
Time of evaluation	8 hours	9 hours	8 hours	8 hours	8 hours	8 hours	8 hours
IWR	-0.36 [-1.28 ; 0.56] 0.4459	NP	-0.50 [-2.17 ; 1.17] 0.5455	-2.50 [-4.17 ; -0.83] **- 0.0045**	-0.34 [-1.47 ; 0.78] 0.5424	-0.68 [-1.80 ; 0.45] 0.2328	-2.76 [-3.88 ; -1.63] **- 0.0001**
DWR	-0.86 [-2.10 ; 0.38] 0.1727	NP	-1.39 [-3.28 ; 0.51] 0.1451	-4.39 [-6.28 ; -2.49] **- 0.0001**	-0.08 [-1.29 ; 1.13] 0.8935	-1.05 [-2.26 ; 0.16] 0.0876	-2.94 [-4.15 ; -1.73] **- 0.0001**
LSEQ Awakening from sleep	-2.93 [-8.06 ; 2.21] 0.2627	-2.12 [-6.93 ; 2.69] 0.3869	-1.92 [-7.04 ; 3.21] 0.4520	-5.61 [-10.74 ; -0.48] **- 0.0330**	1.63 [-4.79 ; 8.04] 0.6137	-0.02 [-6.43 ; 6.40] 0.9962	-2.99 [-9.40 ; 3.43] 0.3555
LSEQ Behavior following awakenig	1.34 [-3.30 ; 5.98] 0.5691	0.24 [-3.98 ; 4.47] 0.9099	-1.56 [-6.36 ; 3.25] 0.5140	-6.50 [-11.30 ; -1.70] **- 0.0095**	8.59 [0.82 ; 16.36] **+ 0.0308**	6.24 [-1.53 ; 14.01] 0.1137	-1.05 [-8.82 ; 6.72] 0.7889
Bond & Lader Alertness	NP	NP	11.64 [-25.54;48.83] 0.5281	41.68 [4.49 ; 78.86 **- 0.0292**	NP	NP	NP

pgm=/SL.80075023/PL800750/BS/pgm_rpt/poolpsyc.sas out=/output/poolpsyc.txt (06MAY2004 - 19:00)

Note: all p-values were of zolpidem-MR compared with placebo.
Note: For LSEQ and bond & Lader, only relevant items related to awakening are presented.
CFF=critical flicker fusion; CRT=choice reaction time; IWR=immediate word recall; DWR=delayed word recall; CTT= compensatory tracking test; DSST= digit symbol substitution test; LSEQ= Leeds Sleep Questionnaire; NP = not performed; - = impairment; + = improved.

Phase III studies

Residual effects were assessed through the digit symbol substitution test (DSST), the Rey auditory learning test (RAVLT) and 2 questions on the morning questionnaire.

Objective measures

- DSST

The DSST was used to assess alertness and vigilance. In this test patients are given a random assortment of numbers. The numbers are associated with a nonsense symbols and a key is printed at the top of the test sheet. The patients' alertness/vigilance is assessed by determining the number of nonsense symbols correctly associated over a 90 second period.

- RAVLT

The RAVLT assesses short-term memory. The investigator reads a list of 15 words five times. After each trial, the patient is asked to recall as many words as possible. Once 5 trials are complete, the investigator reads a second (interference) list of 15 words and the patient is asked to recall as many of the new words as possible. Once the patient has completed the task with the interference list, the patient is asked to recall as many words as possible from the original list.

Questionnaires

- Morning sleepiness

Patients were asked to assess their level of morning sleepiness using a visual analog scale anchored by 0 (very sleepy) and 100 (not at all sleepy).

- Ability to concentrate in the morning

Patients were also asked to assess their ability to concentrate in the morning on a categorical scale which ranged from 1 (excellent) to 4 (poor).

Table 23: Results of DSST testing in EFC4529

Table (12.5.4.1.1) 2 - One-way ANOVA results of the comparison of psychometric test - DSST - zolpidem-MR 12.5 mg versus placebo - Exposed population

	Number of patients	Mean of the difference	95%-Confidence Interval	df	p-value
Days 1,2	211	1.88	[0.23; 3.54]	(1,209)	0.0262 *
Days 15,16	198	0.27	[-1.67; 2.21]	(1,196)	0.7838

<ref>PGM= SL80075023/EFC4529/CSR/BS/PGM_RPT/i1253diary.sas OUT= OUTPUT/i1253diary_2.ged (27NOV2003 - 10:33)

*: p<0.05

(table from sponsor's study report)

Table 24: Results of RAVLT testing in EFC4529

		Number of patients	Mean of the difference	95%-Confidence Interval	df	p-value
Mean of recalled words during trials I to V	Days 1,2	211	0.35	[0.03; 0.67]	(1,209)	0.0335 *
	Days 15,16	198	-0.01	[-0.36; 0.34]	(1,196)	0.9614
Recalled words during trial VI	Days 1,2	211	0.79	[0.25; 1.33]	(1,209)	0.0044 *
	Days 15,16	198	0.12	[-0.45; 0.69]	(1,196)	0.6819

<ref>PGM= SL80075023/EFC4529/CSR/BS/PGM_RPT/i1253diary.sas OUT= OUTPUT/i1253diary_4.ged (27NOV2003 - 10:34)

*: p<0.05

(study report table 12.5.4.1.1.4)

Table 25: Results of subjective assessments for EFC4529

		Number of patients	Mean of the difference	95%-Confidence Interval	df	p-value
VAS on sleepiness in the morning	Days 1,2	212	-3.40	[-9.42; 2.63]	(1,210)	0.2673
	Days 15,16	199	-4.08	[-11.21; 3.05]	(1,197)	0.2601
Ability to concentrate in the morning	Days 1,2	211	0.23	[0.08; 0.38]	(1,209)	0.0030 *
	Days 15,16	198	0.12	[-0.07; 0.31]	(1,196)	0.2132

<ref>PGM= SL80075023/EFC4529/CSR/BS/PGM_RPT/i1253diary.sas OUT= OUTPUT/i1253diary_7.ged (27NOV2003 - 10:35)

*: p<0.05

(study report table 12.5.4.1.2.1)

Table 26: Results of DSST testing in EFC 4530

Table (12.5.4.1.1) 2 - One-way ANOVA results of the comparison of psychometric test - DSST - zolpidem-MR 6.25 mg versus placebo - Exposed population

	Number of patients	Mean of the difference	95%-Confidence Interval	df	p-value
Days 1,2	204	1.42	[0.33; 2.50]	(1,202)	0.0106 *
Days 15,16	200	1.24	[-0.04; 2.53]	(1,198)	0.0584

<ref>PGM= SL80075023/EFC4530/CSR/BS/PGM_RPT/i12523diary.sas OUT= OUTPUT/i12523diary_2.ged (25NOV2003 - 13:49)

*: p<0.05

(table from sponsor's study report)

Table 27: Results of RAVLT testing in study EFC4530

Table (12.5.4.1.1) 4 - One-way ANOVA results of the comparison of psychometric test - RAVLT - zolpidem-MR 6.25 mg versus placebo - Exposed population

		Number of patients	Mean of the difference	95%-Confidence Interval	df	p-value
Mean of recalled words during trials I to V	Days 1,2	202	0.08	[-0.26; 0.42]	(1,200)	0.6561
	Days 15,16	198	0.05	[-0.28; 0.39]	(1,196)	0.7494
Recalled words during trial VI	Days 1,2	202	0.02	[-0.54; 0.59]	(1,200)	0.9313
	Days 15,16	198	0.10	[-0.44; 0.65]	(1,196)	0.7148

<ref>PGM= SL80075023/EFC4530/CSR/BS/PGM_RPT/il2523diary.sas OUT= OUTPUT/il2523diary_4.ged (25NOV2003 - 13:50)

*: p<0.05

(table from sponsor's study report)

Table 28: Results of subjective assessments for study EFC 4530

Table (12.5.4.1.2) 1 - One-way ANOVA results of the comparison of sleep morning questionnaire - zolpidem-MR 6.25 mg versus placebo - Exposed population

		Number of patients	Mean of the difference	95%-Confidence Interval	df	p-value
VAS on sleepiness in the morning	Days 1,2	205	-2.13	[-8.37; 4.12]	(1,203)	0.5027
	Days 15,16	201	-3.37	[-10.41; 3.67]	(1,199)	0.3467
Ability to concentrate in the morning	Days 1,2	204	0.11	[-0.05; 0.27]	(1,202)	0.1594
	Days 15,16	200	0.02	[-0.15; 0.20]	(1,198)	0.8008

<ref>PGM= SL80075023/EFC4530/CSR/BS/PGM_RPT/il2523diary.sas OUT= OUTPUT/il2523diary_7.ged (06JAN2004 - 16:07)

* p<0.05

(table from sponsor's study report)

Summary

In the adult study, the objective measures showed a slight decrease in performance on the RAVLT on D1/D2 which was not apparent on Day 15/16. In the elderly study, the objective measures and the subjective measures showed no next day residual effect.

7.1.12.2 Assessment of drug rebound effect

This was evaluated through analysis of WASO, SE, and LPS results after abrupt drug discontinuation on N22 and N23 during studies EFC 4529 and EFC 4530.

As shown in the table below, a rebound effect on WASO (the primary efficacy measure) was seen in both studies on the initial night after abrupt drug discontinuation. In EFC 4529, the study done in adults, a rebound effect was also seen for SE and LPS. In EFC 4530, the study done in the elderly, a rebound effect was seen for SE but not for LPS.

Table 29: Effect of abrupt drug discontinuation on WASO

		EFC4529		EFC4530	
		Placebo (N=110)	Zolpidem-MR 12.5 mg (N=102)	Placebo (N=106)	Zolpidem-MR 6.25 mg (N=99)
Screening	n	99	94	102	93
	Mean (SD)	91:05 (43:15)	80:10 (35:33)	113:34 (42:07)	111:57 (46:04)
Night 22 - Screening	n	98	92	102	91
	Mean (SD)	-13:27 (46:42)	26:25 (70:44) *	-8:23 (46:13)	29:26 (61:29) *
Night 23 - Screening	n	96	90	101	93
	Mean (SD)	-28:39 (41:06)	-10:33 (56:33) *	-12:23 (49:42)	-8:55 (57:10)

<ref>PGM= SL80075023/OVERALL/NDA0087/BS/PGM_RPT/27457psg.sas OUT= OUTPUT/27457psg_1.ged (23JAN2004 - 14:37)
n = number of patients; SD = standard deviation.
* = statistically significant.
(a reproduction of table 2.7.4.5.7.1. from the sponsor's clinical summary)

7.1.13 Withdrawal Phenomena and/or Abuse Potential

Withdrawal phenomena in the form of rebound effects on WASO, and SE occur on the first night after abrupt discontinuation of this drug. Rebound effects on LPS were seen in adults (EFC 4529) but not in the elderly (EFC 4530). When evaluated by the criteria used for diagnosis of drug withdrawal according to DSM-IV, hypertension (n=1) anxiety (n=2) and nausea (n=3) were seen in the group which received 12.5 mg zolpidem-MR and tremor (n=1) was seen in the group which received 6.25 mg zolpidem-MR though not in the placebo group. [*Reviewer's note: Detailed discussion has been provided in sections 7.1.3.3 and 7.1.12*]

This product has abuse potential due to its neuropsychiatric effects. As agreed at the EOP2 meeting held in January 2002, this product would be a class IV controlled substance, as is the currently marketed zolpidem.

7.1.14 Human Reproduction and Pregnancy Data

Zolpidem tartrate is currently pregnancy category B. Studies to assess the effects of zolpidem on human reproduction and development have not been conducted. Studies to assess the effects of in utero zolpidem exposure on children have not been conducted. Studies in rats showed a trend to dose-related delay in ossification of the skull bones. The no-effect dose for fetal toxicity (rabbits) was 4 mg base/kg or 7 times the maximum human dose on a mg/m2 basis.

Studies in lactating mothers indicate that between 0.004% and 0.019% of the total administered dose is excreted into the milk. The effect of this level of exposure on the receiving infant has not been formally assessed.

7.1.15 Assessment of Effect on Growth

The effect on growth was not evaluated for this NDA as this product is not approved for use in the pediatric population.

7.1.16 Overdose Experience

There were no reported instances of drug overdose with this formulation during the clinical studies. The currently approved label for Ambien notes that zolpidem's sedative hypnotic effect may be reversed by administration of flumazenil.

7.1.17 Postmarketing Experience

Ambien CR has not been marketed so we do not have postmarketing data on this specific formulation. Zolpidem has been and is currently being marketed as an immediate release formulation, Ambien IR. A discussion of the postmarketing information for the immediate release formulation may be found in section 7.2.2.2 of this review.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

7.2.1.1 Study type and design/patient enumeration from studies EFC 4529 and EFC 4530

Table 30: Study type and populations

Study Number	Design	Dosing schedule	Population
EFC 4529	DB, R, PC, PG	2-day placebo "run-in", 21 days of treatment and a 5 day placebo "run-out"	212 adults
EFC 4530	DB, R, PC, PG	2-day placebo "run-in", 21 days of treatment and a 5 day placebo "run-out"	205 elderly adults

7.2.1.2 Demographics

Table 31 : Demographics in Phase I studies

Study population	n	M/F	Ethnicity
Adults	234	138M/96F	White 225 (96.2%) Black 7 (3.0%) Other 2 (<1%)
Elderly	84	42M/42F	White 84 (100%)

Data from table 2.7.4.1.3.1 of clinical summary section of NDA

Table 32: demographics during Phase III studies

Protocol #	Study population	n	M/F	Ethnicity
EFC 4529	Adults	212	89M/123F	White 191 (90.0%) Black 18 (8.4%) Asian 1 (<1%) Other 2 (<1%)
EFC 4530	Elderly	205	88M/117F	White 195 (95.1%) Black 7 (3.4%) Asian 3 (1.4%)

7.2.1.3 Extent of exposure (dose/duration)

Table 33: Exposure during Phase I single dose studies

		Zolpidem-MR 6.25 mg	Zolpidem-MR 12.5 mg
Subjects	n	83	196

Data from table 2.7.4.1.2. of clinical summary section of NDA

Table34: Exposure during Phase III studies- EFC 4529 and EFC 4530

Table (2.7.4.1.2) 2 - Summary of overall extent of exposure in Phase 3 studies

	EFC4529		EFC4530	
	Placebo (N=110)	Zolpidem-MR 12.5 mg (N=102)	Placebo (N=106)	Zolpidem-MR 6.25 mg (N=99)
n	110	102	106	99
Median	21	21	21	21
Mean (SD)	19.9 (4.4)	20.2 (2.8)	20.8 (1.7)	20.5 (2.2)
Min - Max	1 - 27	4 - 23	5 - 23	5 - 22
1 day	4 (3.6 %)	0 (0.0 %)	0 (0.0%)	0 (0.0%)
2-7 days	1 (0.9 %)	1 (1.0 %)	1 (0.9 %)	1 (1.0 %)
8-14 days	1 (0.9 %)	4 (3.9 %)	0 (0.0 %)	2 (2.0 %)
15-21 days	92 (83.6 %)	91 (89.2 %)	100 (94.3 %)	90 (90.9 %)
>21 days	12 (10.9 %)	6 (5.9 %)	5 (4.7 %)	6 (6.1 %)

<ref>PGM= SL80075023/OVERALL/NDA0087/BS/PGM_RPT/2741demo.sas OUT= OUTPUT/2741demo_1.ged (09MAR2004 - 16:48)

n = number of patients; SD = standard deviation; Min = minimum; Max = maximum.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

7.2.2.1 Other studies

Table 35: Additional studies

Study Number	Design	Population
EFC 5202	DB, R, PC, 3-way crossover study	331 adults
PKD 5070	DB, 3 way cross-over	72 adults
PDY 5195	DB, R, 9-way crossover study	54 adults

7.2.2.2 Postmarketing experience

In order to assess the post marketing experience for zolpidem in the marketed formulation, I reviewed the periodic safety update reports submitted to the Ambien NDA (#19-908) for the period from 16 December 2002 through 15 December 2004.

The finding of perhaps the greatest clinical significance was the number of reports (n=42) of hallucinations, predominantly visual although tactile and auditory hallucinations were also described. I observe that most of these spontaneous reports came from people who took ≥2 times the recommended dose for age. This observation would lead me to postulate that there may be a dose-response relationship: If the medicine is taken at ≥2 times the recommended dose for age, the risk of hallucination increases. We know from the controlled studies that there is a baseline risk of hallucination, even when taking the recommended dose.

7.2.2.3 Literature

The sponsor provided an adequate selection of references from the sleep literature for this review. The references addressed a range of important issues such as polysomnographic findings e.g. the mechanism of action of zolpidem in vivo, first night sleep lab effects, ADME issues related to zolpidem. The references were provided as *pdf* files with hotlinks in different sections of the application.

7.2.3 Adequacy of Overall Clinical Experience

In addition to the data accrued during drug development, the agency has amassed post-marketing data on zolpidem since the approval of Ambien on 16 December 1992.

The placebo-controlled trials performed were adequate to assess the question of the drug effect on sleep maintenance (the primary objective) as well as on sleep latency (a secondary objective).

This application exposed an adequate number of subjects to this new formulation with approximately equal number of adult and elderly subjects. The gender ratio was appropriate.

While it may have been desirable to achieve greater ethnic diversity in the population studies, that is a problem endemic to clinical trials and not specific to this development program. Overall the inclusion exclusion criteria were appropriate. Patients with severe or chronically progressive renal or hepatic disease would have been excluded but we already have data indicating that dose reduction is not necessary in the former group and is necessary in the latter to decrease the risk of adverse events. Patients with severe or unstable respiratory insufficiency were excluded from study participation. The sponsor reports that, based on the original formulation, patients with mild to moderate sleep apnea had evidence of reduction in oxygen saturation and total arousal index. It was probably not necessary to repeat those studies for this formulation since the results could be expected to be the same or worse.

The doses and durations of exposure were adequate to assess safety for the use of this product. The sponsor appropriately evaluated participants for next-day residual and rebound effects which have been associated with use of the sedative/hypnotics.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

There was no new preclinical data provided for review in support of this submission. The available preclinical data comes from the NDA for Ambien.

7.2.5 Adequacy of Routine Clinical Testing

The routine clinical testing was limited to vital sign assessment and efforts to assess adverse events as agreed upon at the EOP2 meeting. The methods and questionnaires that the sponsor used were adequate and the assessments were done at an appropriate frequency.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

The information on zolpidem tartrate metabolism, clearance and drug-drug interaction comes primarily from pre- and post-marketing experience with Ambien. The currently approved Ambien label contains information on the enzymatic pathways responsible for drug clearance. The sponsor has included information on significant drug-drug interactions for drugs such as digoxin, fluoxetine, rifampin and itraconazole.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

The class specific adverse events of concern are the next-day residual effects and the rebound effect after abrupt drug discontinuation. The sponsor adequately assessed the study participants for these effects as detailed in section 7.1.12. In summary, there was no next-day residual effect seen in the adult or the elderly participants. Rebound effects were seen on the first night after discontinuation but not the second night.

While it would be good to know if a given surrogate/hypnotic drug have any next-day effect on driving ability, the studies of vigilance and alertness that were done may be considered a sort of surrogate marker for that specific task. Sponsors are currently trying to devise a safe manner of specifically testing driving ability in patients using sedative/hypnotics.

7.2.8 Assessment of Quality and Completeness of Data

The data provided appears to be complete and of excellent quality. The sponsor provided hyperlinks to listings along with CRFs at almost every mention of a patient who had had a significant event during the course of the study. I did not find that there was any additional safety data that I would have wanted in the course of the review.

7.2.9 Additional Submissions, Including Safety Update

Sanofi submitted a 120 day safety update which contained information on 3 studies submitted to the IND: PKD 5070, PDY 5195, EFC 5202. Protocols for these studies were provided in the NDA submission but the studies were ongoing as of the NDA cut off day of 01 December 2003.

The safety data from these studies is presented here but has not been combined with the data from the studies submitted in support of the NDA as final study reports had not been submitted at the time of the 120 day safety update. In the following tables, Ambien denotes the currently marketed product and Zolpidem-MR denotes the investigational product.

Study EFC5202 was a double-blind, randomized, placebo-controlled 3-way crossover study comparing zolpidem-MR 12.5 mg, Ambien 10 mg and placebo in patients with primary insomnia. A protocol summary may be found in Appendix 10.2.

Most of the frequently seen treatment-emergent adverse events (TEAE) were consistent with those reported previously in association with Ambien.

The only TEAE that are not currently mentioned in the Ambien label were ataxia, balance disorder, attention disturbance, muscle cramp, migraine, nystagmus, post-traumatic headache, pharyngolaryngeal pain, nasal congestion, rhinorrhea, contact dermatitis, eczema, skin irritation, and tenderness. Of those TEAE, five occurred in patients who received zolpidem-MR but not in patients who received Ambien or placebo: ataxia; balance disorder; nystagmus; post-traumatic headache; eczema.

[*Reviewer's note: In the table below, I have only included TEAE that were seen in either active treatment arm. TEAE that occurred in the placebo group but not in either active group have not been presented. I have marked in bold font those TEAE that occurred in the treatment arm which received zolpidem 12.5 mg but not in either of the other two treatment arms.*]

Table 36: TEAE occurring at ≥1% incidence during study PDY 5202

Organ class	Preferred term	Placebo (N=111) n (%)	Ambien 10 mg (N=108) n (%)	Zolpidem MR 12.5 mg (N=112) n (%)
Any class	Any TEAE	18 (16.2%)	26 (24%)	29 (26%)
GI	Aptyalism	0	0	1 (1%)
	Abdominal discomfort	0	1 (1%)	0
	Constipation	0	1 (1%)	0
	Diarrhea	1 (1%)	0	1 (1%)
	Nausea	0	1 (1%)	5 (5%)
General disorders	Application site erythema	0	1 (1%)	0
	Application site irritation	0	0	1 (1%)
	Application site reaction	1 (1%)	1 (1%)	1 (1%)
	Fatigue	3 (3%)	1 (1%)	3 (3%)
	Tenderness	0	1 (1%)	0
Infections	Nasopharyngitis	0	0	1 (1%)
	URI	1 (1%)	0	1 (1%)
	Viral infection	0	1 (1%)	0
Musculoskeletal and connective tissue disorders	Back pain	1 (1%)	3 (3%)	0
	Muscle cramp	0	1 (1%)	0
CNS disorders	**Ataxia**	0	0	1 (1%)
	Balance disorder	0	0	1 (1%)
	Disturbance in attention	0	1 (1%)	0
	Dysgeusia	0	1 (1%)	0
	Dizziness	1 (1%)	2 (2%)	1 (1%)
	Headache	6 (5%)	6 (6%)	6 (5%)
	Migraine	0	2 (2%)	0
	Nystagmus	0	0	1 (1%)
	Post-traumatic headache	0	0	1 (1%)
	Somnolence	2 (2%)	6 (6%)	7 (6%)

Table 36 continued: TEAE occurring at ≥1% incidence during study PDY 5202

Organ class	Preferred term	Placebo (N=111) n (%)	Ambien 10 mg (N=108) n (%)	Zolpidem MR 12.5 mg (N=112) n (%)
Psychiatric disorders	Visual hallucination	0	1 (1%)	0
	Confusional state	0	1 (1%)	1 (1%)
Respiratory disorders	Pharyngolaryngeal pain	0	1 (1%)	0
	Nasal congestion	1 (1%)	2 (2%)	0
	Rhinorrhea	0	1 (1%)	0
Skin disorders	**Eczema**	0	0	1 (1%)
	Skin irritation	0	1 (1%)	0
Eye disorders	Corneal erosion	0	0	1 (1%)
	Vision blurred	0	0	1 (1%)
Ear disorders	Vertigo	0	0	1 (1%)
Injury	Fall	0	1 (1%)	1 (1%)
	Arthropod sting	0	0	1 (1%)
	Skin injury	0	0	1 (1%)

* This is a modification of table 2.3.1 in the safety update submitted by sanofi

Study PDY5195 was a double-blind, randomized, 9-way crossover study comparing zolpidem-MR 12.5 mg, Ambien 10 mg and placebo using a model of middle of the night insomnia. Subjects were awakened once at 2.5, 3.5 or 4.5 hours post-dose. The adverse event data is presented below. A protocol summary may be found in Appendix 10.2.

Most of the frequently seen treatment-emergent adverse events (TEAE) were consistent with those reported previously in association with Ambien.

The only TEAE that were not already mentioned in the Ambien label were mouth ulceration, application site irritation, abnormal gait, venipuncture site bruise, back pain, sensation of heaviness, musculoskeletal stiffness, amnesia, abnormal coordination, depressed level of consciousness, disturbance in attention, mental impairment, somnolence, disorientation, irritability, nightmare, panic attack, restlessness, dry throat, nasal congestion, and pharyngolaryngeal pain. Of those TEAE, 3 occurred in patients who received zolpidem-MR but not in patients who received Ambien or placebo: musculoskeletal stiffness; depressed level of consciousness; disturbance in attention.

[*Reviewer's note: In the table below, I have only included TEAE that were seen in either active treatment arm. TEAE that occurred in the placebo group but not in either active group have not been presented. I have marked in bold font those TEAE that occurred in the treatment arm which received zolpidem 12.5 mg but not in either of the other two treatment arms.*]

Table 37: TEAE occurring at ≥1% incidence during study PDY 5195

Organ class	Preferred term	Placebo (N=54) n (%)	Ambien 10 mg (N=54) n (%)	Zolpidem MR 12.5 mg (N=54) n (%)
Any class	Any TEAE	25 (46%)	32 (59%)	37 (69%)
Cardiac	**Tachycardia**	0	0	1 (2%)
	Dyspepsia	1 (2%)	1 (2%)	0
	Nausea	3 (6%)	4 (7%)	10 (19%)
	Retching	0	0	1 (2%)
	Vomiting	1 (2%)	0	1 (2%)
General disorders	Chest discomfort	0	1 (2%)	0
	Fatigue	10 (19%)	8 (15%)	14 (26%)
	Gait abnormal	5 (9.3%)	15 (28%)	23 (43%)
	Venipuncture site bruise	0	2 (4%)	0
Infections	**Nasopharyngitis**	0	0	1 (2%)
Musculoskeletal and connective tissue disorders	Back pain	0	1 (2%)	0
	Sensation of heaviness	0	2 (4%)	5 (9%)
	Musculoskeletal stiffness	0	0	1 (2%)
CNS disorders	Amnesia	0	1 (2%)	0
	Coordination abnormal	0	1 (2%)	4 (7%)
	Depressed level of consciousness	0	0	1 (2%)
	Disturbance in attention	0	0	1 (2%)
	Dizziness	0	14 (26%)	18 (33%)
	Headache	3 (6%)	7 (13%)	3 (6%)
	Lethargy	0	1 (2%)	1 (2%)
	Somnolence	0	5 (9%)	8 (15%)
Psychiatric disorders	Abnormal dreams	0	2 (4%)	0
	Anxiety	0	0	1 (2%)
	Disorientation	0	5 (9%)	5 (9%)
	Euphoria	1 (2%)	1 (2%)	1 (2%)
	Irritability	0	1 (2%)	1 (2%)
	Restlessness	3 (6%)	0	1 (2%)

Table 37 continued

Organ class	Preferred term	Placebo (N=54) n (%)	Ambien 10 mg (N=54) n (%)	Zolpidem MR 12.5 mg (N=54) n (%)
Respiratory disorders	Dry throat	0	1 (2%)	0
	Dyspnea	0	1 (2%)	0
	Nasal congestion	0	1 (2%)	0
	Pharyngolaryngeal pain	0	1 (2%)	0
Vascular disorders	Flushing	0	1 (2%)	0

* This is a modification of table 2.2.1 in the safety update submitted by sanofi

Study PKD5070 was a double-blind, 3 way cross-over placebo-controlled investigation of the influence of zolpidem-MR 12.5 mg and Ambien on the EEG beta band (Greenblatt's model) and the cognitive test and of the PK/PD relationship of zolpidem in healthy young volunteers. The adverse event data is presented below. A protocol summary may be found in Appendix 10.2.

Most of the frequently seen treatment-emergent adverse events (TEAE) were consistent with those reported previously in association with Ambien.

The only TEAE that occurred in patients who received active drug, which were not already mentioned in the Ambien label, were peripheral edema (1%), and irritability (1%). Viral infection occurred in 3% of the subjects who received placebo but none of the subjects who received active drug.

[*Reviewer's note: In the table below, I have only included TEAE that were seen in either active treatment arm. TEAE that occurred in the placebo group but not in either active group have not been presented. I have marked in bold font those TEAE that occurred in the treatment arm which received zolpidem 12.5 mg but not in either of the other two treatment arms.*]

Table 38: TEAE occurring at ≥1% incidence during study PKD 5070

Organ class	Preferred term	Placebo (N=79) n (%)	Ambien 10 mg (N=75) n (%)	Zolpidem MR 12.5 mg (N=74) n (%)
Any class	Any TEAE	16 (20%)	17 (23%)	17 (23%)
Cardiac	**Tachycardia**	0	0	1 (1%)
Eye	Vision blurred	1 (1%)	0	0
GI	Nausea	4 (5%)	5 (7%)	6 (8%)
	Vomiting	2 (3%)	4 (5%)	10(14%)

Organ class	Preferred term	Placebo (N=79) n (%)	Ambien 10 mg (N=75) n (%)	Zolpidem MR 12.5 mg (N=74) n (%)
General disorders	Chest pain	0	1 (1%)	0
	Peripheral edema	0	0	1 (1%)
Infections	Dental caries	0	1 (1%)	0
CNS disorders	Dizziness	4 (5%)	2 (3%)	2 (3%)
	Headache	7 (9%)	5 (7%)	4 (5%)
Psychiatric disorders	Euphoria	0	1 (1%)	0
	Irritability	0	1 (1%)	1 (1%)
Respiratory disorders	Hiccups	0	2 (3%)	3 (4%)

* This is a modification of table 2.1.1 in the safety update submitted by sanofi

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

Zolpidem is capable of producing neuropsychiatric adverse effects such as:

Headache
Most of the reported cases in the 12.5 mg group were mild or moderate though one case was severe enough to lead to study discontinuation. All of the cases in the 6.25 mg group were mild or moderate and none led to study discontinuation.
Dizziness
Most of the reported cases in the 12.5 mg were mild or moderate and lasted less than one day though one case was severe enough to lead to study discontinuation. All of the cases in the 6.25 mg group were mild or moderate, one case led to study discontinuation.
Somnolence
Most of the reported cases were mild or moderate and lasted less than one day. This AE led to study discontinuation in two cases (one moderate and one severe, both in the 12.5 mg group). Most of the complaints of somnolence reflected morning sleepiness.
Nausea
Most of the reported cases were mild or moderate though one case (12.5 mg group) was severe enough to lead to study discontinuation.

Additionally, zolpidem use may be associated with psychomotor retardation, memory impairment, visual disturbance /blurred vision, vertigo, and hallucinations.

Although the sample size in the development plan for zolpidem-MR is small, the Agency has pre- and post-marketing data from the currently marketed Ambien which is consistent with the

findings from this study. The proposed formulation has a similar adverse event profile to the currently marketed product.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

7.4.1.1 Pooled data vs. individual study data

I did not pool the data across studies EFC 4529 and EFC 4530 because they used different doses (12.5 mg and 6.25 mg respectively) in different populations (adults and elderly respectively). I felt that pooling in this instance would not improve precision but might obscure differences.

The safety data for the individual studies has been presented earlier in this section.

7.4.1.2 Combining data

The data has not been combined, see the rationale presented in section 7.4.1.1.

7.4.2 Explorations for Predictive Factors

7.4.2.1 Explorations for dose dependency for adverse findings

The susceptibility to adverse effects of sedative/hypnotic agents is known to correlate with age. In light of this the sponsor recommends using reduced doses in the elderly, as was done in the development program.

Only a single dose was tested in each study population so it is not possible to determine whether there is a dose dependency for adverse findings.

7.4.2.2 Explorations for time dependency for adverse findings

The two trials performed in support of this NDA both lasted for a total of one month. The approved labeling for Ambien notes that with "nightly use for an extended period, pharmacodynamic tolerance or adaptation to some effects of hypnotics may develop. If the drug has a short elimination half-life, it is possible that a relative deficiency of the drug or its active metabolites (i.e., in relationship to the receptor site) may occur at some point in the interval between each night's use. This sequence of events may account for two clinical findings reported to occur after several weeks of nightly use of other rapidly eliminated hypnotics, namely, increased wakefulness during the last third of the night, and the appearance of increased signs of daytime anxiety."

There was not a high incidence of daytime anxiety reported from these trials but there did appear to be a wide variation in the amount of wakefulness seen in the latter part of the night after use of Ambien for 2 weeks. While I do not know if we can actually term increased wakefulness an adverse event on its own in the insomniac population, I believe that wakefulness that is increased over baseline is an adverse event and one that appear to be time dependent [*Reviewer's note: see the detailed description of hourly WASO results in the efficacy section of this review*].

7.4.2.3 Explorations for drug-demographic interactions

The susceptibility to adverse effects of sedative/hypnotic agents is known to correlate with age. In light of this the sponsor recommends using reduced doses in the elderly, as was done in the development program.

7.4.2.4 Explorations for drug-disease interactions

This submission did not contain sufficient information on concomitant diseases to allow meaningful explorations for drug-disease interactions. Although not assessed during this development program, the approved labeling for Ambien notes that this product should be used with caution in patients with compromised respiratory function. The label also states that no dosage adjustment is needed in patients with renal dysfunction though reduced doses should be used in persons with hepatic dysfunction.

7.4.2.5 Explorations for drug-drug interactions

The sponsor evaluated for drug-drug interaction between zolpidem–MR and concomitantly used cytochrome 450 inhibitors during the two Phase 3 studies. While in the adult study, the numbers were too small to assess, in the elderly study there were no significant pharmacodynamic effects seen.

7.4.3 Causality Determination

Zolpidem, as demonstrated in premarketing studies and postmarketing data from Ambien as well as in the current studies done with zolpidem-MR may fairly be considered capable of producing the following adverse effects:

- Psychomotor retardation
- Somnolence (with possible dose/response effects)
- Dizziness
- Nausea
- Memory impairment
- Visual disturbance /Blurred vision
- Vertigo
- Hallucinations

There are other adverse events which have been reported but the causality is less clear in those cases.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The proposed dose of Ambien-MR is based upon the known pharmacokinetic/pharmacodynamic activity of zolpidem as well as well as the data from study PDY 4054. Study PDY 4054 was a double-blind, placebo-controlled, 10-way crossover phase I study which compared the pharmacodynamic effects of eight formulations of zolpidem-MR to the currently marketed immediate release form of zolpidem. Formulation E (12.5 mg) was chosen since it reduced the number of awakenings for up to 5 hours post-dose without statistically significant evidence of next-day residual effects. Elderly patients are known, from experience with Ambien, to be sensitive to lower doses of zolpidem. The sponsor decided to use a half-dose (6.25 mg) in the elderly.

Once daily oral administration of this product is an appropriate dosing regimen.

8.2 Drug-Drug Interactions

The sponsor evaluated for drug-drug interaction between zolpidem–MR and concomitantly used cytochrome 450 inhibitors during the two Phase 3 studies. No pharmacodynamic effects due to use of the combinations were seen in either study. While in the adult study, the numbers were too small to assess, in the elderly study there were no significant pharmacodynamic effects seen.

The current Ambien label addresses interactions seen with CNS-active drugs as well as cimetidine, ranitidine, and digoxin. That language would be appropriate for inclusion in the label for this product as well.

8.3 Special Populations

Gender
The percentage of adult females (59.4%) who reported adverse events was similar to the percentage reported by adult males (52.6%). The percentage of elderly females (38.3%) who reported adverse events was similar to the percentage reported by elderly males (38.5%).

Age
Overall, the percentage of elderly patients who reported adverse events was lower than the percentage of adult patients who reported adverse events.

Ethnicity

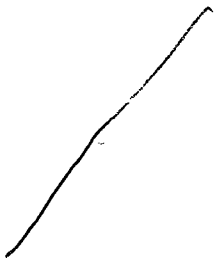
The number of non-Caucasian participants was too small to make any comments on possible interactions of drug and ethnicity.

Although not assessed during this development program, the approved labeling for Ambien notes that this product should be used with caution in patients with compromised respiratory function. The label also states that no dosage adjustment is needed in patients with renal dysfunction though reduced doses should be used in persons with hepatic dysfunction.

8.4 Pediatrics

This product is not indicated for use in children.

In November 1999, an advisory committee considered the use of hypnotics in children and concluded that there was no clear health benefit from the use of hypnotics in the general pediatric population. The Agency did consider that there might be subsets within the pediatric population for whom hypnotics would be indicated and suggested that PK/PD studies might give important information.



8.5 Advisory Committee Meeting

The Agency did not convene an advisory committee meeting related to use of this product in the adult population.

8.6 Literature Review

A comprehensive literature review was not done for this product.

8.7 Postmarketing Risk Management Plan

There was no postmarketing risk management plan submitted for this product.

8.8 Other Relevant Materials

There were no other relevant materials reviewed for this submission.

9 OVERALL ASSESSMENT

9.1 Conclusions

Efficacy
While adequately demonstrating an initial decrease in objectively measured WASO (oWASO) over 8 hours, EFC4529 failed to demonstrate a persistent drug effect since by N15/N16, the decrease in mean total change in oWASO over 8 hours was no longer statistically significant. The exploratory hourly WASO analysis shows that the immediate effect on WASO may last up to 7 hours in adults while the persistent effect lasts up until 5 hours. This product does diminish oWASO for up to 6 hours as an immediate effect in and up to 4 hours as a persistent effect in the elderly. Rebound effects on sleep maintenance, as measured by WASO, are seen on the first night after abrupt drug discontinuation but not subsequently.

Safety
This controlled release product has a similar safety profile to the immediate release product currently being marketed. Withdrawal effects are seen on the first night after abrupt discontinuation in a minority of patients after 3 weeks of use. We do not have any data on whether withdrawal would occur if patients used the drug for a shorter period of time. There may be a dose response relationship since the withdrawal effects were less apparent in the elderly, who received a lower dose. We cannot make a definitive statement due to the small sample size and different populations. Rebound effects on sleep are also seen on the first night after drug cessation. Like the withdrawal effects, the rebound effects appear to be short lived. There are no apparent next day residual effects on attention or vigilance, though there is a relatively high incidence of morning somnolence reported as an adverse event by both adults and the elderly.

9.2 Recommendation on Regulatory Action

The sponsor proposed the following indication for this product: "Ambien CR is indicated for the [redacted] treatment of insomnia. [redacted]

The sponsor's primary goal was to demonstrate that this controlled release product improved sleep maintenance by decreasing wake time after sleep onset, WASO. While adequately demonstrating an initial improvement over 8 hours on Nights 1/2, EFC4529 failed to demonstrate a persistent drug effect since by Nights 15/N16, the improvement was no longer statistically significant. When an exploratory analysis was done to evaluate sleep maintenance over the first 6 hours of the night in study 4529, zolpidem-MR was shown to have statistically significant immediate and persistent positive effects on sleep maintenance. The study done in the elderly, EFC 4530, demonstrated an immediate and persistent positive drug effect on sleep maintenance over the 6 hours studied.

One of the sponsor's secondary goals was to demonstrate that this controlled release product decreased sleep latency (LPS). Both studies demonstrated immediate improvement in decreasing

sleep latency. The study done in the elderly, EFC 4530, demonstrated a persistent drug effect though this was not seen in the adult study, EFC 4529.

An additional secondary goal was to demonstrate that this controlled release product improved sleep duration. Sleep duration reflects the total sleep time. Total sleep time is influenced by both the amount of time that it takes to fall asleep (sleep latency, LPS) and the amount of time that is spent awake after sleep onset (wake time after sleep onset, WASO). While both studies showed improvement in sleep efficiency on nights 1 and 2, only the study in the elderly demonstrated improvement on nights 15 and 16. This result is consistent with the WASO and LPS results described in the preceding two paragraphs. I would argue that it is not an additional benefit —

I can concur that this product has a hypnotic effect and therefore may appropriately be used in the — treatment of insomnia. The current label for the approved product notes that hypnotics should not be used for more than 7-10 days. Hypnotic benefits were clearly demonstrated in both studies on nights 1 and 2. The data from nights 15 and 16 were not as convincing. Since we do not have any measure of drug effectiveness at days 7/8, it is fair to say that there is an immediate effect though persistence of that effect for 2 weeks has not been clearly demonstrated and the point at which the benefit begins to decline cannot be identified. While the common feeling is that a good night's sleep ranges from 7-9 hours, I am unable to find a consensus on the minimal amount of sleep that is needed. I would think that formal study would show a great deal of inter-individual variability. There are some people who would benefit from the short-term (7-10 days) increase in sleep maintenance that is provided by Ambien CR, since the immediate benefit may be expected to last up to 6 (elderly) or 7 hours (adults). The clinical utility of this product when used for a 2 week period is uncertain since the benefit, after a fortnight of use, decreases to 4 (elderly) or 5 hours (adults).

I am recommending an approvable action for this product based on the policy that sponsors must replicate efficacy findings in adequate and well-controlled trials. The sponsor has not yet met this standard as they failed on the primary endpoint in study EFC4529. It may seem to be a bit stringent to request a second trial in adults using PSG measured WASO over 6 hours as the primary endpoint thereby holding the sponsor to the letter of this regulation when one could point to the data from EFC 4529. I think it is important to honor the spirit of the policy and not accept *posthoc* and/or secondary analyses as primary support for drug approval. Ideally studies should be statistically powered to support the primary endpoint. We would run the risk of accepting results from improperly powered studies by agreeing to accept secondary and exploratory endpoints from studies that failed on the primary endpoint, which I feel would set a bad precedent.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

There is no recommended risk management activity for this product.

9.3.2 Required Phase 4 Commitments

There are no required Phase 4 commitments for this product.

9.3.3 Other Phase 4 Requests

There are no other Phase 4 requests for this product.

9.4 Labeling Review

- Changes were made to the clinical pharmacology section
- Changes were made to the clinical trial descriptions
- Changes were made to the indications/use section
- A column describing the TEAE seen at 6.25 mg has been added to the AE table

9.5 Comments to Applicant

- Perform a trial in adults using PSG measured WASO over 6 hours as a primary endpoint
- Consider using a separate PI/PPI for this product

10 APPENDICES

10.1 Review of Individual Study Reports

10.1.1 EFC 4529: Comparison of efficacy and safety of zolpidem-MR 12.5 mg and placebo in patients with primary insomnia. A double-blind, randomized, placebo-controlled, parallel group study.

10.1.1.1 Objectives

- To evaluate the hypnotic efficacy of a 12.5 dose of zolpidem modified release (zolpidem-MR) compared with placebo, using polysomnography (PSG) and patient sleep questionnaires
- To evaluate the residual effects (subjectively by patient's morning questionnaire or objectively by psychometric tests) that may be associated with zolpidem-MR as compared with placebo
- To compare the effect on sleep following abrupt discontinuation between zolpidem-MR and placebo after 21 night of treatment
- To evaluate the clinical safety and tolerability of zolpidem-MR compared with placebo
- To assess the residual plasma concentrations of zolpidem

10.1.1.2 Study design

This was an international, multi-center, randomized, double-blind, parallel-group, placebo-controlled phase 3 study. Forty centers participated: 29 in the United States of America, 5 in Canada and 6 in Australia.

10.1.1.3 Study population and procedures

10.1.1.3.1 Study duration

The study duration was 25 nights per patient, consisting of a 2-day placebo "run-in", 21 days of double-blind treatment and a 2 day placebo "run-out".

10.1.1.3.2 Entry criteria

This study had a planned enrollment of 200 adult patients with primary insomnia based upon DSM-IV and PSG criteria. Patients were to be randomized 1:1::active:placebo.

Inclusion criteria

1. Adults aged 18 to 64 years inclusive
2. Females of childbearing potential (i.e. less than 2 years post-menopausal or not surgically sterile) had to be using acceptable contraception as defined by the protocol. Additionally these women had to have a negative serum pregnancy test prior to the single-blind placebo run-in period
3. Primary insomnia consisting of difficulty in initiating sleep, difficulty in maintaining sleep or non-restorative sleep for at least one month preceding the study visit and clinically significant distress or impairment in social occupational or other important areas of functioning
4. Patient had to complain of at least one hour of wakefulness after sleep onset for at least 3 nights per week over the preceding month
5. Patient had to spend at least 6.5 hours and not more than 9 hours in bed each night over the 2 preceding weeks
6. Based on the PSG recordings obtained during the two screening nights, patients had to demonstrate a mean wake time after sleep onset (WASO) $\geq$ 40 minutes calculated on SN1 and SN2 with neither screening night showing WASO < 30 minutes and total sleep time (TST) of between 3 and 7 hours on both screening nights.
7. Written, signed and dated informed consent must be given by the patient

Exclusion criteria

1. History of hypersensitivity to zolpidem or its excipients
2. Pregnancy or lactation
3. Night shift workers
4. Persons who took a nap 3 or more times per week over the preceding month
5. Consumption of xanthine-containing beverages comprising more than 5 cups or glasses/day
6. Patients who were unable to participate for the entire duration of the study or those who in the opinion of the investigator had the potential to be non-compliant with the obligations inherent in trial participation
7. Participation in another clinical trial in the 2 months before the screening visit
8. Body mass index (BMI) >32 kg/m^2
9. Any of the following conditions based upon medical history and/or PSG: primary hypersomnia, narcolepsy, breathing-related sleep disorder (apnea-hypopnea index >10 per hour of sleep), circadian rhythm sleep disorder, parasomnia, dyssomnia not otherwise specified
10. Severe psychiatric disorder by DSM IV criteria
11. Mental retardation
12. Dementia of Alzheimer's or vascular type
13. History of substance abuse or dependence within the last year
14. History of epilepsy or seizures
15. Myasthenia gravis
16. Evidence of any clinically significant severe or unstable acute or chronically progressive medical or surgical disorder or any condition that might interfere with the ADME of the study drug or might affect patient safety

17. Severe or unstable respiratory insufficiency
18. Serious head injury or stroke within the past year
19. Clinically significant and abnormal electrocardiogram (ECG) or laboratory tests at screening visit [aspartate aminotransferase (AST) or alanine aminotransferase (ALT) 2 times the upper limit of normal (ULN), neutrophils < 1500/mm^3, platelets , 100000/mm^3, creatinine > 200 micromol/L, hemoglobin < 11g/100 mL (male) or < 10g /100 mL (female)]
20. Positive qualitative urine drug screen
21. Use of any OTC or prescription sleep medication, including hypnotics, sedatives, and /or anxiolytics within 2 weeks or 5 half-lives prior to screening (whichever was longer)
22. Use of any substance with psychotropic effects or properties known to affect sleep/wake including but not limited to neuroleptics, morphine/opioid derivatives, sedative antihistamines, stimulants, antidepressants, clonidine within 1 week to 5 half-lives prior to screening (whichever was longer)

10.1.1.3.3 Study medications

Subjects randomized to active treatment were to receive zolpidem-MR 12.5 mg. Identical appearing placebo pills were to be given to the remaining study participants. Both treatment groups were instructed to take their medication 30 minutes prior to lights out when in the sleep laboratory and just before bedtime when at home.

Prohibited concurrent therapy (within 30 days of screening)

- Any over-the-counter or prescription sleep medication or any substance with psychotropic effects or properties known to affect sleep, including but not limited to: neuroleptics, morphine/opioid derivatives, hypnotics and sedatives, anxiolytics, sedative antihistamines, stimulants, antidepressants, clonidine
- Cough/cold preparations were to be discouraged

Permitted concomitant therapy

- Any acute therapy which was not thought to affect sleep
- Any chronic maintenance therapy (except for those prohibited above) that does not interfere with the assessment of a hypnotic agent assuming that said therapy had been prescribed at a stable dose for more than on e month prior to the screening visit and were expected to remain stable for the study duration
- Contraceptives used by female patients

10.1.1.3.4 Study procedures

The first visit was the eligibility visit at which baseline inclusion/exclusion criteria were to be evaluated.

Eligible patients were to have had a screening run in period in which they were to take placebo for 2 nights (SN1/SN2) while in a sleep laboratory. Polysomnogram (PSG) parameters were to have been assessed on screening night 1 (SN1) and screening night 2 (SN2). On screening days 1

and 2, they were to complete the digital symbol substitution test (DSST) and the Ray auditory verbal learning test (RAVLT) so that they would be familiar with those evaluations during the double-blind treatment phase. Throughout the study and especially on those days when they would visit the sleep laboratory, subjects were not supposed to nap, to have heavy exercise within 3 hours of going to bed, or drink alcohol or caffeine containing products. They were also instructed to refrain from activities requiring complete mental alertness or motor coordination for 8 hours after study drug administration.

After the screening period, they were to begin a double-blind treatment period which was to begin with 2 nights (N1/N2) in a sleep laboratory, followed by 12 consecutive nights at home before a scheduled return to the sleep laboratory (N15/N16), they were to return home for 5 more days of outpatient treatment.

The study was to end with a two night single-blind placebo run-out period in the sleep laboratory (N22/N23) in order to assess the effect of abrupt discontinuation of zolpidem-CR.

Polysomnogram (PSG) parameters were to have been assessed on study nights 1, 2, 15, 16, 22 and 23 (N1, N2, N15, N16, N22 and N23).

Plasma was to have been collected for determinations of zolpidem concentration prior to dosing (P00) as well as approximately 9 hours post-dose on the morning following N1 (P01) and the morning following N15 (P02).

Table 39: Study EFC4529 flow chart

STUDY FLOW CHART

Period	SCREENING /RUN-IN PERIOD					TREATMENT PERIOD										RUN-OUT PERIOD			
Visit	Screen	SN1	SD1	SN2	SD2	N1* / D1		N2 / D2		N3-14 /D3-14		N15* / D15		N16 / D16		N17-21/D17-21		N22*/D22		N23 / D23	
Visit Number	1**		2**		3**	4		5				6		7				8		9	
Day	-7					1		2		3 - 14		15		16		17-21		22		23	
Patient Visits	X	X		X		X		X				X		X				X		X	
Informed consent	X																				
Patient Demography	X																				
Med. / Psych. / Sleep history	X																				
Prior/concomitant Meds	X	X		X		X		X				X		X				X		X	
Complete Physical Exam	X																	X			X
Vital signs	X*		X		X		X		X				X		X				X		X
12 Lead ECG	X																				
Clinical Laboratory Tests	X																				
PK Sample						X	X						X								
Eligibility Criteria	X					X															
Evening Questionnaire		X		X		X		X		X		X		X		X		X		X	
PSG		X		X		X		X				X		X				X		X	
Treatments: - placebo administration		X		X														X		X	
- study drug administration						X		X		X		X		X		X					
Morning Questionnaire			X		X		X		X		X		X		X		X		X		X
DSST / RAVLT			X		X		X		X				X		X						
Drug Disp. / Acct.		X[1]			X[2]	X[1]						X[1,4]						X[1,4]			X[2]
Randomization						X[1]															
Sleep Diary / ND 3-14) Disp/Rev								X[3]				X[4]									
Sleep Diary / ND 17-21) Disp/Rev														X[3]				X[4]			
PGI								X				X						X			
Adverse events recorded	X	X	X	X	X	X	X	X	X			X	X	X	X			X	X	X	X

[1] Study Drug Dispensed
[2] Study Drug Accountability
[3] Sleep Diary Dispensed
[4] Sleep Diary Reviewed
[5] Including height and weight
SN = screening night. Day 1 follows Night 1, Day 2 follows Night 2, and so on.
* Night of the week should be constant for these three PSG night pairs if possible.
** Visit 1-3 must occur within one week.

(page 145 of EFC 4529 study report)

10.1.1.3.5 Efficacy measures

Objective

- Mean wake time after sleep onset (WASO) measured by polysomnography readings during the first two nights of randomized treatment (N1, N2).
- Total sleep time (TST) on N1 and N2, to be analysed using sleep efficiency index i.e. TST divided by Time in Bed
- Latency to persistent sleep (LPS) on N1, N2
- WASO on N15, N16
- TST on N15 and N16, to be analysed using sleep efficiency index i.e. TST divided by Time in Bed
- LPS on N15 and N16
- Number of nocturnal awakenings on N1 and N2 as well as on N15 and N16
- Percentage of sleep time spent in each sleep stage (1, 2, 3-4 and REM)

All polysomnography files were to be sent from the study site, after conversion in to a common data format, to a central reading facility. The data obtained after scoring of the files were to be sent directly to the sponsor's data management unit. A paper report of the data was to be sent back from the central reading site to the investigational site.

In order to facilitate randomization, the polysomnograms were to be read at the investigational site initially and the results were to be recorded in the CRF. Once the patient had been randomized, the files from the screening polysomnograms were to be sent to the central reader for review. The only results used in the statistical analysis were those from the central reading site.

Subjective

Global impression scale

Data from patient's morning questionnaire in sleep diary

- Sleep maintenance: WASO, number of awakenings
- Sleep duration: TST
- Sleep induction: Sleep onset latency
- Sleep quality: subjective quality of sleep and refreshing quality of sleep

Data from patient's evening questionnaire

- Disturbances in daily activities

Next day residual effects

Psychometric testing

- DSST, which assesses alertness and vigilence
- RAVLT, which assesses short-term memory

Subjective assessment

- Morning sleepiness
- Ability to concentrate in the morning

Rebound effect
The effect of abrupt drug discontinuation was to be assessed by comparing the change in sleep parameters between baseline (the mean of the screening nights) and each placebo run-out night: N22, N23.

10.1.1.3.6 Statistical analysis

The sponsor specified three populations to be analyzed. The Intent-to-treat (ITT) population, which was the primary population for efficacy analysis, was to consist of all patients exposed to study medication who provided at least one post-baseline efficacy evaluation. The Efficacy-evaluable (EE) population was to exclude those patients who were randomized and treated despite failure to meet entry criteria, those who failed to comply with the study medication dosing schedule and/ or those who received prohibited concomitant medications. The safety population consisted of all randomized patients who took at least one dose of double-blind medication.

The primary efficacy variable was to be the mean change on PSG WASO calculated on the mean of N1 and N2 minus the mean of the two screening nights SN1 and SN2 in comparison with placebo. The central readings of the PSG recordings from the ITT population were to be used for primary analysis. WASO was to be analyzed using a one factor ANOVA. A 95% confidence interval was to be constructed for the difference between zolpidem MR and placebo.

In addition to the primary efficacy analysis, the sponsor planned to perform a covariance analysis using the mean WASO baseline PSG measurements. The sponsor noted that "in the case of a significant heterogeneity at baseline for the primary variable, the planned ANCOVA using WASO at baseline as a covariate was to be considered as primary, "because only this analysis will provide an analysis independent from baseline." Covariance analyses or two-way analyses of variance were also to be performed according to age or gender.

No adjustments were to be made for testing multiple parameters.

10.1.1.3.7 Protocol amendments
Amendment 1 (27 March 2002)
These changes were all made prior to the first patient enrolling in the study.

- Study objectives were clarified
- Eligibility criteria were clarified
- Prohibited over the counter medications were clarified
- Storage conditions for study medications were changed
- Clarifications were made to the subjective testing to be done
- Modifications were made in PK shipping and storage

Amendment 2 (29 May 2002)

- Made minor modifications to the definition of periodic leg movement syndrome

- Added a urinalysis drug screen on N15 for Canadian participants at the request of the Canadian health authorities.

Amendment 3 (07 October 2002)

- Clarified the statistical plan (as shown below) for prioritization of primary and main secondary endpoints.
  Primary endpoint (PSG): WASO N1/N2 and if significant N15/N16
  Secondary endpoints (by order of prioritization)
    PSG sleep efficiency: N1/N2 and if significant N15/N16
    LPS: N1/N2 and if significant N15/N16
    Quality of sleep: N1/N2 and if significant N15/N16
    Others: PGI, refreshing quality of sleep, subjective sleep parameters, PSG and subjective number of awakenings.
  Other evaluation criteria:
  Sleep architecture
  Safety
    Vital signs
    Clinical evaluation
    Adverse events
    Next-day residual effects as measured by DSST, RAVLT
    Rebound effects

10.1.1.4 Study results

10.1.1.4.1 Trial characteristics

This study began on 02 May 2002. The last patient completed the study on 07 November 2002. The majority of the patients were from the USA (29 centers/162 patients), with the remainder from Canada (5 centers/29 patients) and Australia (6 centers/21 patients).

10.1.1.4.2 Demographics

Of the 545 patients screened, 212 patients were eligible for study participation. The majority of the participants were Caucasian (90.1%) and female (58%). The overall mean age was 44.3 years (SD 13 years, range 18-64 years)

The groups were balanced in the duration of the insomnia reported, with an overall median duration of 55 months (range 1-606 months). Approximately one third (33.6%) of the patients in the placebo group had taken a sleep medication within 3 months of beginning the study as compared to 42.2 % of the zolpidem group.

The treatment groups were balanced at baseline for the subjective sleep parameters though unbalanced at baseline for the following PSG parameters: TST, WASO, WASO H1-H3, WASO H4-H6 (see table 41). In addition to the originally planned one-way ANOVA analysis specified

in the protocol, the sponsor performed an ANCOVA analysis to account for the baseline heterogeneity.

Table 40: Demographics for study EFC4529

		Placebo (n=110)	Zolpidem-MR 12.5 mg (n=102)
Gender	Male	51 (46.4%)	38 (37.3%)
	Female	59 (53.6%)	64 (62.7%)
Ethnicity	White	101 (91.8%)	90 (88.2%)
	Black	8 (7.3%)	10 (9.8%)
	Asian	0 (0%)	1 (1%)
	Other	1 (1%)	1 (1%)
Age (years)	n	110	102
	Mean (SD)	45.1 (12.5)	43.6 (13.5)
	Min-Max	18-64	18-64

(EFC 4529 study report page 49, table 10.5.1)

Table 41: Summary of baseline PSG results

		Placebo (N=110)	Zolpidem-MR 12.5 mg (N=102)	Total (N=212)
TST (min:sec)	n	110	102	212
	Median	356:45	370:30	362:00
	Mean (SD)	348:05 (54:15)	361:50 (43:28)	354:42 (49:43)
	Min - Max	136:15 - 455:30	239:45 - 445:15	136:15 - 455:30
Total WASO (min:sec)	n	110	102	212
	Median	88:08	81:15	82:53
	Mean (SD)	93:19 (44:55)	81:28 (35:13)	87:37 (40:53)
	Min - Max	19:00 - 247:15	8:30 - 209:15	8:30 - 247:15
WASO H1 to H3 (min:sec)	n	110	102	212
	Median	14:15	14:08	14:08
	Mean (SD)	21:01 (18:59)	15:51 (13:43)	18:32 (16:49)
	Min - Max	0:00 - 106:30	0:00 - 75:00	0:00 - 106:30
WASO H4 to H6 (min:sec)	n	110	102	212
	Median	33:23	25:38	30:08
	Mean (SD)	38:13 (26:16)	32:33 (22:00)	35:29 (24:25)
	Min - Max	2:30 - 133:00	2:45 - 105:00	2:30 - 133:00
LPS (min:sec)	n	110	102	212
	Median	33:38	33:15	33:23
	Mean (SD)	43:47 (36:47)	41:41 (32:36)	42:46 (34:46)
	Min - Max	2:00 - 192:30	3:00 - 211:30	2:00 - 211:30
Number of awakenings	n	110	102	212
	Median	10	9	10
	Mean (SD)	10.2 (4.2)	9.2 (4.1)	9.7 (4.2)
	Min - Max	3 - 25	2 - 22	2 - 25

<ref>PGM= SL80075023/EFC4529/CSR/BS/PGM_RPT/t106demo.sas OUT= OUTPUT/t106demo_3.ged (25NOV2003 - 13:52)

(Table 10.5.3.2 from EFC 4529 study report)

10.1.1.4.3 Protocol violations

The sponsor excluded 48 patients from the per protocol population as they did not meet inclusion and/or exclusion criteria, see Table 42 below. Four patients from center 840127 were excluded from the per protocol analysis as that center, by sponsor report, was identified as not compliant with GCP.

The sponsor also identified the following deviations:

- Twelve patients had missing or non-scoreable PSG at baseline or a PSG taken just after the double-blind drug intake period: 7 in the placebo group; 5 in the active group.
- Three patients did not adhere to the schedule of visits: 2 in the placebo group; 1 in the zolpidem MR group.
- Five patients took double-blind study medication during the placebo run-out period: 3 in the placebo group; 2 in the active group.

Table 42: Protocol deviations

	Category/Reason	Placebo (N=110)	Zolpidem-MR 12.5 mg (N=102)	Total (N=212)
Inclusion/exclusion criteria	Non primary insomnia	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)
	Mean PSG WASO(SN1,SN2)>=40 min, PSG WASO SN1 and SN2 >=30min. 3h<TST<7h for SN1 and SN2	19 (17.3 %)	8 (7.8 %)	27 (12.7 %)
	Other sleep disorder	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)
	Severe psychiatric disorder	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)
	Positive qualitative drug screen	1 (0.9 %)	1 (1.0 %)	2 (0.9 %)
	OTC or sleep medication within 2 weeks or 5 half-lives prior to screening	0 (0.0 %)	1 (1.0 %)	1 (0.5 %)
	Subst. with properties known to affect sleep/ wake within 1 week or 5 1/2 lives prior to scr	1 (0.9 %)	1 (1.0 %)	2 (0.9 %)
Study procedures	Medication which could have interfered with study results	3 (2.7 %)	5 (4.9 %)	8 (3.8 %)
	PK abnormalities	3 (2.7 %)	7 (6.9 %)	10 (4.7 %)

<ref>PGM= SL80075023/EFC4529/CSR/BS/PGM_RPT/t102dev.sas OUT= OUTPUT/t102dev_1.ged (25NOV2003 - 11:37)

Note: a patient may present several deviations.

(Table 10.2.1.1 from EFC 4529 study report)

The qualitative drug screen was positive for benzodiazepines in one patient in the active treatment arm and for propoxyphene in one patient in the placebo group.

The OTC/sleep medications taken within 5 half-lives or within 2 weeks prior to screening were diazepam (1 patient in active treatment arm), zaleplon (1 patient in placebo treatment arm), valerian root (2 patients in active treatment arm, 1 patient in placebo treatment arm), zolpidem (2 patients in placebo treatment arm), melatonin (1 patient in placebo treatment arm), and triazolam (1 patient in active treatment arm). One of the active treatment arm patients who was taking valerian also took sleepez, another prohibited medication.

The substances with properties known to affect sleep taken within 5 half-lives or within 2 weeks prior to screening were mersyndol (1 patient in placebo treatment arm), fluoxetine (1 patient in active treatment arm), fexofenadine hydrochloride (4 patients in active treatment arm), loratadine (2 patients in active treatment arm, 1 patient on placebo treatment arm), cetirizine hydrochloride (1 patient in placebo treatment arm). One patient in the placebo group took diphenhydramine, fexofenadine and propacet, all within 5 half-lives or within 2 weeks prior to screening.

The medications which could have interfered with study results were loratadine (2 patients in placebo treatment arm), fexofenadine hydrochloride (3 patients in active treatment arm), oxycocet (1 in placebo treatment arm), cetirizine hydrochloride (1 patient in active treatment arm). One patient in the active treatment group took loratadine as well as an OTC preparation containing acetaminophen and pseudophedrine.

10.1.1.4.4 Pharmacokinetics

The sponsor found mean zolpidem plasma concentrations of 51.2 (SD=42.1) on Day 1 and 59.2 (SD=48.2) on Day 15.

A large between subject variability was noted.

10.1.1.4.5 Efficacy endpoints (as prioritized by the sponsor)

- Change in mean total WASO from Hour 1-Hour 8 (oWASO, measured by PSG)
  The results for this pre-specified primary endpoint have been discussed in detail in Section 6 of this review.

- Sleep efficiency (SE, measured by PSG)
  This was a pre-specified secondary endpoint. The sponsor's ANOVA analysis showed a statistically significant effect for the active drug on N1/N2 (p=0.0002) but not N15/N16 (p=0.4401).

  The sponsor's ANCOVA analysis showed an effect on N1/N2, with 13% vs. 5.5% increases in sleep duration (active compared with placebo, p<0.0001). That effect persisted on N15/N16, with 9.4 % vs. 6.4 % increases in sleep duration (active compared with placebo, p<0.0172).

- Latency to persistent sleep (LPS, measured by PSG)
  This was a pre-specified secondary endpoint. The sponsor's ANOVA analysis showed a statistically significant effect for the active drug on N1/N2 (p=0.0411) but not N15/N16 (p=0.2704).

  The sponsor's ANCOVA analysis showed an effect for the active drug on N1/N2, with decreases of 23:48 min vs. 13:30 min (active compared with placebo, p<0.0001). That effect persisted on N15/N16, with decreases of 21:20 min vs. 13:47 min (active compared with placebo, p=0.0338).

- Quality of sleep
  This was a pre-specified secondary endpoint. The sponsor's ANOVA analysis showed an immediate positive effect for the active drug on N1/N2 though this effect was not demonstrated on N15/N16.

- Patient's global impression (PGI) item 1 (aid to sleep)
  This was a pre-specified secondary endpoint. The sponsor's analysis showed an immediate effect on N1/N2 which persisted on N15/N16 when 82% of the active group responded favorably as opposed to 37% of the placebo group.

- Refreshing quality of sleep
  This was a pre-specified secondary endpoint. The sponsor's ANOVA analysis showed an immediate positive effect for the active drug on N1/N2 though not on N15/N16.

- Subjective WASO
  This was a pre-specified secondary endpoint. The sponsor's ANOVA analysis showed a statistically significant effect for the active drug on N1/N2 ($p=0.0006$) but not N15/N16 ($p=0.2427$).

  The sponsor's ANCOVA analysis showed an effect on N1/N2, with decreases of 35:49 min vs. 7:46 min (active compared with placebo, $p=0.0006$).

- Subjective TST
  This was a pre-specified secondary endpoint. The sponsor's ANOVA analysis showed a statistically significant effect for the active drug on N1/N2 ($p<0.0001$) but not N15/N16 ($p=0.2301$).

  The sponsor's ANCOVA analysis showed an effect on N1/N2, with increases of 67:43 min vs. 27:51 min (active compared with placebo, $p<0.0001$). That effect persisted on N15/N16, with 9.4 % vs. 6.4 % increases in sleep duration (active compared with placebo, $p<0.0172$).

- Subjective sleep onset latency
  This was a pre-specified secondary endpoint. The sponsor's ANOVA analysis showed a statistically significant effect for the active drug on N1/N2 ($p=0.0024$) but not N15/N16 ($p=0.1344$).

  The sponsor's ANCOVA analysis showed an effect on N1/N2, with decreases of 29:39 min vs. 11:23 min (active compared with placebo, $p=0.0024$).

- Number of awakenings after sleep onset (NAASO, measured by PSG)
  This was a pre-specified secondary endpoint. The sponsor's ANOVA analysis showed a statistically significant effect for both N1/N2 and N15/N16.

The sponsor's ANCOVA analysis showed an effect on N1/N2, with decreases of 3 vs. 0.9 (active compared with placebo, p<0.0001). That effect persisted on N15/N16, with decreases of 2.7 vs. 0.8 (active compared with placebo, p<0.0001).

- Subjective number of awakenings
  This was a pre-specified secondary endpoint. The sponsor's ANOVA analysis showed a statistically significant effect for active drug on both N1/N2 and N15/N16.

  The sponsor's ANCOVA analysis showed an effect on N1/N2, with decreases of 2.7 vs. 1.0 (active compared with placebo, p=0.0001). That effect persisted on N15/N16, with decreases of 2.2 vs. 1.1 (active compared with placebo, p=0.0298).

- Difficulty in activities due to sleep problems
  This was a pre-specified secondary endpoint. The sponsor's ANOVA analysis did not show a statistically significant effect for active drug on either N1/N2 (p=0.0790) or N15/N16 (p=0.0706).

- WASO per hour and during the different parts of the night
  This was an exploratory endpoint in the analysis. The results have been discussed in detail in section 6 of this review.

- NAASO during the different parts of the night
  This was an exploratory endpoint in the analysis and does not appears to have been addressed in the study report,

- PGI items 2,3,4 (latency to sleep, TST, an the appropriateness of the sleep medication in terms of strength, respectively)
  This was an exploratory endpoint in the analysis. The patients in the active treatment arm rated all three items more favorably than the placebo group did.
- Sleep architecture
  This was an exploratory endpoint in the analysis. In most cases only slight differences were seen between the treatment groups.

10.1.1.4.6 Safety

A detailed analysis of the safety results may be found in Section 7 of this review, Integrated Review of Safety.

10.1.1.5 Reviewer's Summary

The sponsor concluded that Ambien-CR 1) led to a decrease in oWASO during the first 6 hours of sleep though not in Hours 7 and 8, 2) led to decreased sleep latency, and 3) did not cause next day effects in the patients who received active drug. The subjective reports, by the sponsor's analysis demonstrated a persistent drug effect when compared to placebo. The sponsor attributes

the decrease in objectively measured WASO/TST and subjectively reported sleep quality to a sleep laboratory effect on N15/N16.

I conclude that Ambien-CR demonstrated an immediate effect (N1/N2) on sleep maintenance during Hour 1-Hour 6 though not during the entire night as represented by Hour 1- Hour 8. As shown by the results from nights 15/16, Ambien-CR did not demonstrate a persistent effect during Hour 1-Hour 8, thereby failing to meet the pre-specified primary endpoint in the latter instance. I do not understand the rationale behind the sponsor's contention that a sleep laboratory effect existed on N15/N16 but not N1/N2 so I am unable to attribute the decrease in objectively measured WASO, TST and sleep quality on N15/N16 to that effect.

APPEARS THIS WAY
ON ORIGINAL

10.1.2 EFC 4530: Comparison of efficacy and safety of zolpidem-MR 6.25 mg and placebo in elderly patients with primary insomnia. A double-blind, randomized, placebo-controlled, parallel group study.

10.1.2.1 Objectives

- To evaluate the hypnotic efficacy of a 6.25 dose of zolpidem modified release (zolpidem-MR) compared with placebo, using polysomnography (PSG) and patient sleep questionnaires
- To evaluate the residual effects (subjectively by patient's morning questionnaire or objectively by psychometric tests) that may be associated with zolpidem-MR as compared with placebo
- To compare the effect on sleep following abrupt discontinuation between zolpidem-MR and placebo after 21 night of treatment
- To evaluate the clinical safety and tolerability of zolpidem-MR compared with placebo
- To assess the residual plasma concentrations of zolpidem

10.1.2.2 Study design

This was an international, multi-center, randomized, double-blind, parallel-group, placebo-controlled phase 3 study. Forty centers participated: 16 in the United States of America, 7 in Canada, 6 in Germany, 4 in France, 2 in Mexico and 5 in Argentina.

10.1.2.3 Study population and procedures

10.1.2.3.1 Study duration

The study duration was 25 nights per patient, consisting of a 2-day placebo "run-in", 21 days of double-blind treatment and a 2 day placebo "run-out".

10.1.2.3.2 Entry criteria

This study had a planned enrollment of 200 elderly patients with primary insomnia based upon DSM-IV and PSG criteria. The patients were to be randomized 1:1::active:placebo.

Inclusion criteria

1. Adults aged 65 years and older
2. Primary insomnia consisting of difficulty in initiating sleep, difficulty in maintaining sleep or non-restorative sleep for at least one month preceding the study visit and clinically significant distress or impairment in social occupational or other important areas of functioning
3. Patient had to complain of at least one hour of wakefulness after sleep onset for at least 3 nights per week over the preceding month

4. Patient had to spend at least 6.5 hours and not more than 9 hours in bed each night over the 2 preceding weeks
5. Based on the PSG recordings obtained during the two screening nights, patients had to demonstrate a mean wake time after sleep onset (WASO) $\geq$ 40 minutes calculated on SN1 and SN2 with neither screening night showing WASO < 30 minutes and total sleep time (TST) of between 3 and 7 hours on both screening nights.
6. Written, signed and dated informed consent must be given by the patient

Exclusion criteria

1. History of hypersensitivity to zolpidem or its excipients
2. Night shift workers
3. Persons who took a nap 3 or more times per week over the preceding month
4. Consumption of xanthine-containing beverages comprising more than 5 cups or glasses/day
5. Patients who were unable to participate for the entire duration of the study or those who in the opinion of the investigator had the potential to be non-compliant with the obligations inherent in trial participation
6. Participation in another clinical trial in the 2 months before the screening visit
7. Body mass index (BMI) >32 kg/m^2
8. Any of the following conditions based upon medical history and/or PSG: primary hypersomnia, narcolepsy, breathing-related sleep disorder (apnea-hypopnea index >15 per hour of sleep), circadian rhythm sleep disorder, parasomnia, dyssomnia not otherwise specified i.e. periodic leg movement syndrome. [A leg movement was to be defined as a burst of anterior tibialis muscle activity with a duration between onset and resolution of 0.5-5.0 seconds, with an amplitude of at least a doubling of the baseline amplitude. The leg movement must be separated from a subsequent leg movement by at least 5 seconds and not more than 90 seconds. The leg movements were to be associated with an arousal or awakening to be considered an event, and the arousal/awakening must have followed the leg movement onset by not more than 3 seconds. The periodic leg movement exclusion criterion was to be defined as a PLMAI$\geq$10 events/hour of sleep. Leg movements associated with wake and respiratory events were not to be counted.]
9. Severe psychiatric disorder by DSM IV criteria
10. Mental retardation
11. Dementia of Alzheimer's or vascular type
12. History of substance abuse or dependence within the last year
13. History of epilepsy or seizures
14. Myasthenia gravis
15. Parkinson' disease
16. Evidence of any clinically significant severe or unstable acute or chronically progressive medical or surgical disorder or any condition that might interfere with the ADME of the study drug or might affect patient safety
17. Severe or unstable respiratory insufficiency
18. Serious head injury or stroke within the past year
19. Clinically significant and abnormal electrocardiogram (ECG) or laboratory tests at screening visit [aspartate aminotransferase (AST) or alanine aminotransferase (ALT) 2

times the upper limit of normal (ULN), neutrophils < 1500/mm^3, platelets , 100000/mm^3, creatinine > 200 micromol/L, hemoglobin < 11g/100 mL (male) or < 10g /100 mL (female)]

20. Positive qualitative urine drug screen
21. Use of any OTC or prescription sleep medication, including hypnotics, sedatives, and /or anxiolytics within 2 weeks or 5 half-lives prior to screening (whichever was longer)
22. Use of any substance with psychotropic effects or properties known to affect sleep/wake including but not limited to neuroleptics, morphine/opioid derivatives, sedative antihistamines, stimulants, antidepressants, clonidine within 1 week to 5 half-lives prior to screening (whichever was longer)

10.1.2.3.3 Study medications

Subjects randomized to active treatment were to receive zolpidem-MR 12.5 mg. Identical appearing placebo pills were to be given to the remaining study participants. Both treatment groups were instructed to take their medication 30 minutes prior to lights out when in the sleep laboratory and just before bedtime when at home.

Prohibited concurrent therapy (within 30 days of screening)

- Any over-the-counter or prescription sleep medication or any substance with psychotropic effects or properties known to affect sleep, including but not limited to: neuroleptics, morphine/opioid derivatives, hypnotics and sedatives, anxiolytics, sedative antihistamines, stimulants, antidepressants, clonidine
- Cough/cold preparations were to be discouraged

Permitted concomitant therapy

- Any acute therapy which was not thought to affect sleep
- Any chronic maintenance therapy (except for those prohibited above) that does not interfere with the assessment of a hypnotic agent assuming that said therapy had been prescribed at a stable dose for more than on e month prior to the screening visit and were expected to remain stable for the study duration

10.1.2.3.4 Study procedures

The first visit was the eligibility visit at which baseline inclusion/exclusion criteria were to be evaluated.

Eligible patients were to have had a screening run in period in which they were to take placebo for 2 nights (SN1/SN2) while in a sleep laboratory. Polysomnogram (PSG) parameters were to have been assessed on screening night 1 (SN1) and screening night 2 (SN2). On screening days 1 and 2, they were to complete the digital symbol substitution test (DSST) and the Ray auditory verbal learning test (RAVLT) so that they would be familiar with those evaluations during the double-blind treatment phase. Throughout the study and especially on those days when they would visit the sleep laboratory, subjects were not supposed to nap, to have heavy exercise within 3 hours of going to bed, or drink alcohol or caffeine containing products. They were also

instructed to refrain from activities requiring complete mental alertness or motor coordination for 8 hours after study drug administration.

After the screening period, they were to begin a double-blind treatment period which was to begin with 2 nights (N1/N2) in a sleep laboratory, followed by 12 consecutive nights at home before a scheduled return to the sleep laboratory (N15/N16), they were to return home for 5 more days of outpatient treatment.

The study was to end with a two night single-blind placebo run-out period in the sleep laboratory (N22/N23) in order to assess the effect of abrupt discontinuation of zolpidem-CR.

Polysomnogram (PSG) parameters were to have been assessed on study nights 1, 2, 15, 16, 22 and 23 (N1, N2, N15, N16, N22 and N23).

Plasma was to have been collected for determinations of zolpidem concentration prior to dosing (P00) as well as approximately 9 hours post-dose on the morning following N1 (P01) and the morning following N15 (P02).

Table 42: Study flow chart

Period	SCREENING /RUN-IN PERIOD					TREATMENT PERIOD											RUN-OUT PERIOD			
Visit	Screen	SN1	SD1	SN2	SD2	N1* / D1		N2 / D2		N3-14 /D3-14		N15* / D15		N16 / D16		N17-21/D17-21		N22*/D22		N23 / D23	
Visit Number	1**	2**		3**		4		5		6		7						8		9	
Day	-7					1		2		3 - 14		15		16		17-21		22		23	
Patient Visits	X	X		X		X		X				X		X				X		X	
Informed consent	X																				
Patient Demography	X																				
Med. / Psych. / Sleep history	X																				
Prior/concomitant Meds	X	X		X		X		X				X		X				X		X	
Complete Physical Exam	X																	X			X
Vital signs	X*		X		X		X		X				X		X				X		X
12 Lead ECG	X																				
Clinical Laboratory Tests	X																				
PK Sample						X	X						X								
Eligibility Criteria	X					X															
Evening Questionnaire		X		X		X		X		X		X		X		X		X		X	
PSG		X		X		X		X				X		X				X		X	
Treatments:																					
- placebo administration		X		X														X		X	
- study drug administration						X		X		X		X		X		X					
Morning Questionnaire			X		X		X		X		X		X		X		X		X		X
DSST / RAVLT			X		X		X		X				X		X						
Drug Disp. / Acct.		X*			X*	X*						X* -						X*-*			X*
Randomization						X															
Sleep Diary (ND 3-14) Disp/Rev									X*			X*									
Sleep Diary (ND 17-21) Disp/Rev															X*			X*			
PGI									X			X						X			
Adverse events recorded	X	X	X	X	X	X	X	X	X			X	X	X	X			X	X	X	X

Study Drug Dispensed
Study Drug Accountability
Sleep Diary Dispensed
Sleep Diary Reviewed
Including height and weight
SN = screening night. Day 1 follows Night 1, Day 2 follows Night 2, and so on.
Night of the week should be constant for these three PSG night pairs if possible.
* Visit 1-3 must occur within one week

(EFC4530 final study report, p. 130)

10.1.2.3.5 Efficacy measures

Objective (PSG based)

- Mean wake time after sleep onset (WASO) measured by subtracting the mean of the screening nights (SN1, SN2) from the mean of the first two treated nights (N1, N2).
- Sleep efficiency: mean change measured by subtracting the mean of the screening nights (SN1, SN2) from the mean of the first two treated nights (N1, N2).

- Latency to persistent sleep (LPS): mean change measured by subtracting the mean of the screening nights (SN1, SN2) from the mean of the first two treated nights (N1, N2).
- WASO on N15, N16: mean change measured by subtracting the mean of the screening nights (SN1, SN2) from the mean of N15 and N16.
- Sleep efficiency on N15, N16: mean change measured by subtracting the mean of the screening nights (SN1, SN2) from the mean of N15 and N16.
- LPS on N15 and N16: mean change measured by subtracting the mean of the screening nights (SN1, SN2) from the mean of N15 and N16.
- Number of awakenings
- Evaluation of sleep architecture (Stages 1, 2, 3/4 , REM)

All polysomnography files were to be sent from the study site, after conversion in to a common data format, to a central reading facility. The data obtained after scoring of the files were to be sent directly to the sponsor's data management unit. A paper report of the data was to be sent back from the central reading site to the investigational site.

In order to facilitate randomization, the polysomnograms were to be read at the investigational site initially and the results were to be recorded in the CRF. Once the patient had been randomized, the files from the screening polysomnograms were to be sent to the central reader for review. The only results used in the statistical analysis were those from the central reading site.

Subjective
Global impression scale
Data from patient's morning questionnaire in sleep diary

- Sleep maintenance: WASO, number of awakenings
- Sleep duration: TST
- Sleep induction: Sleep onset latency
- Sleep quality: refreshing quality of sleep

Data from patient's evening questionnaire

- Disturbances in daily activities due to sleep difficulties

Next day residual effects
Psychometric testing

- DSST, which assesses alertness and vigilence
- RAVLT, which assesses short-term memory

Subjective assessment

- Morning sleepiness
- Ability to concentrate in the morning

Rebound effect
The effect of abrupt drug discontinuation was to be assessed by comparing the change in WASO between baseline (the mean of the screening nights) and each placebo run-out night: N22, N23.

10.1.2.3.6 Statistical analysis

The Intent-to-treat (ITT) population, which was the primary population for efficacy analysis, was to consist of all patients exposed to study medication who provided at least one post-baseline efficacy evaluation. The safety population consisted of all randomized patients who took at least one dose of double-blind medication. The per-protocol population excludes patients from the ITT population who were randomized and failed to comply adequately with the study medication dosing schedule or who received prohibited concomitant medications.

The primary efficacy variable was to be the mean change on PSG WASO calculated on the mean of N1 and N2 minus the mean of the two screening nights SN1 and SN2 in comparison with placebo. The central readings of the PSG recordings from the ITT population were to be used for primary analysis. WASO was to be analyzed using a one factor ANOVA. A 95% confidence interval was to be constructed for the difference between zolpidem MR and placebo.

In addition to the primary efficacy analysis, the sponsor planned to perform a covariance analysis using the mean WASO baseline PSG measurements. The sponsor noted that "in the case of a significant heterogeneity at baseline for the primary variable, the planned ANCOVA using WASO at baseline as a covariate was to be considered as primary, "because only this analysis will provide an analysis independent from baseline." Covariance analyses or two-way analyses of variance were also to be performed according to age or gender.

10.1.2.3.7 Protocol amendments

Amendment 1 (18 March 2002)
These changes were all made prior to the first patient enrolling in the study.

- Eligibility criteria were clarified e.g. exclusion criteria for substance abuse/dependence, specific type and duration of prior sleep disturnbance, sleep history criteria
- Prohibited over the counter medications were clarified
- Storage conditions for study medications were changed
- Clarifications were made to the subjective testing to be done
- Modifications were made in PK shipping and storage

Amendment 2 (7 October 2002)

- Added Brazil to the list of participating countries
- Raised the apnea-hypopnea index to >15/hour of sleep and periodic leg movements arousal index (PLMAI ≥20/hour) to reflect the age of the study population
- Modified the definition of leg movement to require an amplitude of at least 25% of baseline
- Added Parkinson's disease to the list of excluded conditions since it is associated with concomitant parasomnia as well as disorgers of vigilence
- Clarified that the secondary efficacy results would be prioritized using a step-down procedure and stopping as soon as N1, N2 for a given endpoint was not significant at eh 5% level.
- Clarified that LOCF would be used in the case of dropouts prior to night 15

- A one-factor ANOVA was to be used to analyze the immediate effects. Another ANOVA would be used to evaluate persistence of effects.
- Clarified the use of RAVLT and DSST after each night of polysomnography recording except N22 and N23.

10.1.2.3.8 Changes in statistical analysis made before the blind was broken

A fourth population was added to the proposed analysis plan. This population (completers) included all patients who had been randomized, took at least one dose of study medication and provided efficacy data on N1 (and/or N2) and on N15 (and/or N16).

The per protocol population (PP) was defined and patients with at least one of the following findings were excluded from the analysis:

- Patients who did not fulfill DSM IV criteria for primary insomnia
- Patients who did not fulfill the following criteria: mean PSG WASO on SN1 and SN2 $\geq$ 40 min and no screening night with PSG WASO <30 min and 3 hours <TST<7 hours.
- Missing on non-scorable PSG at baseline
- Sleep disorder other than insomnia
- Severe psychiatric disorder
- PSG omitted just after double-blind drug intake
- Use of medication which may have interfered with the study results
- Poor compliance (defined as below 80%)
- Zolpidem detection in pharmacokinetic sample for patients randomized to placebo

The total WASO (over 8 hours) was replaced with WASO during the first 6 hours of the night wherever applicable.

The evaluation for rebound effects after drug discontinuation was to include mean changes from baseline in TST and LPS as well as WASO.

10.1.2.3.9 Changes in statistical analysis made after the blind was broken

The testing of the efficacy endpoints was done using a step-down Hochberg procedure for protecting the global type I error. This required testing of the primary endpoint forst and if either both N1/N2 and N15/N16 were significant at the 0.05 level or one was significant at the 0.025 level, the first secondary endpoint was tested. The procedure was repeated for the subsequent secondary endpoints in the pre-specified prioritized order. This testing method was discussed with the FDA on the day of the unblinding.

Other changes to the statistical analysis plan included

- Replacement of ANOVA by ANCOVA for parameters which were unbalanced at baseline
- Replacement of ANOVA by ANCOVA for age analysis
- Exploratory analyses for WASO were added to evaluate the response to treatment for each hour during the night

- ANOVA, ANCOVA and non-parametric Wilcoxon tests were compared for efficacy parameters
- Age effect was evaluated as part of the pharmacokinetic evaluation
- In the analysis of the adverse effects, statistical comparisons were performed when incidence of a preferred term in the active group was ≥5%

10.1.2.4 Study results

10.1.2.4.1 Trial characteristics

This study began on 30 September 2002. The last patient completed the study on 30 September 2003. The majority of the patients were from the USA (16 centers/103 patients), with the remainder from Canada (7 centers/49 patients), Germany (6 centers/28 patients), Argentina (5 centers/13 patients), France (4 centers/7 patients), Mexico (2 centers/5 patients).

10.1.2.4.2 Demographics

Of the 396 patients screened, 205 patients were eligible for study participation. The majority of the participants were Caucasian (95.1%) and female (57%). The overall mean age was 70.2 years (SD 4.5 years, range 64-87 years).

Table 44: Demographics for study EFC4530

		Placebo (n=106)	Zolpidem-MR 6.25 mg (n=99)
Gender	Male	49 (46.2%)	39 (39.4%)
	Female	57 (53.8%)	60 (60.6%)
Ethnicity	White	101 (95.3%)	94 (94.9%)
	Black	3 (2.8%)	4 (4.0%)
	Asian	2 (1.9%)	1 (1.0%)
Age (years)	n	106	99
	Mean (SD)	70.1 (4.2)	70.3 (4.8)
	Min-Max	65-83	64-87

(study report page 47, table 10.5.1.1)

The groups had a mean duration of insomnia of 154 months with a range of 2 to 720 months. The median durations were lower in the zolpidem-MR group 86 months than in the placebo group, 97 months. Approximately one third of the patients in each group had taken a sleep medication within 3 months of beginning the study.

The treatment groups were balanced at baseline for the subjective sleep parameters and most of the objective parameters.

Table 45: Screening PSG results

		Placebo (N=106)	Zolpidem-MR 6.25 mg (N=99)	Total (N=205)
TST (min:sec)	n	104	99	203
	Median	341:15	347:00	343:00
	Mean (SD)	335:13 (51:54)	336:21 (49:38)	335:46 (50:41)
	Min - Max	122:00 - 432:15	171:45 - 436:15	122:00 - 436:15
WASO H1 to H6 (min:sec)	n	104	99	203
	Median	64:23	62:45	62:45
	Mean (SD)	70:15 (33:37)	67:16 (33:41)	68:48 (33:36)
	Min - Max	9:00 - 166:30	14:00 - 205:15	9:00 - 205:15
Total WASO (min:sec)	n	104	99	203
	Median	109:38	104:00	106:30
	Mean (SD)	113:22 (41:52)	112:48 (46:20)	113:06 (44:00)
	Min - Max	27:15 - 205:45	21:15 - 294:15	21:15 - 294:15
LPS (min:sec)	n	104	99	203
	Median	28:45	31:30	29:30
	Mean (SD)	35:43 (27:58)	36:52 (24:10)	36:16 (26:08)
	Min - Max	1:45 - 182:15	5:15 - 124:15	1:45 - 182:15
Number of awakenings	n	104	99	203
	Median	12	11	11
	Mean (SD)	12.1 (4.1)	10.8 (3.4)	11.5 (3.8)
	Min - Max	5 - 28	2 - 21	2 – 28

<ref>PGM= SL8007502J/EFC4530/CSR/BS/PGM_RPT/t106demo.sas OUT= OUTPUT/t106demo_5.qad (25NOV2003 - 13:41)

(Table 10.5.3.2 from EFC4530 study report)

10.1.2.4.3 Protocol violations

The sponsor excluded 24 patients from the per-protocol analysis. It should be noted that a given patient might have more than one violation.

Protocol violations

- Positive qualitative drug screen
  - Opiate (1 in the placebo group, 1 in the active group)
  - Amphetamines (1 in the placebo group)
- OTC or sleep mediation within 2 weeks or 5 half lives prior to screening
  - Zolpidem (1 in the placebo group, 1 in the active group)
  - Clonazepam (1 in the placebo group)
  - Hydroxyzine (1 in the active group)
  - Herbal preparation NOS (1 in the placebo group)
  - Zopiclone (1 in the active group)
  - Lorazepam (1 in the placebo group)
  - Spasmine (1 in the placebo group)
  - Lormetazepam (1 in the active group)
  - Hypericum extract (1 in the active group)
- Substances with properties known to affect sleep/wake within 1 week or 5 half-lives prior to screening
  - Desloratadine (1 in the active group)
  - Clonidine (1 in the placebo group)

  - Hydrocodone (1 in the placebo group)
  - Acetaminophen with codeine (1 in the placebo group, 1 in the active group)
  - Loratadine (1 in the placebo group, 1 in the active group)
  - Cetirizine (1 in the active group)
  - Fexofenadine (1 in the placebo group, 1 in the active group)
  - Meclozine (1 in the active group)
  - Cyclobenzaprine (1 in the placebo group)
  - Doxylamine (1 in the active group)
  - Ambroxol (1 in the active group)
  - Potassium iodide (1 in the placebo group)
- Concomitant medication which could have interfered with the study results
  - Acetaminophen with codeine (2 in the placebo group, 1 in the active group)
  - Clonidine (1 in the placebo group)
  - Cetirizine (1 in the active group)
  - Tramadol (1 in the active group)
  - Fexofenadine (1 in the placebo group)
- Mean PSG WASO on SN1 and SN2 $\geq$ 40 min and no screening night with PSG WASO < 30 min and TST between 3 and 7 hours (2 in the placebo group, 3 in the active group)
- Poor compliance (1 in the placebo group, 1 in the active group)
- PK abnormalities (2 in the placebo group, 1 in the active group)
- Missing or non-scoreable PSG at baseline or PSG not just after double-blind drug intake (2 patients in the placebo group)

10.1.2.4.4 Pharmacokinetics

The sponsor found mean zolpidem plasma concentrations of 38.0 (SD=29.1) on Day 1 and 39.2 (SD=32.8) on Day 15. A large between subject variability was noted.

10.1.2.4.5 Efficacy endpoints

Efficacy endpoints (as prioritized by the sponsor)

- Change in mean total WASO from Hour 1-Hour 6 (oWASO, measured by PSG)
  The results for this pre-specified primary endpoint are in Section 6 of this review.

- Sleep efficiency (SE, measured by PSG)
  This was a pre-specified secondary endpoint. The sponsor's ANCOVA analysis showed a statistically significant effect for the active drug on N1/N2 ($p<0.0001$) but not N15/N16 ($p=0.4509$).

- Latency to persistent sleep (LPS, measured by PSG)
  This was a pre-specified secondary endpoint. The sponsor's ANCOVA analysis showed an effect for the active drug on N1/N2, with decreases of 17:10 min vs. 6:55 min (active compared with placebo, $p=0.0001$). That effect persisted on N15/N16, with decreases of 14:18 min vs. 8:30 min (active compared with placebo, $p=0.0255$).

- Quality of sleep
  This was a pre-specified secondary endpoint. The treatment groups were not equal for this characteristic at baseline. The sponsor's ANCOVA analysis showed an immediate positive effect for the active drug on N1/N2 though this effect was not demonstrated on N15/N16.

- Patient's global impression (PGI) item 1 (aid to sleep)
  This was a pre-specified secondary endpoint. The sponsor's analysis showed an immediate effect which persisted on N15/N16 when 66% of the active group responded favorably as opposed to 49% of the placebo group.

- Refreshing quality of sleep
  This was a pre-specified secondary endpoint. The sponsor's ANOVA analysis showed an immediate positive effect for the active drug on N1/N2 (p=0.0014) though not on N15/N16 (p=0.1081).

- Subjective WASO
  This was a pre-specified secondary endpoint. The sponsor's analysis showed a statistically significant effect for the active drug on N1/N2 (p=0.0101) but not N15/N16 (p=0.1620).

- Subjective TST
  This was a pre-specified secondary endpoint. The sponsor's analysis showed a statistically significant effect for the active drug on N1/N2 (p=0.0006) but not N15/N16 (p=0.2143).

- Subjective sleep onset latency
  This was a pre-specified secondary endpoint. The sponsor's analysis showed a statistically significant effect for the active drug on N1/N2 (p=0.0421) but not N15/N16 (p=0.8636).

- Number of awakenings after sleep onset (NAASO, measured by PSG)
  This was a pre-specified secondary endpoint. The sponsor's analysis showed an effect on N1/N2. That effect was not seen on N15/N16.

- Subjective number of awakenings
  This was a pre-specified secondary endpoint. The sponsor's analysis showed a statistically significant effect for active drug on both N1/N2 and N15/N16.

- Difficulty in activities due to sleep problems
  This was a pre-specified secondary endpoint. The sponsor's analysis did not show a statistically significant effect for active drug on either N1/N2 or N15/N16.

- WASO per hour

This was an exploratory endpoint in the analysis. The results have been discussed in detail in section 6 of this review.

- WASO during the different parts of the night (H1-H3, H4-H6 and H7-H8 respectively)
  This was an exploratory endpoint in the analysis. The results have been discussed in detail in section 6 of this review.

- PGI items 2,3,4 (latency to sleep, TST, an the appropriateness of the sleep medication in terms of strength, respectively)
  This was an exploratory endpoint in the analysis. The patients in the active treatment arm rated all three items more favorably than the placebo group did.

- Sleep architecture
  This was an exploratory endpoint in the analysis. In most cases only slight differences were seen between the treatment groups.

10.1.2.4.6 Safety

A detailed analysis of the safety results may be found in Section 7 of this review, Integrated Review of Safety.

10.1.2.5 Reviewer's Summary

I conclude that Ambien-CR demonstrated an immediate effect (N1/N2) on sleep maintenance during Hour 1-Hour 6 though not during the entire night as represented by Hour 1- Hour 8. As shown by the results from nights 15/16, Ambien-CR did demonstrate a persistent effect during Hour 1-Hour 6, thereby meeting the pre-specified primary endpoint.

10.1.3 EFC 5202

Title:
Evaluation of the hypnotic properties of zolpidem-MR 12.5 mg and Ambien 10 mg (marketed product) compared to placebo in patients with primary insomnia. A double-blind, randomized, placebo-controlled, 3-way crossover study.

Summary:
This study utilized healthy volunteers (n=90) to compare the sleep maintenance provided by each study drug, as measured by PSG WASO.

This double-blind, randomized, 3-way crossover study compared zolpidem-MR 12.5 mg, Ambien 10 mg and placebo.

The study was completed by the submission of the 120 day safety report. The available adverse event information has been presented in section 7.2.9.

No deaths or SAEs were reported during this study.

One participant withdrew due to an adverse event.

- A subject (# 840110013) discontinued due to severe confusion, fall, ataxia, and somnolence experienced after the second ingestion of Ambien 12.5 mg. The subject recovered within 24 hours.

10.1.4 PDY 5195

Title:
A controlled study of the effects of zolpidem-MR 12.5 mg versus Ambien (10 mg) using a model of middle of the night insomnia

Summary:
This study utilized healthy volunteers (n=54) to evaluate drug effect on latency to persistent sleep at 3, 4, and 5 hours after administration. Subjects were awakened once at 2.5, 3.5 or 4.5 hours post-dose. This double-blind, randomized, 9-way crossover study compared zolpidem-MR 12.5 mg, Ambien 10 mg and placebo.

The study was completed by the submission of the 120 day safety report. The available adverse event information has been presented in section 7.2.9.

No deaths, SAEs or discontinuations were reported during this study.

10.1.5 PKD 5070

Title:
A double-blind, 3 way cross-over placebo-controlled investigation of the influence of zolpidem-MR 12.5 mg and Ambien on the EEG beta band (Greenblatt's model) and the cognitive test and of the PK/PD relationship of zolpidem in healthy young volunteers.

Summary:
This study utilized healthy volunteers (n=72) to study whether the drugs administered had sustained activity. The PK/PD relationship was also evaluated.

The study was completed by the submission of the 120 day safety report. The available adverse event information has been presented in section 7.2.9.

No deaths or SAEs were reported during this study.

One participant in each group withdrew due to an adverse event.

- A subject (# 840001001) discontinued due to hypertension experienced 6 days after ingestion of Ambien 10 mg. Initially the recorded systolic blood pressure was 143 mm Hg, with a diastolic blood pressure of 92 mm HG and a heart rate of 100 bpm. Fifteen minutes later the recorded systolic blood pressure was 136 mm Hg, with a diastolic blood pressure of 86 mm HG and a heart rate of 88 bpm. No treatment was given.
- A subject who had been treated with placebo (# 840001017) discontinued due to urticaria attributed to ingestion of a peanut. Diphenhydramine was given as treatment.

10.1.6 ALI 5057

Title
Effect of food on the pharmacokinetics profile of zolpidem following single oral administration of zolpidem-MR 12.5 mg in healthy young male and female subjects

Summary:
This study evaluated the effect of food on the pharmacokinetic profile of zolpidem-MR 12.5 mg in 48 healthy volunteers.

No deaths or SAEs were reported during this study.

One participant withdrew due to an adverse event.

- A 23 year old woman (# 50) discontinued due to vomiting experienced on day 1.

10.1.7 BDR5477

Title:
Relative bioavailability study comparing a new tablet formulation(MRbis) of zolpidem and the reference tablet formulation (MR) at 6.25 mg after single oral administration in healthy male and female subjects. Open, randomized, crossover and single center study.

Summary:
This study evaluated the relative bioavailability and bioequivalence of zolpidem administered as a new tablet 6.25 mg formulation after single oral administration in comparison to that obtained after administration of the 6.25 mg formulation used in the Phase 3 trial.

No deaths, SAEs or discontinuations were reported during this study.

10.1.8 BDY5478

Title:
Relative bioavailability study comparing a new tablet formulation (MRbis) of zolpidem and the reference tablet formulation (MR) at 12.5 mg after single oral administration in healthy male and female subjects. Open, randomized, crossover and single center study.

Summary:
This study evaluated the relative bioavailability and bioequivalence of zolpidem administered as a new tablet 12.5 mg formulation after single oral administration in comparison to that obtained after administration of the 12.5 mg formulation used in the Phase 3 trial.

No deaths, SAEs or discontinuations were reported during this study.

10.1.9 GAR4624

Title:
Relative and absolute bioavailability of new zolpidem oral formulations (biphasic tablet) compared to Stilnox and injectable zolpidem, following single administration to normal young male subjects. Open, randomized, crossover and single center study.

Summary:
This study evaluated the relative bioavailability and plasma PK profile of the biphasic formulation as compared to the marketed formulation as well as evaluating the absorption profile and absolute bioavailability of the new formulation using IV administration as reference. This study enrolled 24 volunteers.

No deaths, SAEs or discontinuations were reported during this study.

10.1.10 PDY4054

Title:
A double-blind, placebo-controlled, 10-way crossover phase I study comparing the pharmacodynamic effects of eight galenic formulations of zolpidem-MR versus the currently marketed immediate release form of zolpidem in healthy adults

Summary:
The primary objective was to evaluate the effect on sleep maintenance using PSG to measure the number of arousals, the total number of arousals during the 8 hours in bed and the total number of arousals during the last four hours.

Formulation E (12.5 mg) was chosen as the study dose for the Phase III adult trial since it was one of the three formulations that reduced the number of awakenings up to 5 hours post-dose and it was the only one to show no statistically significant evidence of residual effects at 8 or 9 hours post-dose. Elderly patients are known, from experience with Ambien, to be sensitive to lower doses of zolpidem. The sponsor decided to use a half-dose for the Phase III study in the elderly.

No deaths or SAEs were reported during this study. Four patients discontinued prematurely: One (#8) due to poor compliance to the protocol; inability to attend the clinic due to "car problems" (#32); depressed mood (#7); agitation, depression, abnormal thinking, insomnia, tremor (#11).

10.1.11 PDY5035

Title:
A double-blind, 4-way crossover, placebo-controlled investigation of the psychomotor and cognitive residual effects of single oral doses of zolpidem-MR 6.25 mg, zolpidem 12.5mg and flurazepam 30 mg in healthy elderly volunteers.

Summary:
This study assessed the residual effects of both 6.25 mg and the 12.5 mg zolpidem-MR doses as well as flurazepam 30 mg in 24 volunteers. No objective or subjective residual effects were detected after ingestion of zolpidem-MR at either dose.

No deaths or SAEs were reported during this study. One patient (#826001005) discontinued prematurely due to poor compliance to the protocol.

10.1.12 PDY5036

Title:
A double-blind, 3-way crossover, placebo-controlled investigation of the psychomotor and cognitive residual effects of single oral doses of zolpidem 12.5mg and flurazepam 30 mg in healthy adult volunteers.

Summary:
This study was intended to replicate the next day residual effects from study 4054 at a different study center. This study assessed the residual effects, in 18 adults, of 12.5 mg zolpidem-MR as well as flurazepam 30 mg. No objective or subjective residual effects were detected after ingestion of zolpidem-MR.

No deaths, SAEs or discontinuations were reported during this study.

34 Page(s) Withheld

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