CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-897

MEDICAL REVIEW

FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANESTHESIA, ANALGESIA AND RHEUMATOLOGY PRODUCTS

DIVISION DIRECTOR'S APPROVAL MEMO

DATE:	April 13, 2006
DRUG:	Vivitrol™ (naltrexone for extended-release injectable suspension)
NDA:	21-897
NDA Code:	Type 4P NDA
SPONSOR:	Alkermes, Inc.
INDICATION:	For the treatment of alcohol dependence

Alkermes, Inc. submitted NDA 21-897 in support of marketing approval for Vivitrol™ (naltrexone for extended-release injectable suspension)[1] on March 31, 2005. An approvable letter was issued on December 23, 2005. The letter noted that the sponsor would need to address the following issues prior to approval:

- the absence of Reproductive Toxicology and Carcinogenicity studies to support the clinical use of the product
- an absence of evidence that the product is safe and effective in patients who had not achieved abstinence prior to the initiation of treatment (see Division Director's Approvable Memo, dated December 23, 2005)

The sponsor has responded to these concerns by agreeing to perform post-marketing studies to assess the deficiency listed in the first bullet, and by agreeing to language in the label that will limit the indicated use of the product to "…patients who are able to abstain from alcohol in an outpatient setting prior to initiation of treatment…"

[1] Vivitrol™ will be marketed in a kit.

Most of the subjects in the efficacy studies achieved initial abstinence through participation in a treatment program or via medical detoxification. There were no subjects who maintained abstinence in the setting of no continued available alcohol. Therefore, Drs. Kashoki and Winchell have recommended that the sponsor perform a post-marketing study to assess the efficacy of Vivitrol™ in patients who are abstinent "by virtue of hospitalization or other mechanism to limit access to alcohol" as these patients are likely to differ in regard to their motivation to stop drinking compared to patients who stop drinking in spite of access to alcohol. The sponsor has agreed to perform this study.

Drs. Kashoki and Winchell have reviewed the updated safety data in this submission and have determined that there are no new safety concerns that would impact the risk to benefit ratio of the product, when compared to the safety data analyzed in the initial application. However, they did find an increase in creatinine phophokinase (CPK) serum levels with prolonged exposure and have recommended addition of these data to the product label. No serious adverse events were associated with these CPK elevations.

Discussion:

The sponsor has adequately addressed the concerns noted in the approvable letter. Of note, however, the absence of Reproductive Toxicology and Carcinogenicity data to fully cover the range of expected human exposure to naltrexone and to the polylactide-co-glycolide vehicle will not be fully elucidated at the time of approval and initial patient exposure. Nevertheless, the available data on reproductive toxicity indicates a low risk, the risk is certainly no more significant than the risk of fetal alcohol syndrome, and this risk can be mitigated by appropriate cautionary language in the product label until further data is available. There is also no evidence to suspect that the carcinogenic effects of the product are of unusual potential potency, and the absence of complete data to fully assess the long-term carcinogenic potential can be explicated in the label, again until further data is available. While our response to the initial application was that these studies should be completed prior to approval, this decision was partially based on the likelihood that the sponsor would be completing further clinical studies to support their proposed indication and, thus, the development program would allow for an adequate period of time to complete the preclinical studies prior to approval. However, the sponsor has proposed an alternate indication that we find acceptable and that will not require additional clinical studies. This new indication limits treatment to the subpopulation of alcoholic patients who will have achieved abstinence prior to treatment with Vivitrol™, the subpopulation that has been demonstrated to clearly benefit from treatment with this product. In light of this new development, and as alcoholism is a serious disease with significant associated morbidity and mortality, and a devastating impact on patients, families and the public health, we must reconsider the overall risk to benefit analysis upon which this application rests. Vivitrol™ is likely to provide alcoholic patients with a higher level of compliance compared to the currently approved treatments and, thus, an improvement in the likelihood that they will be able to successfully maintain abstinence.

As such, it is acceptable to garner the remaining data necessary to fully elucidate the toxicity of this product in the post-marketing setting.

Action: Approval

Bob A. Rappaport, M.D.
Director
Division of Anesthesia, Analgesia and Rheumatology Products
Office of Drug Evaluation II, CDER, FDA

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/s/

Bob Rappaport
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MEDICAL OFFICER

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