CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-897

PHARMACOLOGY REVIEW

2nd cycle

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER:	**21-897**
SERIAL NUMBER:	**000**
DATE RECEIVED BY CENTER:	**14-Feb-2006**
PRODUCT:	**Vivitrol™ (naltrexone for extended-release injectable suspension)**
INTENDED CLINICAL POPULATION:	**Patients seeking treatment for alcohol dependence**
SPONSOR:	**Alkermes® Inc.**
DOCUMENTS REVIEWED:	**Complete response to AE Letter**
REVIEW DIVISION:	**Division of Anesthesia, Analgesia, and Rheumatology Products (HFD-170)**
PHARM/TOX REVIEWER:	**Mamata De, Ph.D.**
PHARM/TOX SUPERVISOR:	**R. Daniel Mellon, Ph.D.**
DIVISION DIRECTOR:	**Bob A. Rappaport, M.D.**
PROJECT MANAGER:	**Lisa Basham-Cruz, M.S.**

Date of review submission to Division File System (DFS): 12-Apr-2006

EXECUTIVE SUMMARY

I. Recommendations

A. Recommendation on approvability

From the pharmacology toxicology perspective, NDA 21-897 may be APPROVED, pending agreement on the labeling and Phase 4 commitments outlined below.

In the original action letter dated December 23, 2005, the Sponsor was requested to address the following nonclinical deficiency:

> *Provide pharmacokinetic/toxicokinetic exposure data in the appropriate species necessary for interpreting the existing carcinogenicity and reproductive toxicology data in the product labeling. In the absence of adequate bridging data, the following nonclinical studies would have to be conducted:*
>
> *a. a Segment I reproductive and developmental toxicology study including toxicokinetic data in a single species with the final drug product formulation;*
>
> *b. Segment II reproductive and developmental toxicology studies in two species including toxicokinetic data with the final drug product formulation;*
>
> *c. a Segment III reproductive and developmental toxicology study including toxicokinetic data with the final drug product formulation; and*
>
> *d. carcinogenicity assessment in two species using the final drug product formulation.*

Following discussions with the Sponsor during a post-action teleconference on January 3, 2006, the Division informed the sponsor of the following (e-mail dated February 7, 2006):

> *The review team has considered your proposal to submit a response to the December 23, 2005 action letter that employs human comparative PK data as an interim bridging strategy and proposes definitive bridging in animals as a Phase 4 study. We are willing to accept for review a response to our action letter that uses your proposed approach to deficiency #2 of our December 23, 2005, action letter, although the review team is not in exact agreement with some aspects of the proposed labeling.*

The Sponsor has not provided adequate nonclinical bridging data, nor have they completed the requested toxicology studies. From the nonclinical perspective, the potential for reproductive toxicity and carcinogenicity of oral naltrexone was adequately assessed to support the approval of the referenced drug product, ReVia®. The exposure to naltrexone via the Vivitrol™ drug product could theoretically alter the potential for naltrexone-related tumor development compared to that of ReVia®. Therefore, with respect to the Vivitrol™ label,

Currently, ReVia® is a Pregnancy Category C drug due to embryocidal and fetotoxic effects noted in rats and rabbits treated orally with naltrexone as described in the ReVia® labeling. Although the exposure to naltrexone may be greater following Vivitrol™ administration, a Pregnancy Category of C is currently the most restrictive category a drug can receive in the absence of well-controlled clinical trial data documenting teratogenic effects in humans.

The results of the carcinogenicity studies conducted for ReVia® and described in the ReVia® package insert are relevant to the Vivitrol™ drug product and should be included in the labeling;

The potential for Vivitrol™ to alter the incidence of the reported testicular mesotheliomas in males and tumors of vascular origin in males and females should be included in the product labeling. However, it is important to note nonclinical carcinogenicity studies are designed to assess the potential for lifelong exposure of a drug to alter tumor formation, and the tumors described in the ReVia® labeling were observed following lifelong exposure of the animals to naltrexone hydrochloride. However, there is no evidence that altering the naltrexone pharmacokinetic profile via Vivitrol™ will significantly change the risk:benefit analysis with respect to this patient population.

Following extensive discussions, the review team has agreed to allow the nonclinical studies requested in the original Approvable letter to be completed during Phase 4. As outlined in Dr. Rappaport's Division Director's Memorandum for this action, from the clinical perspective, specific

quantification of both the potential reproductive toxicity and carcinogenic potential following exposure to naltrexone via Vivitrol™ product is outweighed by the potential clinical benefit that Vivitrol™ may have for this patient population. The reader is referred to Dr. Rappaport's memorandum regarding the specific details supporting the decision to allow the studies to be completed as a phase 4 commitment.

B. Recommendation for nonclinical studies

The following nonclinical studies should be conducted as a Phase 4 commitment:

1. a Segment I reproductive and developmental toxicology study including toxicokinetic data in a single species with the final drug product formulation,

   Protocol Submission: by October 7, 2006
   Study Start: by January 7, 2007
   Final Report Submission: by January 7, 2008

2. Segment II reproductive and developmental toxicology studies in two species including toxicokinetic data with the final drug product formulation,

   Protocol Submission: by October 7, 2006
   Study Start: by January 7, 2007
   Final Report Submission: by January 7, 2008

3. a Segment III reproductive and developmental toxicology study including toxicokinetic data with the final drug product formulation, and

   Protocol Submission: by October 7, 2006
   Study Start: by January 7, 2007
   Final Report Submission: by January 7, 2008

4. Carcinogenicity assessment in two species using the final drug product formulation.

   Protocol Submission: by April 7, 2007
   Study Start: by August 7, 2007
   Final Report Submission: by August 8, 2010

5. In lieu of the animal studies listed in commitments 1 through 4 above, you may be able to obtain adequate

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.