CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-897

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

2nd Cycle

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	**Clinical Pharmacology & Biopharmaceutics (HFD 870)** **Tracking/Action Sheet for Formal/Informal Consults**
From: Srikanth C. Nallani, Ph.D.	**To: DOCUMENT ROOM (LOG-IN and LOG-OUT)** **Please log-in this consult and review action for the specified IND/NDA submission**

DATE: 4/7/2006	IND No.:	NDA No. **21-897**	DATE OF DOCUMENT	2/13/2006
NAME OF DRUG [**Vivitrol**]	PRIORITY CONSIDERATION **Standard**		Date of informal/Formal Consult:	2/13/2006

NAME OF THE SPONSOR: [**Alkermes, 88 Sidney St, Cambridge, MA 02139**]

TYPE OF SUBMISSION
CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS RELATED ISSUE

☐ PRE-IND	☐ DISSOLUTION/IN-VITRO RELEASE	☐ FINAL PRINTED LABELING
☐ ANIMAL to HUMAN SCALING	☐ BIOAVAILABILITY STUDIES	☐ LABELING REVISION
☐ IN-VITRO METABOLISM	☐ IN-VIVO WAIVER REQUEST	☐ CORRESPONDENCE
☐ PROTOCOL	☐ SUPAC RELATED	☐ DRUG ADVERTISING
☐ PHASE II PROTOCOL	☐ CMC RELATED	☐ ADVERSE REACTION REPORT
☐ PHASE III PROTOCOL	☐ PROGRESS REPORT	☐ ANNUAL REPORTS
☐ DOSING REGIMEN CONSULT	☐ SCIENTIFIC INVESTIGATIONS	☐ FAX SUBMISSION
☐ PK/PD- POPPK ISSUES	☐ MEETING PACKAGE (EOP2/Pre-NDA/CMC/Pharmacometrics/Others)	☒ OTHER *(SPECIFY BELOW)*: [Complete Response for Action (12/28/2005) to Original NDA submitted on 3/31/2005]
☐ PHASE IV RELATED		

REVIEW ACTION

☐ NAI (No action indicated)	☐ Oral communication with	☐ Formal Review/Memo (attached)
☐ E-mail comments to:	Name: [ ]	☒ See comments below
☐ Medical ☐ Chemist ☐ Pharm-Tox	☐ Comments communicated in meeting/Telecon. see meeting minutes dated: [ ]	☐ See submission cover letter
☐ Micro ☐ Pharmacometrics ☐ Others		☐ OTHER *(SPECIFY BELOW)*:
(Check as appropriate and attach e-mail)		[ ]

REVIEW COMMENT(S)
☐ **NEED TO BE COMMUNICATED TO THE SPONSOR** ☐ **HAVE BEEN COMMUNICATED TO THE SPONSOR**

COMMENTS/SPECIAL INSTRUCTIONS:
[Current submission consists of Alkermes' response to approvable letter issued on 12/28/2005 for NDA 21-897 submitted on 3/31/2005. With regard to Clinical Pharmacology and Biopharmaceutics comments (# 4, 5 and 6) in the approvable letter, the sponsor agrees to address them in an appropriate post-approval submission. The following is the proposed timeline for the completion of post-marketing commitments (PMC) agreed to by the sponsor:

1. Revise the drug release specifications to include Day 14 and Day 28 drug release information.
The timeline for this PMC will be addressed by the Office of New Drug Quality Assurance.
2. Conduct *in vitro* CYP inhibition studies using conventional CYP substrates and validated analytical methodology.
Protocol Submission: July/2006
Study Start: August/2006
Final Report Submission: May/2007
3. Conduct *in vitro* studies in human hepatocytes to evaluate the potential of naltrexone to induce CYP3A4 and CYP1A2.
Protocol Submission: July/2006
Study Start: August/2006
Final Report Submission: May/2007

Please find the cover letter from sponsor attached to this review. The sponsor also submitted labeling changes, however, none were pertinent to Clinical Pharmcaology and Biopharmaceutics aspects and hence were not reviewed.]

SIGNATURE OF REVIEWER: Srikanth C. Nallani Ph.D.	Date 4/7/2006
SIGNATURE OF TEAM LEADER: Suresh Doddapaneni, Ph.D.	Date 4/7/2006
CC.: HFD # [ ]; TL: [ ]	**Project Manager: Lisa Basham-Cruz** **Date**

4.4 Consent of Supervisor for the proposed Phase IV commitments

Nallani, Srikanth

From: Doddapaneni, Suresh
Sent: Friday, November 18, 2005 8:34 AM
To: Nallani, Srikanth
Subject: FW: Srikanth's NDA-Naltrexone depot formulationl

Srikanth

Print out this e-mail and attach it to the review as Division Director's concurrence. This is in line with OCPB's procedure.

Thanks, Suresh

-----Original Message-----
From: Malinowski, Henry J
Sent: Friday, November 18, 2005 8:28 AM
To: Doddapaneni, Suresh
Subject: RE: Srikanth's NDA-Naltrexone depot formulationl

Suresh,
Looks fine...Hank

-----Original Message-----
From: Doddapaneni, Suresh
Sent: Thursday, November 17, 2005 12:44 PM
To: Malinowski, Henry J
Subject: Srikanth's NDA-Naltrexone depot formulationl

Hank

The review for depot naltrexone product is being finalized. We had the briefing on this on Tuesday. I have extracted from the review, the recommendation/phase IV commitment related language that Srikanth and I drafted. Please provide your feedback.

Thanks, Suresh

1.1 Recommendation

From a Clinical Pharmacology and Biopharmaceutics perspective, NDA 21-897 is acceptable provided that a mutually satisfactory agreement can be reached between the Agency and Alkermes regarding the (a) language in the package insert (b) *in vitro* drug release method, and (c) post marketing commitment to further investigate potential of this product to inhibit or induce CYP enzymes. Specifically,

a) The drug release specifications should be revised with addition of Day 14 and Day 28 drug release information.
b) Conduct *in vitro* CYP inhibition studies using conventional substrates as the submitted data used florescent substrate(s) which tends to introduce non-specificity in detection.
c) Conduct *in vitro* studies in human hepatocytes to evaluate potential of naltrexone to induce CYP3A4 and CYP1A2.

1.2 Phase IV Commitments

a) Conduct *in vitro* CYP inhibition studies using conventional CYP substrates and validated analytical methodology.
b) Conduct *in vitro* studies in human hepatocytes to evaluate potential of naltrexone to induce CYP3A4 and CYP1A2.

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

/s/

Srikanth Nallani
11/21/2005 11:09:54 AM
BIOPHARMACEUTICS

Suresh Doddapaneni
11/21/2005 01:47:33 PM
BIOPHARMACEUTICS

1ST Cycle

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 21-897	Submission Date(s): 03/31/05
Brand Name	Vivitrol® (Naltrexone Long-Acting Injection)
Generic Name	Naltrexone
Reviewer	Srikanth C. Nallani, Ph.D.
Team Leader	Suresh Doddapaneni, Ph.D.
OCPB Division	Division of Pharmaceutical Evaluation II
ORM Division	Division of Anesthesia, Analgesia, , and Rheumatology Products
Sponsor	Alkermes, 88 Sidney St, Cambridge, MA
Relevant IND(s)	61,138
Submission Type; Code	Original NDA; 3P
Formulation; Strength(s)	Extended release microsphere formulation of naltrexone for suspension to be administered by IM injection; 380 mg in 5 mL vials
Indication	Treatment of alcohol dependence
Dosing Regimen	380 mg IM every 4 weeks or once a month

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