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*APPLICATION NUMBER:*

**21-897**

**CLINICAL PHARMACOLOGY AND  
BIOPHARMACEUTICS REVIEW(S)**

2nd Cycle

<b>DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION</b>		<b>Clinical Pharmacology &amp; Biopharmaceutics (HFD 870) Tracking/Action Sheet for Formal/Informal Consults</b>		
From: Srikanth C. Nallani, Ph.D.		To: <b>DOCUMENT ROOM (LOG-IN and LOG-OUT)</b> 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 [ <b>Vivitrol</b> ]	PRIORITY CONSIDERATION <b>Standard</b>		Date of informal/Formal Consult:	2/13/2006
NAME OF THE SPONSOR: [ <b>Alkermes, 88 Sidney St, Cambridge, MA 02139</b> ]				
<b>TYPE OF SUBMISSION</b>				
<b>CLINICAL PHARMACOLOGY/BIPHARMACEUTICS RELATED ISSUE</b>				
<input type="checkbox"/> PRE-IND <input type="checkbox"/> ANIMAL to HUMAN SCALING <input type="checkbox"/> IN-VITRO METABOLISM <input type="checkbox"/> PROTOCOL <input type="checkbox"/> PHASE II PROTOCOL <input type="checkbox"/> PHASE III PROTOCOL <input type="checkbox"/> DOSING REGIMEN CONSULT <input type="checkbox"/> PK/PD- POPPK ISSUES <input type="checkbox"/> PHASE IV RELATED	<input type="checkbox"/> DISSOLUTION/IN-VITRO RELEASE <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> IN-VIVO WAIVER REQUEST <input type="checkbox"/> SUPAC RELATED <input type="checkbox"/> CMC RELATED <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> SCIENTIFIC INVESTIGATIONS <input type="checkbox"/> MEETING PACKAGE (EOP2/Pre-NDA/CMC/Pharmacometrics/Others)	<input type="checkbox"/> FINAL PRINTED LABELING <input type="checkbox"/> LABELING REVISION <input type="checkbox"/> CORRESPONDENCE <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> ANNUAL REPORTS <input type="checkbox"/> FAX SUBMISSION <input checked="" type="checkbox"/> OTHER ( <i>SPECIFY BELOW</i> ): [ Complete Response for Action (12/28/2005) to Original NDA submitted on 3/31/2005 ]		
<b>REVIEW ACTION</b>				
<input type="checkbox"/> NAI (No action indicated) <input type="checkbox"/> E-mail comments to: <input type="checkbox"/> Medical <input type="checkbox"/> Chemist <input type="checkbox"/> Pharm-Tox <input type="checkbox"/> Micro <input type="checkbox"/> Pharmacometrics <input type="checkbox"/> Others (Check as appropriate and attach e-mail)	<input type="checkbox"/> Oral communication with Name: [     ]	<input type="checkbox"/> Formal Review/Memo (attached) <input checked="" type="checkbox"/> See comments below <input type="checkbox"/> See submission cover letter <input type="checkbox"/> OTHER ( <i>SPECIFY BELOW</i> ): [     ]		
<b>REVIEW COMMENT(S)</b>				
<input type="checkbox"/> <b>NEED TO BE COMMUNICATED TO THE SPONSOR</b> <input type="checkbox"/> <b>HAVE BEEN COMMUNICATED TO THE SPONSOR</b>				
<b>COMMENTS/SPECIAL INSTRUCTIONS:</b> [ 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: <ol style="list-style-type: none"> <li>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.</li> <li>Conduct <i>in vitro</i> CYP inhibition studies using conventional CYP substrates and validated analytical methodology.            Protocol Submission: July/2006            Study Start: August/2006            Final Report Submission: May/2007</li> <li>Conduct <i>in vitro</i> 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</li> </ol> Please find the cover letter from sponsor attached to this review. The sponsor also submitted labeling changes, however, none were pertinent to Clinical Pharmacology and Biopharmaceutics aspects and hence were not reviewed. ]				
<b>SIGNATURE OF REVIEWER: Srikanth C. Nallani Ph.D.</b> <b>SIGNATURE OF TEAM LEADER: Suresh Doddapaneni, Ph.D.</b>			Date 4/7/2006 Date 4/7/2006	
CC.: HFD # [     ]; TL: [     ]			<b>Project Manager: Lisa Basham-Cruz</b> 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 formulation

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 formulation

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 formulation

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.

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

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

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

1<sup>st</sup> 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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