

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-897

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

1.0 MODULE 1: ADMINISTRATIVE INFORMATION AND PRESCRIBING INFORMATION

1.3.5.2 PATENT CERTIFICATION WITH RESPECT TO ANY PATENT WHICH CLAIMS THE DRUG

Paragraph II Certification

Alkermes, Inc. is filing the NDA for Vivitrex[®] (naltrexone long-acting injection) under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act [21 U.S.C 355 (b)(2)], because the NDA relies in part for approval upon investigations that were not conducted by or for Alkermes and for which Alkermes has not obtained a right of reference or use from the person by or for whom the investigations were conducted. Specifically, the NDA for Vivitrex references and relies in part on the NDA for ReVia (naltrexone hydrochloride) (NDA 18-932).

Alkermes hereby certifies that, in our opinion and to the best of our knowledge, (a) the only patent that claims the drug that is the subject of NDA 18-932 for ReVia -- and on which investigations that are relied upon by Alkermes for approval of the NDA for Vivitrex were conducted or that claims an approved use for such drug and for which information is required to be filed under section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act and 21 C.F.R. § 314.53 -- is United States Patent No. 3,332,950 (the "950 Patent"), and (b) the '950 has expired.

We note that the NDA for ReVia previously listed in the Orange Book United States Patent No. 3,957,982 (the "982 Patent") with an expiration date of May 18, 1993. However, Alkermes believes this listing was incorrect, because the '982 Patent is directed to a "method for contraception by the application of combination-type sequential preparations" and does not claim naltrexone or a use of naltrexone that is or was the subject of NDA 18-932 for ReVia. Alkermes believes that the patent number that should have been listed for NDA 18-932 for ReVia is the '950 patent, which does claim naltrexone and also has expired. Alkermes thus makes this Paragraph II certification to the '950 patent.

The NDA for Vivitrex does not seek to rely on data from any other reference listed drugs, and thus we believe that no additional patent certifications are required. See 21 C.F.R. 314.50(i); 54 Fed. Reg. 28872, 28875 (July 10, 1989).

EXCLUSIVITY SUMMARY

NDA # 21-897

SUPPL # N/A

HFD # 170

Trade Name Vivitrol

Generic Name naltrexone for extended-release injectable suspension

Applicant Name Alkermes

Approval Date, If Known April 13, 2006

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505(b)(2)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

3 Years

e) Has pediatric exclusivity been granted for this Active Moiety?

YES NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)

IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of

summary for that investigation.

YES NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES NO

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

ALK21-003

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

- a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1

YES NO

Investigation #2

YES NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

- b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1

YES NO

Investigation #2

YES NO

Investigation #1

YES

Explain:

!
!

! NO

! Explain:

Investigation #2

YES

Explain:

!
!

! NO

! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES NO

If yes, explain:

Name of person completing form: Lisa Basham-Cruz

Title: Regulatory Project Manager

Date: April 10, 2006

Name of Office/Division Director signing form: Bob Rappaport, MD

Title: Director, DAARP

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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this page is the manifestation of the electronic signature.**

/s/

Bob Rappaport
4/13/2006 03:12:19 PM

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA : 21-897 Supplement Type (e.g. SE5): _____ Supplement Number: _____

Stamp Date: March 31, 2005 Action Date: 2nd cycle: April 13, 2006

HFD 170 Trade and generic names/dosage form: Vivitrol (naltrexone for extended-release injectable suspension)

Applicant: Alkermes, Inc. Therapeutic Class: alcoholism

Indication(s) previously approved:

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: the treatment of alcohol dependence in patients who are able to abstain from alcohol in an outpatient setting prior to initiation of treatment with Vivitrol.

Is there a full waiver for this indication (check one)?

- Yes: Please proceed to Section A.
- No: Please check all that apply: Partial Waiver Deferred Completed
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Other: _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____ kg _____ mo. _____ yr. 0 Tanner Stage _____
Max _____ kg _____ mo. _____ yr. 11 Tanner Stage _____

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed

Other: _____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg _____ mo. _____ yr. 12 Tanner Stage _____
Max _____ kg _____ mo. _____ yr. 16 Tanner Stage _____

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed

Other: _____

Date studies are due (mm/dd/yy): Final Report: October, 2010

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

cc: NDA 21-897
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 12-22-03)

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: _____

Is there a full waiver for this indication (check one)?

Yes: Please proceed to Section A.

No: Please check all that apply: ___ Partial Waiver ___ Deferred ___ Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

Products in this class for this indication have been studied/labeled for pediatric population

Disease/condition does not exist in children

Too few children with disease to study

There are safety concerns

Other: _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for partial waiver:

Products in this class for this indication have been studied/labeled for pediatric population

Disease/condition does not exist in children

Too few children with disease to study

There are safety concerns

Adult studies ready for approval

Formulation needed

Other: _____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Comments:

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

cc: NDA 21-897
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 10-14-03)

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/s/

Lisa Basham-Cruz
4/13/2006 03:01:11 PM

**1.0 MODULE 1: ADMINISTRATIVE INFORMATION AND PRESCRIBING
INFORMATION**

1.3.3 DEBARMENT CERTIFICATION (SECTION 306(K)(I) OF THE FDC ACTS)

Alkermes, Inc. hereby certifies that it did not and will not use, in any capacity, the services of any person debarred under Section 306 of the Federal Food, Drug and Cosmetic Act in connection with this New Drug Application (NDA).

Signed by:


Priya Jambhekar

Title:

Global Vice President, Regulatory and Government Affairs

Date:

3/31/05

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information		
NDA 21-897	Efficacy Supplement Type SE-	Supplement Number
Drug: VIVITROL (naltrexone for extended-release injectable suspension)		Applicant: Alkermes, Inc.
RPM: Lisa Basham-Cruz		HFD-170 Phone # 301-796-1175
<p>Application Type: <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) (This can be determined by consulting page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)</p> <p>If this is a 505(b)(2) application, please review and confirm the information previously provided in Appendix B to the NDA Regulatory Filing Review. Please update any information (including patent certification information) that is no longer correct.</p> <p><input type="checkbox"/> Confirmed and/or corrected</p>	<p>Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)):</p> <p>NDA 18-932: Revia (oral naltrexone)</p>	
❖ Application Classifications:		
<input type="checkbox"/> Review priority	<input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority	
<input type="checkbox"/> Chem class (NDAs only)	Type 3	
<input type="checkbox"/> Other (e.g., orphan, OTC)		
❖ User Fee Goal Dates	1 st cycle: 12/31/05; 2 nd cycle: 4/16/06	
❖ Special programs (indicate all that apply)	<input checked="" type="checkbox"/> None <input type="checkbox"/> Subpart H <input type="checkbox"/> 21 CFR 314.510 (accelerated approval) <input type="checkbox"/> 21 CFR 314.520 (restricted distribution) <input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> CMA Pilot 1 <input type="checkbox"/> CMA Pilot 2	
❖ User Fee Information		
<input checked="" type="checkbox"/> User Fee	<input checked="" type="checkbox"/> Paid UF ID number 3006032 (4928)	
<input type="checkbox"/> User Fee waiver	<input type="checkbox"/> Small business <input type="checkbox"/> Public health <input type="checkbox"/> Barrier-to-Innovation <input type="checkbox"/> Other (specify)	
<input type="checkbox"/> User Fee exception	<input type="checkbox"/> Orphan designation <input type="checkbox"/> No-fee 505(b)(2) (see NDA Regulatory Filing Review for instructions) <input type="checkbox"/> Other (specify)	
❖ Application Integrity Policy (AIP)		

(Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? () Yes () No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).

If "No," continue with question (5).

- (5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? () Yes () No

(Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).

If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).

If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.

❖ Exclusivity (approvals only)	
<ul style="list-style-type: none"> • Exclusivity summary • Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.) 	No
<ul style="list-style-type: none"> • Is there existing orphan drug exclusivity protection for the "same drug" for the proposed indication(s)? Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification. 	() Yes, Application # _____ (X) No
❖ Administrative Reviews (Project Manager, ADRA) (indicate date of each review)	

General Information	
❖ Actions	
• Proposed action	(X) AP () TA () AE () NA
• Previous actions (specify type and date for each action taken)	AE; December 23, 2005
• Status of advertising (approvals only)	(X) Materials requested in AP letter () Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	(X) Yes () Not applicable
• Indicate what types (if any) of information dissemination are anticipated	(X) None () Press Release () Talk Paper () Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	
• Most recent applicant-proposed labeling	
• Original applicant-proposed labeling	X
• Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings (indicate dates of reviews and meetings)	X
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	Revia
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	X
• Applicant proposed	
• Reviews	X
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	X
• Documentation of discussions and/or agreements relating to post-marketing commitments	X
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	X
❖ Memoranda and Telecons	
❖ Minutes of Meetings	
• Type C meeting (indicate date)	5/4/01
• Type C meeting	8/8/02
• Pre-NDA meeting P/T & Clinical (indicate date)	11/2/04
• Pre-NDA CMC	3/4/05
• Post Action Meeting	1/24/06
❖ Advisory Committee Meeting	
• Date of Meeting	N/A
• 48-hour alert	
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	N/A

Summary Application Review	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) (indicate date for each review)	DD 1 st cycle: 12/23/05 DD 2 nd cycle: 4/13/06 Med TL 1 st cycle: 12/22/05 Med TL 2 nd cycle: 4/11/06
Clinical Information	
❖ Clinical review(s) (indicate date for each review)	1 st cycle: 12/19/05 2 nd cycle: 4/11/06
❖ Microbiology (efficacy) review(s) (indicate date for each review)	NA
❖ Safety Update review(s) (indicate date or location if incorporated in another review)	Med 1 st cycle review, page 146; 2 nd cycle review, page 9.
❖ Risk Management Plan review(s) (indicate date/location if incorporated in another rev)	NA
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	X
❖ Demographic Worksheet (NME approvals only)	NA
❖ Statistical review(s) (indicate date for each review)	12/16/05
❖ Biopharmaceutical review(s) (indicate date for each review)	1 st cycle: 11/21/05 2 nd cycle: 4/7/06
❖ Controlled Substance Staff review(s) and recommendation for scheduling (indicate date for each review)	NA
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	9/13/05
• Bioequivalence studies	NA
CMC Information	
❖ CMC review(s) (indicate date for each review)	1 st cycle: 12/16/05 2 nd cycle: 4/7/06
❖ Environmental Assessment	
• Categorical Exclusion (indicate review date)	Page 196 CMC 1 st cycle review
• Review & FONSI (indicate date of review)	NA
• Review & Environmental Impact Statement (indicate date of each review)	NA
❖ Microbiology (validation of sterilization & product sterility) review(s) (indicate date for each review)	9/23/05 and 10/24/05
❖ Facilities inspection (provide EER report)	Date completed: (X) Acceptable () Withhold recommendation
❖ Methods validation	() Completed (X) Requested () Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	12/16/05 TL memo 1 st cycle: 12/21/05 TL memo 2 nd cycle: 4/12/06
❖ Nonclinical inspection review summary	NA
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	NA
❖ CAC/ECAC report	NA

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this page is the manifestation of the electronic signature.**

/s/

Lisa Basham-Cruz
4/20/2006 02:06:01 PM

Basham-Cruz, Lisa

From: Priya Jambhekar [Priya.Jambhekar@Alkermes.com]
Sent: Tuesday, April 11, 2006 1:37 PM
To: Basham-Cruz, Lisa
Cc: Priya Jambhekar
Subject: RE: Phase 4 commitments and more....

Hi Lisa,

We have reviewed the phase IV commitments proposed by the Agency and we are in agreement with your proposal as it stands. Please call me if there are any questions.

Priya

From: Basham-Cruz, Lisa [mailto:lisa.bashamcruz@fda.hhs.gov]
Sent: Tue 4/11/2006 12:31 PM
To: Priya Jambhekar
Subject: Phase 4 commitments and more....

Priya, Bob is going thru the label and wants the "Ns" removed from the clinical studies section as attached. He is not finished reviewing it, but I will send changes as they are made.

Also, the Phase 4 commitments are below. Please send me a reply email reflecting your concurrence.

<<draft-labeling-package-insert-clean-final.doc>>

1. Conduct a pediatric study under PREA for the treatment of alcohol dependence in patients ages 12 through 16 who are able to abstain from alcohol in an outpatient setting prior to initiation of treatment with Vivitrol.

Protocol Submission: April, 2007
Study Start: October, 2007
Final Report Submission: April, 2011

2. Conduct a clinical study to determine whether Vivitrol is effective in patients who are abstinent by virtue of hospitalization or other mechanism to limit access to alcohol, rather than patients who are abstinent in spite of access to alcohol. As these populations are likely to differ with respect to level of motivation and/or alcoholism severity, this is a relevant question important to clinicians deciding whether or not patients being discharged from alcohol-free settings would benefit from treatment with Vivitrol upon discharge.

Protocol Submission October 2006
Study Start: April —
Study Report Submission October 2009

3. Perform a Segment I reproductive and developmental toxicology study including

4/11/2006

toxicokinetic data in a single species with the final drug product formulation,

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

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

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

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

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

6. Conduct carcinogenicity assessment in two species using the final drug product formulation.

Protocol Submission: April 2007
Study Start: August 2007
Final Report Submission: August 2010

7. In lieu of the animal studies listed in commitments 1 through 4 above, you may be able to obtain adequate pharmacokinetic/toxicokinetic exposure data in the appropriate species necessary for interpreting the existing carcinogenicity and reproductive toxicology data on oral naltrexone in the product labeling. Bridging data will be needed for the mouse, rat, pregnant rat and pregnant rabbit. The following timelines should be followed for this option:

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

8. 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

9. 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

10. Develop an immediate hypersensitivity skin test to Vivitrol drug product, naltrexone drug substance, and carboxymethylcellulose (CMC). Perform a study with this test to detect immediate hypersensitivity in patients who have been exposed to Vivitrol. Include appropriate controls to assess whether there is a direct, non-immune, histamine releasing effect of Vivitrol drug product, naltrexone drug substance, and CMC.

Protocol Submission: October 2006

Study Start: March 2007
Final Study Report Submission: October 2007

11. Develop in vitro tests for drug-specific IgE, IgG, and IgM to Vivitrol drug product, naltrexone drug substance, and carboxymethylcellulose. Perform a study using these tests to detect drug specific IgE, IgG, and IgM to Vivitrol drug product, naltrexone drug substance, and CMC.

Protocol Submission: October 2006

Study Start: March 2007
Final Study Report Submission: October 2007

12. Develop an in-vivo test for delayed hypersensitivity testing or patch testing to detect Type IV or delayed hypersensitivity reactions to Vivitrol and its components (naltrexone, carboxymethylcellulose).

Protocol Submission: October 2006

Study Start: March 2007
Final Study Report Submission: October 2007

The following are considered agreements, rather than commitments (since they are not actually studies) but also need your concurrence.

1. Revise the drug release specifications to include Day 14 and Day 28 drug release information.
2. Tighten the in-vitro drug release acceptance criteria to an acceptable range and assess the need to establish a specification to control percent crystallinity of naltrexone in the microspheres based on the manufacturing experience with five consecutive commercial scale batches or on one-year manufacturing experience from the date of approval of the NDA, whichever comes first, and submit the results of this evaluation in a CBE-30 supplement.

Lisa Basham-Cruz, MS

Regulatory Project Manager

Division of Anesthesia, Analgesia and Rheumatology Products

301-796-1175

New email: lisa.bashamcruz@fda.hhs.gov

3-1-06



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 21-897

Alkermes Inc.
88 Sidney Street
Cambridge, MA 02319

Attention: Priya Jambhekar
Global VP, Regulatory and Government Affairs

Dear Ms. Jambhekar:

We acknowledge receipt on February 16, 2006, of your February 14, 2006, resubmission to your new drug application for Vivitrol[®] (naltrexone for extended-release injectable suspension).

We consider this a complete, class 1 response to our December 23, 2005, action letter. Therefore, the user fee goal date is April 16, 2006.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We reference the waiver granted on April 27, 2005 for the pediatric study requirement for ages 0 through 11. We also reference the deferral granted on April 27, 2005, for the pediatric study requirement for ages 12 through 16 years until 5 years after the date of approval of this NDA.

If you have any questions, call me at 301-796-1175.

Sincerely,

{See appended electronic signature page}

Lisa Basham-Cruz, MS
Regulatory Project Manager
Division of Anesthesia, Analgesia and
Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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

/s/

Lisa Basham-Cruz
3/1/2006 04:39:04 PM

88 Sidney Street
Cambridge
Massachusetts
02139 4136
USA

Telephone
617 494-0171
Facsimile
617 494-9263
www.alkermes.com



February 14, 2006

PRIORITY REVIEW NDA

Robert Rappaport, MD
Division Director
Division of Anesthesia, Analgesia and Rheumatology Products
Office of Drug Evaluation II
Food and Drug Administration (HFD-170)
10903 New Hampshire Avenue
Building 22, Room 3169
Silver Spring, MD 20993-0002

RE: NDA 21-897 Sequence 0043
Vivitrex[®] (naltrexone long-acting injection), 380 mg in 5 mL vials
now referred to as Vivitrol[™] (naltrexone for extended-release injectable
suspension)

Amendment to the NDA – Complete Response to the Approvable Letter
Dated December 23, 2005

Dear Dr. Rappaport:

Reference is made to: Alkermes, Inc.'s NDA 21-897, submitted for Vivitrex (naltrexone long-acting injection) on March 31, 2005; the Approvable Letter dated December 23, 2005; the subsequent notification dated December 28, 2005, of Alkermes' intent to file an amendment to the NDA (Sequence 0039, Cover Letter); the Type A meeting with the Agency on January 3, 2006, to discuss the Approvable Letter; Alkermes' proposal, dated January 10, 2006, to address deficiency number 2 in the Approvable Letter (Sequence 0040, Cover Letter); Alkermes' amendment to the proposal (Sequence 0041, Cover Letter), dated January 31, 2006; and the Agency's e-mail, dated February 07, 2006, regarding the proposal to address deficiency number 2.

This submission comprises a complete response to the December 23, 2005, Approvable Letter. The submission is organized as follows:

Robert Rappaport, MD
February 14, 2006

TAB	ATTACHMENT	TOPIC
1	-	Cover Letter, including an item-by-item response to the Approvable Letter
1	1	Annotated Package Insert
1	2	Annotated Patient Package Insert
2	-	Revised Draft Labeling for <ul style="list-style-type: none">• Package Insert (PI)• Patient Package Insert (PPI)
3	-	Safety Update Report

We appreciated your prompt review of Alkermes proposal to address deficiency number 2. We thank you in advance for your review of this submission. Please do not hesitate to contact me should you have any questions or require additional information.

Sincerely,



Priya Jambhekar
Global Vice President, Regulatory and Government Affairs
Phone: 617-583-6547
Fax: 617-621-0693
Cell: 617-823-4888 / 617-438-6711
Email: priya.jambhekar@alkermes.com

Tab 1: Item-by-Item Response to the Approvable Letter Dated December 23, 2005

A. Approvability Deficiencies

Excerpt From Approvable Letter:

We have completed our review of this application, as amended, and it is approvable. Before the application may be approved, however, it will be necessary for you to address the following deficiencies.

Agency Comment #1:

1. You have not provided evidence of efficacy of Vivitrol in alcohol-dependent patients who are actively drinking at the time of treatment initiation.

 Alternatively, propose labeling to restrict the use of the product to alcohol-dependent patients who have refrained from drinking _____, prior to treatment initiation.

Note that if you elect this latter option, we would expect you to conduct a post-approval study to determine whether Vivitrol is effective in patients whose pre-treatment abstinence is enforced (i.e. via hospitalization) rather than spontaneous (as was the case with the population studied in your efficacy trial, ALK21-003).

Alkermes Response:

Alkermes accepts the Agency's alternative recommendation and, with this amendment, proposes labeling to restrict the use of VIVITROL to a subgroup of alcohol-dependent patients. Alkermes also commits to conduct a post-approval study as requested by the Agency. Please refer to the annotated labeling that follows this letter (Tab 1, Attachment 1) for detailed comments.

Impact to Vivitrex eCTD:

No replacement files need to be submitted to the Vivitrex eCTD to support Alkermes' response at this time. Alkermes will submit replacement files for all printed labeling upon finalization.

Agency Comment #2:

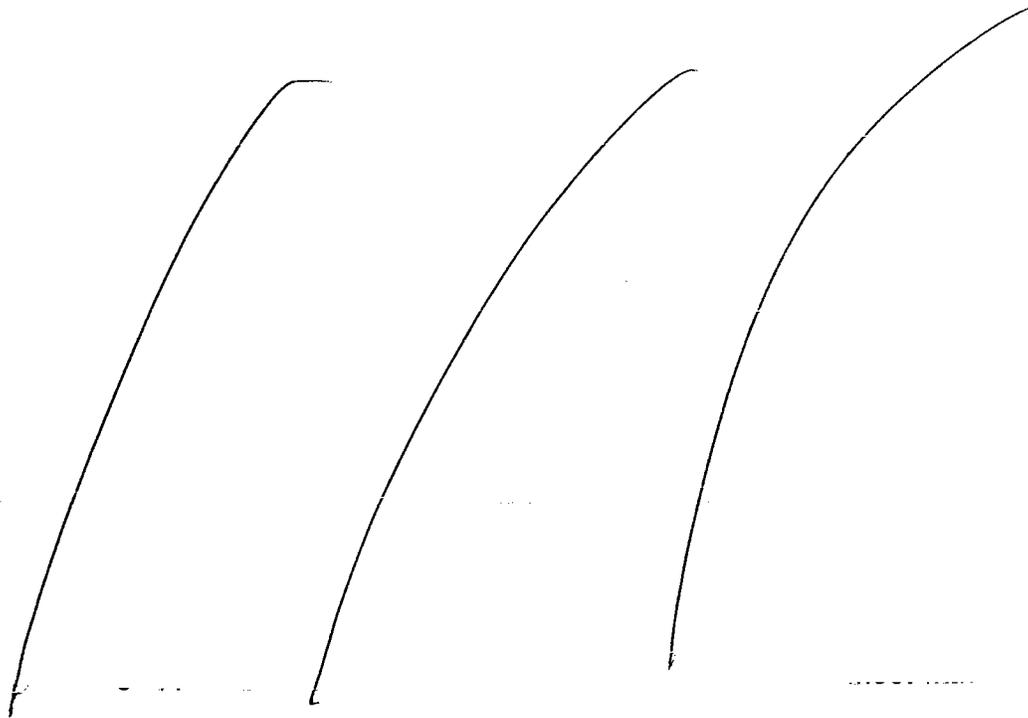
2. Provide pharmacokinetic/toxicokinetic exposure data in the appropriate species necessary for interpreting the existing carcinogenicity and reproductive toxicology data in the product labeling. In the absence of adequate bridging data, the following nonclinical studies would have to be conducted:
 - 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.

Alkermes Response:

Reference is made to the January 3, 2006, Type A meeting between the Agency and Alkermes to discuss deficiencies outlined in the Approvable Letter. During this teleconference, the Agency agreed to receive Alkermes' proposed methodology to correlate the oral naltrexone toxicology data with that of VIVITROL such that a health care provider could be adequately informed in the labeling about the toxicity profile of VIVITROL. The Agency agreed to review the proposal in advance of this amendment.

Alkermes submitted a written proposal in response to deficiency number 2 on January 10, 2006 (Sequence 0040, Cover Letter). Following receipt of the Agency minutes of the January 3, 2006, meeting (Sequence 0042, Cover Letter), Alkermes submitted an amendment to the proposal on January 31, 2006 (Sequence 0041, Cover Letter). On February 7, 2006, the Agency communicated the following notification to Alkermes:



Impact to Vivitrex eCTD:

No replacement files need to be submitted to the Vivitrex eCTD to support Alkermes' response.

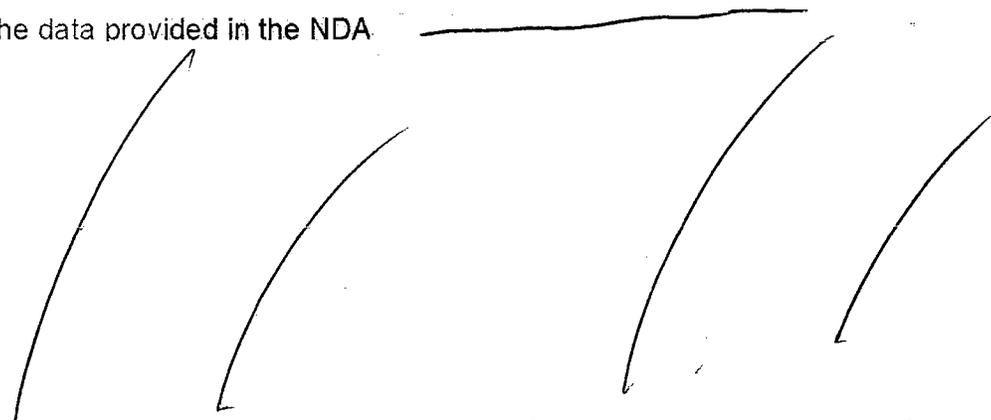
B. Issues Not Related to Approvability

Excerpt From Approvable Letter:

In addition, we have the following comments for your consideration, which are not approvability issues:

Agency Comments #3 through #7:

3. To further evaluate the allergenic potential of Vivitrol, conduct a trial to ascertain whether patients develop naltrexone-specific, naltrexone-carboxymethylcellulose-specific, and carboxymethylcellulose-specific antibodies (IgG, IgM, and IgE¹) following Vivitrol administration. Evaluate whether development of these specific antibodies is associated with adverse events of urticaria and angioedema.
4. Revise the drug release specifications to include Day 14 and Day 28 drug release information.
5. Conduct *in vitro* CYP inhibition studies using conventional CYP substrates and validated analytical methodology.
6. Conduct *in vitro* studies in human hepatocytes to evaluate the potential of naltrexone to induce CYP3A4 and CYP1A2.
7. The data provided in the NDA



Therefore, provide additional data on percent crystallinity and *in vitro* drug release for all commercial scale batches of Vivitrol. Also, provide stability updates from the ongoing stability studies. Based on these data, the need to revise the *in vitro* drug release specifications and to establish a specification to control the percent crystallinity in Vivitrol will be assessed.

Alkermes Response:

Alkermes agrees with each of the above points raised by the Agency and understands that each may be addressed as post-approval commitments. Alkermes expects to begin developing protocols for the studies recommended in items 3, 5, and 6 promptly following NDA approval, and will submit the data and analysis from each study upon completion in a post-approval submission. Alkermes will also begin gathering the data

¹ Agency letter repeats IgG twice and IgE is missing. Please comment if Alkermes' interpretation is incorrect.

Robert Rappaport, MD
February 14, 2006

needed to address items 4 and 7, and will submit updated specifications for VIVITROL in an appropriate post-approval submission.

Impact to Vivitrex eCTD:

No replacement files need to be submitted to the Vivitrex eCTD to support Alkermes' response.

**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
4/7/2006 12:22:40 PM
BIOPHARMACEUTICS

Suresh Doddapaneni
4/7/2006 12:27:15 PM
BIOPHARMACEUTICS

Signed 3/29/06

MEMORANDUM

Division of Medication Errors and Technical Support
Office of Drug Safety
WO 22, Mailstop 4447, HFD-420
Center for Drug Evaluation and Research

To: Bob Rappaport, MD
Director, Division of Anesthesia, Analgesia, and Rheumatology Products
HFD-170

From: Kristina C. Arnwine, PharmD, Safety Evaluator
Division of Medication Errors and Technical Support, HFD-420

Through: Linda Kim-Jung, PharmD, Acting Team Leader
Denise Toyer, PharmD, Deputy Director
Carol Holquist, RPh, Director
Division of Medication Errors and Technical Support, HFD-420

Date: March 3, 2006

Subject: ODS Consult 02-0073-3, Vivitrol (Naltrexone for Extended-release Injectable Suspension) 380 mg
NDA 21-897

This memorandum is in response to a March 2, 2006 request from your Division for a final review of the proprietary name, Vivitrol. The insert labeling and patient package insert labeling were provided for review and comment. However, revised container labels and carton labeling were not submitted for review and comment. DMETS refers to ODS Consult 02-0073-1 for our previous container label and carton labeling comments.

The proposed proprietary name was found acceptable by DMETS on October 26, 2005 (ODS Consult 02-0073-2). Since the initial review of Vivitrol, DMETS has not identified any additional names with the potential for sound-alike and/or look-alike confusion with Vivitrol.

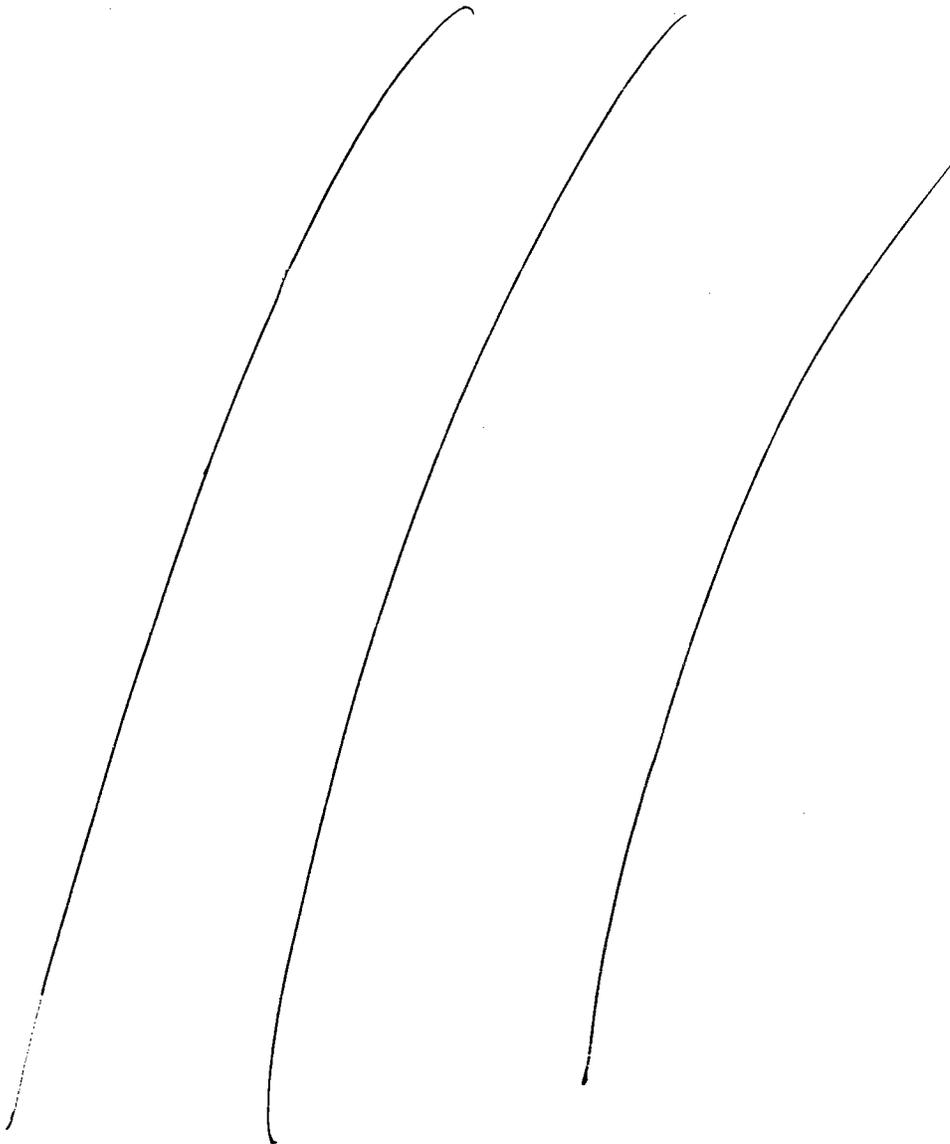
In the review of the insert labeling and patient package insert of Vivitrol, DMETS attempted to obtain a model "Dose Kit," prior to review of the labels and labeling. However, in the interest of time, DMETS decided to proceed with the review of the labels and labeling prior to receipt of the model. DMETS has identified the following areas of possible improvement, which might minimize potential user error.

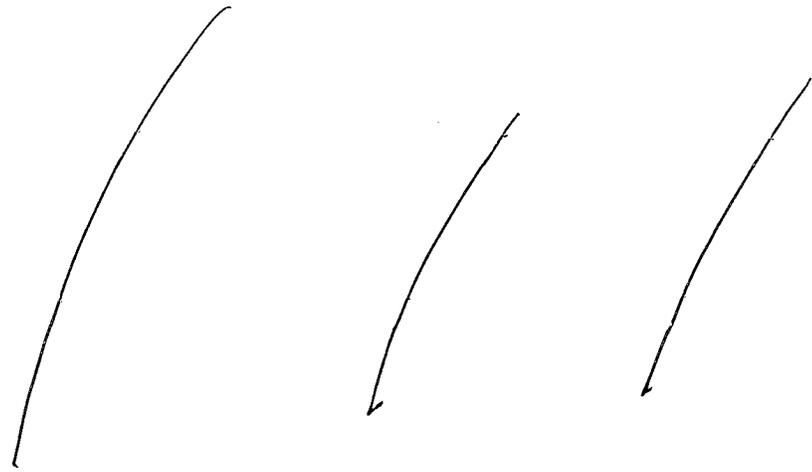
A. GENERAL COMMENTS

1. The final milligram per milliliter concentration after reconstitution is not listed anywhere on the labels and labeling. Thus it is impossible for practitioners to determine what volume of suspension is to be administered for the prescribed dose, especially if the prescribed dose differs from 380 mg. Moreover, postmarketing evidence demonstrates that the lack of a final milligram per milliliter concentration included on the labels and labeling increases the potential for dosing errors. Include the resultant concentration on the container label, carton and insert labeling.
2. DMETS questions the need for a 20-gauge ½ inch needle for product preparation. The kit contains three needles with varying lengths (2 x 20-gauge 1½ inch and 1 x 20-gauge ½ inch). This may cause confusion and error as healthcare practitioners may inadvertently use the 1½ inch needle for reconstitution and then switch to the shorter ½ inch needle for the intramuscular (IM) injection. Additionally, some practitioners may not switch the needles prior to administration. Thus, we recommend supplying only one needle length (1½ inch).

3. DMETS notes that an extra needle (20 gauge 1½ inch) is supplied in the Dose Kit. Instructions are included in the labeling regarding use of the spare needle in the event of blood aspirating or the needle getting clogged. DMETS questions what the propensity is for these events to occur. If it became evident during clinical trials that more than one needle was often needed for administration of Vivitrol injection due to the needle clogging, practitioners should be warned in the labels and labeling of the likelihood of this occurring. DMETS acknowledges that injections of thick solutions using a 20 gauge needle may result in needle clogging. However, it seems reasonable that after this has occurred, the healthcare practitioner would switch to an 18 gauge needle to ensure that the dose is administered and to prevent the likelihood of having to stick the patient a third time if the second 20 gauge needle clogs. Although the 18 gauge needle is more painful it would potentially prevent a third needle stick. Therefore, if Vivitrol has a propensity to clog, DMETS suggests that an 18 gauge needle be included in lieu of a second 20 gauge needle.

B. PACKAGE INSERT LABELING





C. PATIENT PACKAGE INSERT LABELING

Submit the Patient Package Insert Labeling to the Division of Surveillance, Research, and Communication Support (DSRCS) for review and comment.

In summary, DMETS has no objections to the use of the proprietary name, Vivitrol. We recommend implementation of the above label and labeling comments in addition to the label and labeling comments forwarded in ODS 02-0073-1. Additionally, the Division of Drug Marketing, Advertising, and Communications (DDMAC) finds the name Vivitrol acceptable from a promotional perspective. Please submit revised drafts of container labels, carton, package insert, and patient package insert labeling when available for review and comment. We would be willing to meet with the Division for further discussion if needed. If you have any questions or need clarification, please contact Diane Smith at 301-796-0538.

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

/s/

Kristina Arnwine
3/29/2006 03:42:21 PM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
3/29/2006 03:44:07 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
3/29/2006 03:49:06 PM
DRUG SAFETY OFFICE REVIEWER



**DEPARTMENT OF HEALTH & HUMAN
SERVICES**

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-897

Alkermes, Inc.
88 Sidney Street
Cambridge, MA 02139-4136

Attention: Priya Jambhekar
Global Vice President, Regulatory and Government Affairs

Dear Ms. Jambhekar:

Please refer to your New Drug Application (IND) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Vivitrol® (naltrexone for extended-release injectable suspension).

We also refer to the meeting between representatives of your firm and FDA on January 3, 2006. The purpose of the meeting was to discuss the deficiencies noted in your December 23, 2005 approvable letter.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-1175.

Sincerely,

{See appended electronic signature page}

Lisa Basham-Cruz, MS
Regulatory Project Manager
Division of Anesthesia, Analgesia and
Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

Meeting Minutes

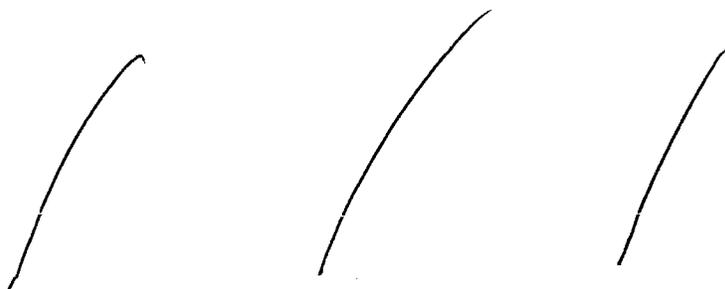
Meeting Type: A
Meeting Category: Post-Action
Meeting Date: January 3, 2006
Meeting Format: Teleconference
Application Type and Number: NDA 21-897
Product Name: Vivitrol® (naltrexone for extended-release injectable suspension)
Sponsor: Alkermes, Inc.
Meeting Chair: Celia Winchell, MD; Division of Anesthesia, Analgesia and Rheumatology Products
Meeting Recorder: Lisa Basham-Cruz, MS
Attendees:

Applicant	Title
Dr. Elliot Erich	Chief Medical Officer
Dr. Bernard Silverman	Vice President, Clinical Affairs
Dr. Gary Riley	Vice President, Toxicology
Priya Jambhekar	Vice President , Regulatory Affairs
FDA	Title
Bob Rappaport, MD	Director, DAARP
Celia Winchell, MD	Clinical team Leader, Addiction Drug Products
Dan Mellon, PhD	Supervisory Pharmacologist
Srikanth Nallani, PhD	Biopharmaceutics Reviewer
Lisa Basham-Cruz, MS	Regulatory Project Manager, DAARP

Background: The original NDA was submitted on March 31, 2005. The original PDUFA date, September 31, 2005, was extended three months due to a major clinical supplement submitted on September 7, 2005. An approvable letter was issued on December 23, 2005, citing deficiencies associated with inadequate clinical data to support the proposed indication and insufficient preclinical support for the proposed drug product. The applicant submitted a request, dated December 28, 2005, for a Type A meeting.

Minutes:

Following introductions, the applicant addressed deficiency number two in the approvable letter, which addressed the need for pharmacokinetic/toxicokinetic exposure data in the appropriate species in order to interpret the existing carcinogenicity and reproductive toxicology data for the product labeling. The applicant stated that the approved oral naltrexone product Revia, the referenced drug, is supported by reprotoxicity and carcinogenicity data that is described in the approved label as mg/m^2 . They proposed



The applicant asked whether this study is required for approval or if the Division would accept the pharmacokinetic study as a post-marketing commitment. Dr. Mellon responded that the Division would require the data for the NDA in order to write a useful label. Dr. Mellon summarized that the PK evaluation is required because we do not know that the carcinogenicity data for oral naltrexone is applicable to Vivitrol due to differences in how the two formulations are metabolized. The applicant noted that the rat does not produce 6, β -naltrexol and therefore the levels of naltrexone produced by Vivitrol are likely more relevant to the human exposure. Dr. Mellon stated that this is one reason that a PK study is needed. The applicant stated that they are able to propose labeling language

_____ , and asked whether the Division is willing to accept a proposal. Dr. Mellon responded that this will not be acceptable. The applicant asked whether the differences in metabolism can be addressed using information from the literature. Dr. Mellon responded that this may be possible, but that the literature would have to exactly define what was administered and inform of the exposure levels for the data to be useful. Dr. Winchell stated that the applicant may submit a proposal for consideration, but the Division is not prepared at this time to say whether such an approach would be considered a complete response to the deficiency cited in the approvable letter in lieu of the requested PK study. She stated that the Division would be willing to evaluate the proposal to determine whether it would, in principle, be acceptable to address the deficiency.

The sponsor asked if they could discuss specific aspects of their proposed labeling. Dr. Rappaport stated that labeling will be discussed during the review of the applicant's complete response to the approvable letter. Dr. Winchell added that, if the applicant would like specific explanations regarding the Division's proposed draft labeling, the Division may be able to provide explanations in writing, if needed, but that another meeting is not necessary at this time.

ACTION ITEM:

The applicant will submit a proposal for consideration by the Division for a method to correlate the oral naltrexone toxicology data with that of Vivitrol such that the healthcare provider can be adequately informed in the label about the toxicity of Vivitrol.

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this page is the manifestation of the electronic signature.**

/s/

Lisa Basham-Cruz
1/24/2006 05:39:53 PM

Basham-Cruz, Lisa

From: Harapanhalli, Ravi S
Sent: Friday, December 23, 2005 12:27 PM
To: Jani, Parinda
Cc: Rappaport, Bob A; Harapanhalli, Ravi S; Duffy, Eric P; Boal, Jila H
Subject: FW: Injectable Suspension, Extended-Release Nomenclature

Another e-mail string

Ravi S. Harapanhalli, Ph.D.
Chief, CMC Branch V (Pre-marketing)
(Anesthesia, Analgesia, Rheumatology, Medical Imaging, Hematology, and Oncology Products)
Division III, ONDQA
Center for Drug Evaluation and Research, FDA,
Bldg. 22, Room # 2414
10903 New Hampshire Avenue,
Silver Spring, MD 20993-0002
Phone: 301 796 1676; Fax: 301 796 9850

-----Original Message-----

From: Poochikian, Guiragos K
Sent: Monday, October 31, 2005 5:16 PM
To: Harapanhalli, Ravi S; Mille, Yana R; Boal, Jila H; Lin, Sue Ching; Lewis, David B; Bertha, Craig M; Holquist, Carol A
Subject: RE: Injectable Suspension, Extended-Release Nomenclature

What I meant is that the name will be
[
Vivitrol for Extended-release Injectable Suspension
(naltrexone for Extended-release Injectable Suspension)

Vivitrol (naltrexone) for Extended-release Injectable Suspension

-----Original Message-----

From: Harapanhalli, Ravi S
Sent: Monday, October 31, 2005 5:09 PM
To: Poochikian, Guiragos K; Mille, Yana R; Boal, Jila H; Lin, Sue Ching; Lewis, David B; Bertha, Craig M; Holquist, Carol A
Subject: RE: Injectable Suspension, Extended-Release Nomenclature

How about placing the parenthesis at the end?

Ravi S. Harapanhalli, Ph.D.
Chief, CMC Branch V (Pre-marketing)
(Anesthesia, Analgesia, Rheumatology, Medical Imaging, Hematology, and Oncology Products)
Division III, ONDQA
Center for Drug Evaluation and Research, FDA,
Bldg. 22, Room # 2414
10903 New Hampshire Avenue,
Silver Spring, MD 20993-0002
Phone: 301 796 1676; Fax: 301 796 9850

-----Original Message-----

From: Poochikian, Guiragos K
Sent: Monday, October 31, 2005 5:07 PM
To: Harapanhalli, Ravi S; Mille, Yana R; Boal, Jila H; Lin, Sue Ching; Lewis, David B; Bertha, Craig M; Holquist, Carol A
Subject: RE: Injectable Suspension, Extended-Release Nomenclature

Unless there is any objection we will proceed with option 1, i.e., [DRUG] for Extended-release Injectable

Suspension.

-----Original Message-----

From: Harapanhalli, Ravi S
Sent: Monday, October 31, 2005 4:12 PM
To: Poochikian, Guiragos K; Mille, Yana R; Boal, Jila H; Lin, Sue Ching; Lewis, David B; Bertha, Craig M; Holquist, Carol A
Subject: RE: Injectable Suspension, Extended-Release Nomenclature

Guirag,

The sample that was reconstituted on Friday was homogenous milky suspension and settled over an hour. It is truly a suspension.

Ravi S. Harapanhalli, Ph.D.
Chief, CMC Branch V (Pre-marketing)
(Anesthesia, Analgesia, Rheumatology, Medical Imaging, Hematology, and Oncology Products)
Division III, ONDQA
Center for Drug Evaluation and Research, FDA,
Bldg. 22, Room # 2414
10903 New Hampshire Avenue,
Silver Spring, MD 20993-0002
Phone: 301 796 1676; Fax: 301 796 9850

-----Original Message-----

From: Poochikian, Guiragos K
Sent: Monday, October 31, 2005 2:56 PM
To: Mille, Yana R; Harapanhalli, Ravi S; Boal, Jila H; Lin, Sue Ching; Lewis, David B; Bertha, Craig M; Holquist, Carol A
Subject: RE: Injectable Suspension, Extended-Release Nomenclature

Is the final decision to proceed with option 1?

-----Original Message-----

From: Mille, Yana R
Sent: Monday, October 31, 2005 12:33 PM
To: Poochikian, Guiragos K; Harapanhalli, Ravi S; Boal, Jila H; Lin, Sue Ching; Lewis, David B; Bertha, Craig M; Holquist, Carol A
Subject: Injectable Suspension, Extended-Release Nomenclature

Hi,

As expected, USP was able to turn the 'extended-release injection' nomenclature issue around very quickly. I presented them with the two options that we discussed

1) [DRUG] for Extended-release Injectable Suspension

2) [DRUG] Extended-release for Injectable Suspension

and, while it was a split vote, the majority were in favor of Option 1. [In case you are interested, 73% voted for Option 1, vs. 27% who favored Option 2.]

Yana

Basham-Cruz, Lisa

From: Harapanhalli, Ravi S
Sent: Friday, December 23, 2005 12:24 PM
To: Jani, Parinda
Cc: Rappaport, Bob A; Harapanhalli, Ravi S; Boal, Jila H; Duffy, Eric P
Subject: FW: Injectable Suspension, Extended-Release Nomenclature

Parinda,

When we document the findings in our reviews we make sure that the recommendations from various consults are accurately captured. According to the CDER MAPP, selection of the established name is within the purview of LNC/CMC and this is our position.

Thank you

Ravi S. Harapanhalli, Ph.D.
Chief, CMC Branch V (Pre-marketing)
(Anesthesia, Analgesia, Rheumatology, Medical Imaging, Hematology, and Oncology Products)
Division III, ONDQA
Center for Drug Evaluation and Research, FDA,
Bldg. 22, Room # 2414
10903 New Hampshire Avenue,
Silver Spring, MD 20993-0002
Phone: 301 796 1676; Fax: 301 796 9850

-----Original Message-----

From: Poochikian, Guiragos K
Sent: Monday, October 31, 2005 5:07 PM
To: Harapanhalli, Ravi S; Mille, Yana R; Boal, Jila H; Lin, Sue Ching; Lewis, David B; Bertha, Craig M; Holquist, Carol A
Subject: RE: Injectable Suspension, Extended-Release Nomenclature

Unless there is any objection we will proceed with option 1, i.e., [DRUG] for Extended-release Injectable Suspension.

-----Original Message-----

From: Harapanhalli, Ravi S
Sent: Monday, October 31, 2005 4:12 PM
To: Poochikian, Guiragos K; Mille, Yana R; Boal, Jila H; Lin, Sue Ching; Lewis, David B; Bertha, Craig M; Holquist, Carol A
Subject: RE: Injectable Suspension, Extended-Release Nomenclature

Guirag,

The sample that was reconstituted on Friday was homogenous milky suspension and settled over an hour. It is truly a suspension.

Ravi S. Harapanhalli, Ph.D.
Chief, CMC Branch V (Pre-marketing)
(Anesthesia, Analgesia, Rheumatology, Medical Imaging, Hematology, and Oncology Products)
Division III, ONDQA
Center for Drug Evaluation and Research, FDA,
Bldg. 22, Room # 2414
10903 New Hampshire Avenue,
Silver Spring, MD 20993-0002
Phone: 301 796 1676; Fax: 301 796 9850

-----Original Message-----

From: Poochikian, Guiragos K
Sent: Monday, October 31, 2005 2:56 PM
To: Mille, Yana R; Harapanhalli, Ravi S; Boal, Jila H; Lin, Sue Ching; Lewis, David B; Bertha, Craig M; Holquist, Carol A
Subject: RE: Injectable Suspension, Extended-Release Nomenclature

Is the final decision to proceed with option 1?

-----Original Message-----

From: Mille, Yana R
Sent: Monday, October 31, 2005 12:33 PM
To: Poochikian, Guiragos K; Harapanhalli, Ravi S; Boal, Jila H; Lin, Sue Ching; Lewis, David B; Bertha, Craig M; Holquist, Carol A
Subject: Injectable Suspension, Extended-Release Nomenclature

Hi,

As expected, USP was able to turn the 'extended-release injection' nomenclature issue around very quickly. I presented them with the two options that we discussed

1) [DRUG] for Extended-release Injectable Suspension

2) [DRUG] Extended-release for Injectable Suspension

and, while it was a split vote, the majority were in favor of Option 1. [In case you are interested, 73% voted for Option 1, vs. 27% who favored Option 2.]

Yana



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-897

INFORMATION REQUEST LETTER

Alkermes, Inc.
88 Sydney Street
Cambridge, MA 02139-4136

11/2/05

Attention: Priya Jambhekar
Global Vice President, Regulatory and Government Affairs

Dear Ms. Jambhekar:

Please refer to your March 31, 2005, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Vivitrol (Naltrexone for Extended-release Injectable Suspension).

We also refer to your submission dated May 9, 2005.

We have reviewed the carton and container label section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

Four large, curved, handwritten lines, possibly indicating a signature or a large mark.

2 Page(s) Withheld

 Trade Secret / Confidential

✓ Draft Labeling

 Deliberative Process

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

/s/

Sara Stradley
11/2/2005 11:58:36 AM

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

DATE: October 28, 2005

TO: Rob Rappaport, M.D.
Director
Division of Anesthesia, Analgesia and Rheumatology Products, HFD-170

THROUGH: Mark Avigan, M.D., C.M.
Director
Division of Drug Risk Evaluation, HFD-430

FROM: Gita Akhavan-Toyserkani, Pharm.D.
Safety Evaluator
Division of Drug Risk Evaluation, HFD-430

SUBJECT: Post-marketing Safety Review of Hepatotoxicity with Oral Naltrexone Use.

PID# D050478

Confidential: Contains Verispan data; not to be used outside of the FDA without clearance from Verispan.

EXECUTIVE SUMMARY

This consult is in response to a request made by the Division of Anesthesia, Analgesia and Rheumatology Products (DAARP) to review the post-marketing data for hepatotoxicity with oral naltrexone use in AERS (Adverse Event Reporting System).¹ The current product labeling for ReVia[®] (oral naltrexone) contains a boxed warning, which states that ReVia[®] has the capacity to cause hepatocellular injury when given in excessive doses, but it does not appear to be a hepatotoxin at the recommended doses; Revia is contraindicated in acute hepatitis or liver failure.

As of August 22, 2005, there were a total of 706 adverse event reports in AERS associated with naltrexone. Additional AERS searches were conducted to identify cases of hepatotoxicity in association with naltrexone. The search identified 59 serious and non-serious reports (domestic and foreign). Most of the cases (25) originated in the United States. Twenty nine cases were found to have hepatic-related events possibly associated with naltrexone use. Of the 29 cases, 13 cases involved patients who were using naltrexone for alcohol dependence, 9 for opioid dependence, 3 for pruritus, 3 for behavior disorder, and 1 for weight reduction.

¹ Dr. Mwango Kashoki, a medical officer in DAARP, requested an AERS case review of hepatotoxicity with naltrexone use because a subcutaneous formulation of naltrexone is currently under review in DAARP.

The reported adverse events included increased hepatic enzymes, hepatitis, jaundice, cholestasis, fulminant liver failure and/or liver transplant. These cases were categorized according to the extent of liver injury using the ODS case definition for hepatotoxicity (see Case Definition Section of this review). There were 4 cases of severe life-threatening injury with liver failure (Category 4); 4 cases of moderately severe to definitely life-threatening liver injury (Category 3B); 3 cases of moderately severe to possibly life-threatening liver injury (Category 3A) and 18 cases of mild (Category 1 or Category 2) liver injury.

Analysis of the cases suggested that the majority of the patients 72% (18/25) were receiving the recommended 50mg daily dose. The highest reported dose was 200mg daily in one patient. There was a wide range in time to onset (first day as per reporter to 10 months). In the 13 of the 29 cases, hepatic transaminases exceeded three times the ULN. Of these 13 cases, 7 were accompanied with an increase in serum bilirubin level. The highest hepatic transaminase elevation in the case series exceeded 84 times the ULN and the highest total bilirubin exceeded 42 times the ULN. The pattern of liver injury could be determined in 7 cases; cholestatic liver injury occurred in 5 cases, hepatocellular injury in 1 case, and a mixed injury pattern in 1 case. There were 4 reports of positive dechallenge where the transaminase levels returned to normal or trended towards baseline after discontinuation of naltrexone. There were no reports of rechallenge in the case series.

Serious outcomes included 8 hospitalizations, 2 life-threatening events, and 3 deaths. Two of the 3 deaths were not liver-related; the causes of death were upper gastrointestinal bleed and esophageal bleed respectively. There was one report of death secondary to an acute liver failure in a 3-year-old patient on naltrexone for self-destructive behavior. This case was confounded by a prior history of a liver transplant and the concomitant use of an immunosuppressive medication in addition to naltrexone at the time of the event. According to the biopsy report, while morphological changes support the diagnosis of acute allograft rejection; however, associated underlying adverse drug reaction may have also contributed to lobular inflammation noted in the biopsy (see additional details in the case summary).

The mechanism of liver injury from naltrexone use is not clear from the cases. We were not able to find a dose-response relationship in AERS cases. The majority of the cases that had dosages reported were receiving the recommended once daily 50mg dose (72%). Although, the box warning states that ReVia does not appear to be a hepatotoxin at the recommended doses, the most frequently reported dose in the case series was the recommended 50mg once daily. Therefore, additional studies to more fully elucidate the hepatotoxic potential of naltrexone and its metabolites and any possible dose relationship may be necessary.

Seventeen cases (16/29, 55%) were confounded by pre-existing liver disease (5), concomitant use of other drugs that are labeled for hepatotoxicity (10), and positive viral serology (4); three cases contained more than one potentially contributing factor. In this group of patients whose liver function might already be compromised by alcoholic hepatitis, viral hepatitis, and/or concurrent potentially hepatotoxic medications, it is difficult to determine a clear association of naltrexone induced liver injury. However, in patients with pre-existing liver insults (i.e. alcohol) or other predisposing factors, naltrexone may increase the likelihood of a hepatic adverse event.

In conclusion, most of the cases reported mild-to-moderate liver injury (18/29; 62%). There were 4 cases of severe life-threatening injury with liver failure and 7 cases showed evidence of liver injury severe enough to cause disruption in clearance of bilirubin per lab values or clinical presentation of jaundice/icterus (Category 3A -3; Category 3B -4). The majority of the cases were confounded with other contributory factors. However, a concurrent condition, does not exclude the possible contributory role of naltrexone, such as an additive effect. This case series supports a possible

association between naltrexone and serious hepatic injury including hepatitis and liver failure. We recommend keeping the box warning in the current labeling at this time.

BACKGROUND AND PRODUCT LABELING²

Naltrexone hydrochloride is a μ -opioid receptor antagonist. It was first approved under the trade name Trexan[®] (NDA 18-932) in November 1984. After the New Drug Application was filed, DuPont evaluated naltrexone for several indications other than addiction

— In 1994, it was approved for the indication of alcohol dependence and was marketed under the trade name ReVia[®]. Currently, naltrexone is indicated for the treatment of alcohol dependence and for the blockade of exogenously administered opioids and manufactured by several generic companies. The recommended dose is one tablet (naltrexone 50mg) once daily.

The naltrexone (ReVia[®]) product labeling states that the evidence of the hepatotoxic potential of naltrexone is derived primarily from a placebo controlled study in which it was administered to obese subjects at a dose approximately five-fold that recommended for the blockade of opiate receptors (300 mg per day). In that study, 5 of 26 subjects receiving naltrexone had increased levels of serum transaminases, with ALT ranging from 121 to 532; (3 to 19 times their baseline values) after three to eight weeks of treatment. Two of the subjects had elevations of serum bilirubin with peak total bilirubin of 1.8 mg per deciliter and 1.3 respectively, and alkaline phosphatase was not elevated in any subjects in the obesity study.³ Although the patients involved were generally clinically asymptomatic and the transaminase levels of all patients on whom follow-up was obtained returned to (or toward) baseline values in a matter of weeks, the lack of any transaminase elevations in any of the 24 placebo patients in the same study was persuasive evidence that ReVia[®] is a direct (i.e., not idiosyncratic) hepatotoxin.

According to the labeling, this conclusion is also supported by evidence from other placebo controlled studies in which exposure to ReVia[®] at doses above the amount recommended for the treatment of alcoholism or opiate blockade (50 mg/day) consistently produced more numerous and more significant elevations of serum transaminases than placebo. Transaminase elevations in 3 of 9 patients with Alzheimer's disease who received ReVia[®] (at doses up to 300 mg/day) for 5 to 8 weeks in an open clinical trial have been reported. Although no cases of hepatic failure due to ReVia[®] administration were reported in clinical trials, physicians are advised to consider this as a possible risk of treatment and to use the same care in prescribing ReVia[®] as they would other drugs with the potential for causing hepatic injury.

In the above mentioned studies, additional information about possible biopsy reports or effects on coagulation (i.e. PTT and INR) was not available. According to the labeling, studies to evaluate possible interactions between ReVia[®] and drugs other than opiates have not been performed. Information about possible interactions with alcohol or safety concerns with alcohol use is not addressed in the labeling. Furthermore, in the labeling clear guidelines on monitoring for liver injury is not available. The labeling states that evaluations, using appropriate batteries of test to detect liver injury are recommended at a frequency appropriate to the clinical situation and the dose of ReVia.[®] In

² REVIA (naltrexone hydrochloride) product labeling, available at URL.
<http://www.fda.gov/cder/ogd/rld/18932s14.pdf>. Accessed 8/24/05.

³ Pfohl DN, Allen JJ, Atkinson RL, Knopman DS, Malcolm RJ, Mitchell JE, Morley JE. Naltrexone hydrochloride (Trexan): a review of serum transaminase elevations at high dosage. NIDA Res Monogr. 1986;67:66-72.

the precautions section, patients are advised to stop taking ReVia® immediately and see a doctor if patients develop abdominal pain lasting more than a few days, dark urine, or yellowing of the eyes.

The current labeling for the drug contains the following box warning:

Box Warning:

- REVIA has the capacity to cause hepatocellular injury when given in excessive doses.
- REVIA is contraindicated in acute hepatitis or liver failure, and its use in patients with active liver disease must be carefully considered in light of its hepatotoxic effects. The margin of separation between the apparently safe dose of REVIA and the dose causing hepatic injury appears to be only five-fold or less.
- REVIA does not appear to be a hepatotoxin at the recommended doses.
- Patients should be warned of the risk of hepatic injury and advised to stop the use of REVIA and seek medical attention if they experience symptoms of acute hepatitis.

DRUG USE DATA⁴

Verispan's Vector One™: National (VONA) a national-level projected prescription and patient-centric tracking service which provides a comprehensive overview of the national performance of all prescription drugs dispensed by retail pharmacies, indicated that approximately prescriptions were dispensed for naltrexone tablets from initial marketing through July 2005.

Table 1 contains the number of total prescriptions dispensed by retail pharmacies throughout the U.S. from the time period indicated above. **This information is not to be used outside of the FDA without prior clearance by Verispan.**

Table 1. US prescriptions dispensed for naltrexone, 1993 through July 2005

Drug	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	YTD JUL/2005
TOTAL MARKET													

From the drug use data it was determined that mean days of therapy, or the average number of days of therapy dispensed to the patients for naltrexone is approximately 27.5 days; this number could not be stratified by indication.⁵ The estimated population exposure to naltrexone for 1993-2004 is person-years.⁶ The optimum duration of naltrexone maintenance therapy has not been established but should be based on individual requirements and response. In general, patients formerly physically dependent on opiates need a minimum of 6 months to make the behavioral changes necessary to maintain opiate cessation, and naltrexone therapy may be beneficial during this period. For patients

⁴ Citation: Verispan Vector One: National , Years 1993-July 2005 Extracted 08-23-05. Source Files:D050478A naltrexone.qry. Drug Use Specialist: Laura Governale. Total includes New and Refill prescriptions.

⁵ Citation: Verispan Vector One: National , Years 1993-July 2004 Extracted 10-19-05. Source Files:D050478A naltrexoneRXDays.qry. Drug Use Specialist: Laura Governale.

⁶ Estimated mean prescription duration of 27.5 days used in calculations of reporting rates. Total prescriptions 1993-2004 = _____ X 27.5)/365 = _____ person-years exposure.

unable to successfully deal with the temptation of opiate use, maintenance naltrexone therapy may be necessary throughout the course of a comprehensive opiate cessation program.⁷

CASE DEFINITION⁸

The following case definitions were used to categorize the extent of liver injury:

Category 1: Very mild or poorly characterized liver injury—Serum ALT or AST elevated but <3 times the upper limit of normal* (ULN); normal TB and prothrombin time (PT).

*ULN varies depending on the laboratory, but the following can be used as a guide for ULN: AST ~42 IU/L, ALT ~30 IU/L, TB ~1 mg/dL

Category 2: Mild-to-moderate liver injury—serum transaminase elevations with no evidence of overall liver function loss. This may also include reports of hepatitis NOS, with no lab data and reports of elevations in transaminases without signs or symptoms of overall loss of liver function

Category 3: Moderately severe liver injury—liver injury causing acute impairment of liver function w/inability to make enough PT or clear bilirubin from the blood sufficiently. Impaired liver function without liver failure. Reported clinical signs or symptoms might include jaundice, coagulopathy, and elevated bilirubin. Further sub-categorization can be determined using the following:

A. Possibly threatening: At least 3x ULN ALT or AST and (elevation of bilirubin to <3 x ULN or PT (INR) to < 1.5).

B. Definitely threatening: At least 3x ULN ALT or AST and INR > 1.5 or bleeding events (hematuria, bleeding gums, etc.), or jaundice or elevation of bilirubin to at least 3 x ULN

Category 4: Severe life-threatening injury with liver failure—severe liver injury with secondary impairment of brain or kidney function. Death, liver transplantation, placement on a liver transplant list, or evidence of altered mental status (encephalopathy) in the setting of acute liver injury (elevated transaminases, bilirubin, or jaundice). Reported clinical signs and symptoms may include coagulopathy or renal function impairment. This category will also include reports with a diagnosis of liver failure without supporting clinical or laboratory data. The biggest distinction between 3 and 4 is neurologic and kidney involvement. This will also include reports with a diagnosis of liver failure without supporting clinical or laboratory data.

SELECTION OF CASES

As of August 22, 2005, there were a total of 706 adverse event reports in AERS associated with naltrexone. Additional AERS searches were conducted to identify cases of hepatotoxicity in association with naltrexone.

⁷ DuPont Pharmaceuticals. Trexan[®] (naltrexone hydrochloride) in opioid addiction: a comprehensive product monograph. Wilmington, DE; 1985 March

⁸ DDRE Case Definition Working Group (CDWG), ODS Working Case Definitions for Postmarketing ADR Review; Acute liver Injury. Revised May 2003. Available on CDERnet at URL: <http://cdernet/ods/Workroom/Case%20definition%20working%20group/Case%20Definitions/Acute%20liver%20injury.doc>

AERS was searched from time of marketing to 8/22/05 for the ingredient name naltrexone and the trade names Trexan[®] and ReVia[®]. The following MedDRA high-level group terms (HLGTs) and preferred term (PT) were used to conduct the AERS search: *hepatic and hepatobiliary disorders* (HLGT); *hepatobiliary investigations* (HLGT); and *liver transplant* (PT). The search identified 59 serious and nonserious reports (domestic and foreign). All reports were given an initial review and grouped into categories based on inclusion (Case Definition) and exclusion criteria.

Exclusions:

Cases were excluded if they had alternative causes of liver injury such as viral hepatitis, concurrent hepatotoxic medications and cases where pre-existing chronic liver disease were suspected. Five duplicate reports and 25 additional cases were excluded based on the following:

- Information was insufficient (2)
- The primary event was not hepatotoxicity (4)
- The event was more likely to be attributed to another drug [Antabuse (3), Tylenol overdose (1)] or patient was not on oral naltrexone at the time of event (6)
- Diagnosis of viral hepatitis unlikely related to naltrexone (10)
- Pre-existing liver disease such as Wilson’s disease (1)
- Pancreatic cancer metastasized to the liver and lymph nodes (1) and biliary obstruction (1)

The 29 remaining cases were categorized by the ODS case definition (detailed above) and summarized below. A line listing of the cases are provided in Attachment 1.

SUMMARY OF CASES

Thirty-one reports of hepatotoxicity in association with naltrexone are included in this case series.

Table 2. Demographic and clinical characteristics of the 29 naltrexone cases associated with hepatotoxicity.

Age (n=25)*	Median 32 year; range 3-60 years		
Gender (n=26)	Female-7; male-19		
Location:	US-25; Foreign-4		
Report type:	Direct-6; 15-day-11; Periodic-12		
Report year:	1984-1	1993-1	2000-4
	1985-2	1994-3	2003-1
	1987-2	1996-7	
	1988-1	1997-2	
	1990-1	1998-2	
	1992-1	1999-1	
Hepatic injury category:	Category 4 (Severe life-threatening injury with liver failure)-4		
	Category 3 (Moderately severe liver injury)- 7		
	Category 2 (Mild-to-moderate liver injury) -9		

* In Table 1, n in parentheses (i.e. n=27) indicates the number of cases out of the total 29 cases for which the information was available.

Category 1 (Very mild or poorly characterized liver injury)- 9

Outcome:	Death- 3; Hospitalization- 8; Life-threatening -2; Other- 9; unspecified- 7
Indication:	Alcohol dependence-13; Opioid dependence- 8; Pruritus-3; Other-3; unspecified-2
Daily Dose (mg/day): (n=25)	Estimated daily dose range 25mg-200mg; Median dose 50mg- 18
Time to Onset (n=23):	Estimated range: 1 day-10 months, Median time of 45 days
Dechallenge/Rechallenge:	Positive dechallenge-4, Rechallenge -0

Most of the cases (25) originated in the United States. The age of patients ranged from 3 to 60 years with the median age of 32 years. Approximately 66% of the patients (19 of 29) were male. Of the 29 cases, 13 cases involved patients who were using naltrexone for alcohol dependence, 9 cases for opioid dependence, 3 for pruritus, 2 cases of behavior disorder, and 1 case of weight reduction.

The doses in the cases ranged from 50mg per day (recommended dose) to 200mg per day as the maximum reported dose. Of the cases that reported doses, 72% (18/ 25) received the recommended daily dose of 50mg; 1 case reported 75mg once daily; 2 cases reported administering naltrexone 3 times a week (50-50-100mg or 100-100-150mg); 2 case reported 100-150mg daily and 1 case reported 200mg daily. There was a wide range in time to onset (first day as per reporter to 10 months) with median time of 45 days.

The patients presented with fatigue, nausea, fever, rash, abdominal pain, jaundice/icterus and increased ammonia levels. The reported adverse events in the 31 cases included increased hepatic enzymes, hepatitis, jaundice, cholestasis, fulminant liver failure and liver transplant. The majority of the patients (18/29, 62%) experienced Category 1 (9 cases) or Category 2 (9 Cases) liver injury; that is very mild to moderate liver injury as evidence by increased hepatic transaminases, without disruption in coagulation or clearance of bilirubin. Nine cases showed evidence of liver injury severe enough to cause disruption in clearance of bilirubin per lab values or clinical presentation of jaundice/icterus (Category 3A-3; Category 3B-4). There were 4 cases of severe life-threatening injury with liver failure (Category 4). There was one case of liver transplant confounded with a history of chronic intrahepatic cholestasis on naltrexone for pruritus.

In the 13 of the 29 cases, hepatic transaminases exceeded three times the ULN. Of these 13 cases, 7 were accompanied with an increase in serum bilirubin level. The highest hepatic transaminase elevation in the case series exceeded 84 times the ULN and the highest total bilirubin exceeded 42 times the ULN. The pattern of liver injury could be determined in 7 cases; cholestatic liver injury occurred in 5 cases, hepatocellular injury in 1 case, and a mixed injury pattern in 1 cases. There were 4 reports of positive dechallenge where the transaminase levels returned to normal or trended towards baseline after discontinuation of naltrexone. There were no reports of rechallenge in the case series.

Seventeen cases (17/29, 58%) were confounded by pre-existing liver disease (5), concomitant use of other drugs that are labeled for hepatotoxicity (11), and positive viral serology (4); three cases contained more than one potentially contributing factor. In this group of patients whose liver function might already be compromised by alcoholic hepatitis, viral hepatitis, and/or concurrent potentially hepatotoxic medications, it was difficult to determine a clear association of naltrexone induced liver injury. However, a concurrent condition, does not exclude the possible contributory role of naltrexone. Furthermore, in patients with pre-existing liver insults (i.e. alcohol) or other predisposing factors, naltrexone could possibly increase the likelihood of a hepatic adverse event.

Serious outcomes included 8 hospitalizations, 2 life-threatening events, and 3 deaths. Two of the 3 deaths were not liver-related; the causes of death were upper gastrointestinal bleed and esophageal bleed. There was one report of death secondary to an acute liver failure in a 3-year-old patient, but this case was confounded by a prior history of a liver transplant and the concomitant use of an immunosuppressive medication in addition to naltrexone at the time of the event. This was the only case in this case series that contained a liver biopsy report. The liver biopsy indicated a possible drug induced injury secondary to naltrexone use (see case summary below).

A representative case of a Category 3A liver injury from a study is summarized below.

AERS ISR 3005873-5, US, 1997, Category 3A

A 20-year-old Hispanic male patient with no known preexisting medical condition was participating in a double blind placebo trial of naltrexone for alcohol treatment. The patient was on 50mg of naltrexone twice daily for 6 weeks. He was not on any concomitant medications. His baseline bilirubin levels was 1.0 and increased to 2.4 by week 6 and repeat labs two weeks later showed a continued elevation. The patient's study medication was discontinued after week 6. According to the reporter the patient had negative breathalyzers since prior to the treatment. Outcome was not reported and there were no follow up reports.

There was 1 case report that included a liver biopsy summarized below.

AERS ISR 3626221-3, US, 2000, Category 4

A 3-year-old with a history of a liver transplant presented with jaundice and elevated liver enzymes in July of 2000. The patient was on Prograf and ReVia (50mg hs and 25mg am) for self-destructive behavior. The patient was admitted to the hospital for an organ rejection and ReVia was discontinued. The patient died of _____ with the cause of death as cerebellar edema from acute liver failure and Candida sepsis. Morphological changes in the biopsy showed moderate to marked mixed inflammation in the portal area composed of prominent eosinophils, lymphocytes and occasional plasma cells. Bile duct damage and vasculitis were identified. Hepatic parenchyma showed lobular inflammation composed of lymphocytes and occasionally eosinophils. Also, noted in hepatic parenchyma were increased apoptosis, steatosis, reactive hepatocytes, and focal bile accumulation. Occasional central veins showed perivenular inflammation. According to the biopsy report, while morphological changes support the diagnosis of acute allograft rejection, associated underlying adverse drug reaction may also have contributed to lobular inflammation noted in the biopsy

Summarized below are 3 example cases confounded with other contributing factors such as viral hepatitis and concomitant use of hepatotoxic medication. However, due to the temporal relationship of naltrexone use and increase in liver enzyme levels, the contributory role of naltrexone could not be ruled out.

AERS ISR 3286811-7, US, 1998, Category 4

A patient (age and gender unknown) was admitted to the hospital via the emergency room for **fulminant liver failure** while taking ReVia for pruritus. The patient had a history of hepatitis B and C in the 1970s and a history of liver dysfunction prior to ReVia therapy. No further information was provided.

AERS ISR 3173613-5, US, 1998, Category 4

A 45 year-old female was hospitalized for 11 days due to elevated liver enzymes and delirium secondary to liver failure. The patient was on naltrexone 50mg once daily for alcoholism for 4 and ½ months. The patient was also possibly on concurrent Antabuse, Effexor, Ambien,

Buspar, Tylenol and Axid without further information. Clinical data showed **AST 2496, AIK 2396 and a total bilirubin 18.4**. According to the reporter, patient had normal liver function prior to using ReVia and returned to normal again after discontinuation of Revia. The patient had not used alcohol prior to hospitalization.

AERS ISR 1468997, US, 1994, Category 3B

A physician reported that a 39 year-old male patient taking Trexan 50mg daily for alcohol craving, developed nausea, vomiting and malaise. Trexan was discontinued after 22 days of therapy when the patient reported to the drug treatment center with **icterus** and increased difficult swallowing. The patient was admitted to the hospital with severe hepatitis and fever. The following hepatic laboratory values were obtained (the highest value for each test): **ALT 2540 IU/L, AST 2680 IU/L, total bilirubin 41.8 mg/dl**. Prior to taking the first dose of naltrexone, patient had a mildly elevated AST of 41 IU/L and ALT of 66 IU/L and a total bilirubin of 0.7 mg/dl. Over the next few days, the patient's symptoms decreased and his clinical status improved. Hepatitis serologies were positive for acute hepatitis B and C and the patient was found to be HIV positive.

There were 2 cases of increased ammonia levels summarized below. The second case is confounded with a history of cirrhosis and elevated ammonia levels prior to Trexan use.

AERS ISR 1764106-8, Germany, 1996, Category 4

A 33-year-old male began therapy with Revia 50mg once daily for alcohol addiction. Twenty days later he developed severe elevation of hepatic enzymes. **ALT 933 IU/L, AST 204 IU/L, AP 204 IU/L and total bilirubin 9.9mg/dl**. He also experienced **elevated ammonia level (107ug/dl) and** was hospitalized. Viral hepatitis serology was negative. An EEG revealed aberrations, which were interpreted as signs of a drug toxicity; cholestasis worsened during the first days of hospitalization. Naltrexone was discontinued and there was subsequent reduction of liver enzymes. Twelve days after discontinuation, the lab findings were as follows: ALT 176 IU/L, AST 39 IU/L, AP 133 IU/L, total bilirubin 1.5mg/dl.

AERS ISR 1417692, US, 1993, Category 1

A 42-year-old male with a history of alcoholic cirrhosis began Trexan therapy 50mg once daily and sertraline 50m once daily for alcoholism and depression, respectively. The patient was also taking vitamin B complex. Approximately two weeks prior to starting Trexan and Zoloft, the patient was found to have elevated ammonia level. Twenty days after starting therapy, the patient developed mental confusion. Trexan and Zoloft were discontinued and 10 days later, the patient had some improvement. Despite the history of cirrhosis, the patient had normal prothrombin time and transaminases were within normal limits. The patient also had some ascites (not further clarified). The reporting physician indicated that the patient's mental confusion may have been due to a Trexan-sertraline interaction, Trexan or progression of liver disease.

DISCUSSION/CONCLUSION

Currently, oral naltrexone is contraindicated in patients with acute hepatitis and liver failure. The labeling for naltrexone includes a box warning for risk of hepatocellular injury when given in excess doses. In this consult, 29 cases of hepatotoxicity in association with oral naltrexone were reviewed. The reported adverse events included increased hepatic enzymes, hepatitis, jaundice, cholestasis, fulminant liver failure and/or liver transplant. There were 4 cases of severe life-threatening injury with liver failure (Category 4); 4 cases of moderately severe to definitely life-threatening liver injury

(Category 3B); 3 cases of moderately severe to possibly life-threatening liver injury (Category 3A) and 18 cases of mild (Category 1 or Category 2) liver injury.

The mechanism of liver injury from naltrexone use is not clear from the cases. We were not able to find a dose-response relationship in AERS cases. The majority of the cases that had dosages reported were receiving the recommended once daily 50mg dose (72%). The highest dose that was reported was 200-mg once daily. Although, the box warning states that ReVia does not appear to be a hepatotoxin at the recommended doses, the most frequently reported dose in the case series was the recommended 50mg once daily. Therefore, additional studies to more fully elucidate the hepatotoxic potential of naltrexone and its metabolites and any possible dose relationship may be necessary.

Naltrexone is used in detoxified opioid addicts or alcohol users which compromise a younger population. From the case series the median age was found to be 32, with a range of 3 to 60. Of note, elderly patients may be more susceptible to hepatotoxic effects of drugs and more likely to develop adverse liver events related to naltrexone than younger subjects.

In this case series, 13 (44%) were being treated for alcohol dependence. In a group of patients whose liver function might already be compromised by alcoholic hepatitis, viral hepatitis and concurrent potentially hepatotoxic medications, it difficult to determine a clear association of naltrexone induced liver injury. However, a concurrent condition, does not exclude the possible contributory role of naltrexone. Furthermore, in patients with pre-existing liver insults (i.e. alcohol) or other predisposing factors, naltrexone may increase the likelihood of a hepatic adverse event.

In conclusion, most of the cases reported mild-to-moderate liver injury (18/29; 62%). There were 4 cases of severe life-threatening injury with liver failure, for which the narratives were provided; and 7 cases showed evidence of liver injury severe enough to cause disruption in clearance of bilirubin per lab values or clinical presentation of jaundice/icterus (Category 3A -3; Category 3B -4). The majority of the cases were confounded with other contributory factors. However, a concurrent condition, does not exclude the possible contributory role of naltrexone, such as an additive effect. This case series supports a possible association between naltrexone and serious hepatic injury including hepatitis and liver failure. We recommend keeping the box warning in the current labeling at this time.

**APPEARS THIS WAY
ON ORIGINAL**

Gita Akhavan-Toyserkani, Pharm.D. Safety Evaluator
Division of Drug Risk Evaluation, Office of Drug Safety, HFD-430

Concur:

Lauren Lee, Pharm.D., Team Leader
Division of Drug Risk Evaluation, Office of Drug Safety, HFD-430

**APPEARS THIS WAY
ON ORIGINAL**

CC: NDA# 18-932 (ReVia[®], Trexan[®])
HDF-170 Rappaport/Kashoki/Basham-Cruz
HFD-430 Avigan/Johann-Liang/Birdsong/Lee/Akhavan-Toyserkani

**APPEARS THIS WAY
ON ORIGINAL**

ISR	Age	Sex	Country	Outcome	Indication	Dose mg/day	Time to Onset	AP	ALT	AST	T.Bill	Liver Category
559194	36	F	US	OT	Opioid dependence	100-150mg	5 months		56	47		1
649628	U	U	US	OT	Weight Reduction	50mg	4.5 months		46			1
1417692	42	M	US		Alcohol dependence	50mg	19 days					1
1684859	38	M	US		Alcohol dependence	50mg		93	76	30	1.1	1
1920842	31	M	FR	HO	Alcohol dependence	50mg	10 days		78	43		1
3222192	U	U	US	HO		50mg		130				1
3475885	32	M	GB	HO	Opioid dependence	25-50mg	1 day				1.3	1
3480940	6	F	NL	HO	Pruritis	200mg	2 months					1
4205251	16	M	US	HO	Pruritis	50mg						1
1551976	42	M	US		Opioid dependence	100-100-150mg; M-W-F	6 months		314	152		2
1854098	U	F	US		Alcohol dependence		7 days	349	281	165		2
499103	34	M	US	OT			5 days					2
800846	8	F	US	OT	Self-destructive behaviour		3 months					2
1845635	60	M	US		Alcohol dependence	50mg				182	40	2
335163	26	M	US	OT	Opioid dependence	50mg	10 months		303			2
335164	38	M	US	OT	Opioid dependence	50mg	4 months		305			2
303175	19	F	US	OT	Opioid dependence	50mg	62 days		1010	410	0.7	2

Attachment 1-Line Listing of Liver Injury Cases* Reported for Naltrexone (29 cases)

(*Category 1: Very mild or poorly characterized liver injury; Category 2: Mild-to-moderate liver injury; Category 3: Moderately severe liver injury [a. Possibly life-threatening; B. Definitely life-threatening]; Category 4: Severe life-threatening with liver failure)

Attachment 1-Line Listing of Liver Injury Cases* Reported for Naltrexone (29 cases) (*Category 1: Very mild or poorly characterized liver injury; Category 2: Mild-to-moderate liver injury; Category 3: Moderately severe liver injury [a. Possibly life-threatening, b. Definitely life-threatening]; Category 4: Severe life-threatening with liver failure)												
ISR	Age	Sex	Country	Outcome	Indication	Dose mg/day	Time to Onset	AP	ALT	AST	T.Bill	Liver Category
453585	33	M	US	OT	Opioid dependence	50-50-100mg M-W-F	3 months	203	404	166		2
1737862	29	F	US	HO	Opioid dependence	50mg	6 weeks					3A
3005873	20	M	US	OT	Alcohol dependence	100mg	6 weeks				2.4	3A
3632769	52	M	US		Alcohol dependence	50 MG	2 weeks		127	53		3A
1468997	39	M	US	LT	Alcohol dependence	50mg	22 days		2540	2680	41.8	3B
1528214	45	M	US	DE	Alcohol dependence	50mg	5 months	401	55	176	3	3B
1774884	49	M	US	DE	Alcohol dependence	50mg	3-4 weeks				4.8	3B
1845299	43	M	US		Alcohol dependence	50mg	15 days					3B
1764106	33	M	DE	HO	Alcohol dependence	50mg	21 Days	213	1080	381	8.8	4
3173613	45	F	US	LT	Alcohol dependence	50MG	4.5 months	2396	2496		18.4	4
3286811	U	U	US	HO	Pruritis							4
3626221	3	M	US	DE	Self-destructive behaviour	75mg		718	1699	2033	7.7	4

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this page is the manifestation of the electronic signature.**

/s/

Gita Akhavan-Toyserkani
10/28/2005 01:30:53 PM
DRUG SAFETY OFFICE REVIEWER

Mark Avigan
10/31/2005 01:07:57 PM
DRUG SAFETY OFFICE REVIEWER



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-897

DISCIPLINE REVIEW LETTER

Alkermes, Inc.
88 Sydney Street
Cambridge, MA 02139-4136

10/28/05

Attention: Priya Jambhekar
Global Vice President, Regulatory and Government Affairs

Dear Ms. Jambhekar:

Please refer to your March 31, 2005, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Vivitrol (naltrexone injection).

We also refer to your submission dated August 16, 2005.

We have completed our review of the suggested tradename Vivitrol and we find it acceptable at this time. However, if the approval of this application is delayed beyond 90 days from the date of this letter, the name must be reevaluated to rule out any objections based upon approval of other proprietary or established names from this date forward.

If you have any questions, call Lisa E. Basham-Cruz, Regulatory Project Manager, at 301-796-1175.

Sincerely,

{See appended electronic signature page}

Sara Stradley, MS
Supervisory Consumer Safety Officer
Division of Anesthesia, Analgesia and
Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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

/s/

Sara Stradley
10/28/2005 10:15:04 AM

CONSULTATION RESPONSE
DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(DMETS; White Oak 22, Mail Stop 4447)

DATE RECEIVED: August 17, 2005	DESIRED COMPLETION DATE:	ODS CONSULT #:
DOCUMENT DATE: August 16, 2005	September 9, 2005	02-0073-2

TO: Bob Rappaport, MD
 Director, Division of Anesthesia, Analgesia, and Rheumatology Products
 HFD-170

THROUGH: Lisa Basham-Cruz
 Project Manager
 HFD-170

PRODUCT NAME:
Vivitrol
 (Naltrexone Injection)
 380 mg/5 mL (76 mg/mL)

NDA SPONSOR: Alkermes

NDA #: 21-897

SAFETY EVALUATOR: Laura Pincock, Pharm.D.

RECOMMENDATIONS:

1. DMETS has no objections to the use of the proprietary name "Vivitrol." This is considered a final decision. However, if the approval of this application is delayed beyond 90 days from the signature date of this document, the name must be re-evaluated. A re-review of the name will rule out any objections based upon approval of other proprietary or established names from the signature date of this document.
2. Revised container labels, carton and insert labeling were not submitted for review and comment. DMETS refers to ODS Consult 02-0071-1 for our previous label and labeling comments.
3. DDMAC finds the proprietary name "Vivitrol" acceptable from a promotional perspective.
4. Please consult Guiragos Poochikian, Acting Chair, of the CDER Labeling and Nomenclature Committee on the proper designation of the established name.

Denise P. Toyer, Pharm.D.
 Deputy Director
 Division of Medication Errors and Technical Support
 Office of Drug Safety
 Phone: (301) 796-0549 Fax: (301) 796-9865

Carol Holquist, RPh
 Division Director
 Division of Medication Errors and Technical Support
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Division of Medication Errors and Technical Support (DMETS)
Office of Drug Safety
HFD-420; WO 22, Mail Stop 4447
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: August 29, 2005
NDA# 21-897
NAME OF DRUG: Vivitrol
(Naltrexone Injection)
380 mg/5 mL (76 mg/mL)
NDA HOLDER: Alkermes

*****NOTE: This review contains proprietary and confidential information that should not be released to the public.*****

I. INTRODUCTION:

This consult was written in response to a request from the Division of Anesthesia, Analgesia, and Rheumatology Products (HFD-170), for assessment of the proprietary name, "Vivitrol" regarding potential name confusion with other proprietary and/or established drug names. The established name, naltrexone injection, was previously reviewed under the tradename Vivitrex in ODS Consult 02-0071-1 dated June 27, 2005. DMETS did not recommend the use of Vivitrex

κ. Additionally, DMETS recommended that the proper designation of the established name (naltrexone long acting injection) be referred to the FDA's Labeling and Nomenclature Committee. Subsequently, the Sponsor has proposed "Vivitrol" as an alternative tradename. Revised labels and labeling were not submitted for review and comment at this time. DMETS refers to ODS Consult 02-0071-1 for our previous label and labeling comments.

PRODUCT INFORMATION

Vivitrol is naltrexone microencapsulated within a polylactide-co-glycolide matrix, an opioid antagonist indicated for the treatment of alcohol dependence. Vivitrol is to be administered by a healthcare professional. The recommended dose is 380 mg given intramuscularly every 4 weeks or once a month. Treatment with Vivitrol should be part of an appropriate management program for alcohol dependence. Vivitrol is to be supplied in single use kits containing one 380 mg vial of Vivitrol, one vial of diluent (4 mL), one 5 mL syringe, one ½" 20 gauge needle, and two 1 ½" 20 gauge needles with safety device.

II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of several standard published drug product reference texts^{1,2} as well as several FDA databases³ for existing drug names which sound-alike or look-alike to Vivitrol to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted⁴. The Saegis⁵ Pharma-In-Use database was searched for drug names with potential for confusion. An expert panel discussion was conducted to review all findings from the searches. In addition, DMETS conducted three prescription analysis studies for each proposed name consisting of two written prescription studies (inpatient and outpatient) and one verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

A. EXPERT PANEL DISCUSSION (EPD)

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name Vivitrol. Potential concerns regarding drug marketing and promotion related to the proposed names were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. DDMAC has no objections to the tradename "Vivitrol" from a promotional perspective.
2. The Expert Panel identified nine proprietary names that were thought to have the potential for confusion with Vivitrol. These products are listed in Table 1 (pages 4 to 5), along with the dosage forms available and usual dosage.
3. The Expert Panel made an additional comment that Vivitrol "looks similar to volutrol", a type of intravenous infusion set used in infants. A volutrol is an inline receptacle between the patient's catheter set and the bag of parenteral fluids.

¹ MICROMEDEX Integrated Index, 2005, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.

² Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

³ AMF Decision Support System [DSS], the Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests, New Drug Approvals 98-04, and the electronic online version of the FDA Orange Book.

⁴ WWW location <http://www.uspto.gov/tmdb/index.html>.

⁵ Data provided by Thomson & Thomson's SAEGIS™ Online Service, available at www.thomson-thomson.com

Table 1: VIVITROL: Potential Sound-Alike/Look-Alike Names Identified by DMETS Expert Panel

Product Name	Dosage form(s), Established name	Usual adult dose*	Other**
Vivitrol	Naltrexone long acting injection Injection: 380 mg/ 5 mL vial	380 mg IM monthly	N/A
Nicotrol	Nicotine Nasal spray: 0.5 mg/actuation Inhaler: 10 mg Transdermal patch: 5 mg, 10 mg, 15 mg	<u>Nasal Spray:</u> 1 spray into each nostril 1—2 times each hour as needed whenever the patient feels the need to smoke. Two sprays (one into each nostril) is considered one dose. <u>Inhaler:</u> 24 to 64 mg (6 to 16 cartridges) per day for up to 12 weeks followed by a gradual reduction in dosage over a period of up to 12 weeks. <u>Patches:</u> Patients > 100 pounds, smoking at least 10 cigarettes/day and/or without cardiovascular disease: Initially, one 15 mg patch on intact skin for 16 hrs/day (i.e., apply upon waking and remove at bedtime) for 4—12 weeks. Following initial regimen, reduce to one 10 mg patch for 16 hrs/day for the next 2—4 weeks and then one 5 mg patch for 16 hrs/day for 2—4 weeks.	LA
Levitol	Penbutalol Tablets: 20 mg	20—40 mg PO per day. Maximum dosage is 80 mg/day PO.	LA
Vivactil	Protriptyline Tablets: 5 mg, 10 mg	5—10 mg PO three times per day; titrated in 10 mg increments at weekly intervals, depending on response and adverse effects. When satisfactory improvement has been reached, dosage should be reduced to the smallest amount that will maintain relief of symptoms.	LA
Vistaril	Hydroxyzine Pamoate (oral), Hydroxyzine Hydrochloride (injection) Capsules: 25 mg, 50 mg Oral Suspension: 25 mg/ 5 mL Injection: 25 mg/mL, 50 mg/mL	<u>GAD:</u> 50—100 mg PO four times daily, adjusted to patient response. <u>Pruritis:</u> 25 mg PO 3—4 times per day. <u>Sedation/antiemetic:</u> 25 mg to 100 mg IM every 4-6 hrs as needed.	LA
Ovidrel	Choriogonadotropin Alfa Pre-filled syringe for injection: 250 mcg/0.5 mL	<u>Fertility (adult females):</u> 250 mcg SC as a single dose one day after the last dose of menotropins or FSH pre-treatment.	LA
			LA
Limbitrol Limbitrol DS	Amitriptyline Hydrochloride,/Chlordiazepoxide, Tablet: 12.5 mg/5 mg, 25 mg/10 mg (DS)	1 tablet PO 3—4 times per day. Adjust dose as tolerated and required. The dosage should not exceed 1 tablet six times per day.	LA
Visicol	Sodium Phosphate (Dibasic) (Anhydrous)/Sodium Phosphate (Monobasic) (Monohydrate) Tablet: 0.398 g /1.102 g	40 tablets taken in the following manner: The evening before, 3 tablets should be taken with at least 8 ounces of clear liquids every 15 minutes for a total of 20 tablets. The day of the colonoscopy procedure, (starting 3—5 hours before the procedure) 3 tablets should be taken every 15 minutes for a total of 20 tablets.	LA, SA
Imitrex	Sumatriptan Tablet: 25 mg, 50 mg, 100 mg	Oral: 25-100 mg at the onset of migraine. If only partial relief occurs or	LA

Product Name	Dosage form(s), Established name	Usual adult dose*	Other**
Vivitrol	Naltrexone long acting injection Injection: 380 mg/ 5 mL vial	380 mg IM monthly	N/A
	Injection: 6 mg/0.5 mL Nasal Spray: 5 mg/spray, 10 mg/spray, 20 mg/spray	if the headache returns at 2 hours, a second dose may be given. Nasal: 5-20 mg as above. SC: 6 mg as above	
*Frequently used, not all-inclusive. **LA (look-alike), SA (sound-alike)			

B. PHONETIC and ORTHOGRAPHIC COMPUTER ANALYSIS (POCA)

As part of the name similarity assessment, proposed names are evaluated via a phonetic/orthographic algorithm. The proposed proprietary name is converted into its phonemic representation before it runs through the phonetic algorithm. The phonetic search module returns a numeric score to the search engine based on the phonetic similarity to the input text. Likewise, an orthographic algorithm exists which operates in a similar fashion. All names considered to have significant phonetic or orthographic similarities to Vivitrol were discussed by the Expert Panel (EPD).

C. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

Three separate studies were conducted within the Centers of the FDA for the proposed proprietary names to determine the degree of confusion of Vivitrol with marketed U.S. drug names (proprietary and established) due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. The set of studies (i.e., inpatient, outpatient, and verbal study for each name) employed a total of 124 health care professionals (pharmacists, physicians, and nurses). This exercise was conducted in an attempt to simulate the prescription ordering process. An inpatient order and outpatient prescription were written, each consisting of a combination of marketed and unapproved drug products and a prescription for Vivitrol (see page 6). These prescriptions were optically scanned and one prescription was delivered to a random sample of the participating health professionals via e-mail. In addition, the outpatient orders were recorded on voice mail. The voice mail messages were then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
<p><u>Outpatient RX:</u></p> <p><i>Vivitrol 380mg</i> <i>Return to clinic in 4 weeks</i> <i>for injection</i> <i>#1 vial</i></p>	<p>"Vivitrol, 380 mg, to be used in the clinic every 4 weeks for injection, dispense 1 vial"</p>
<p><u>Inpatient RX:</u></p> <p><i>Vivitrol Injection 380mg, IM as directed</i></p>	

2. Results for Vivitrol:

None of the interpretations of the proposed name overlap, sound similar, or look similar to any currently marketed U.S. product. The majority of misinterpretations were misspelled/phonetic variations of the proposed name, Vivitrol. See Appendix A for the complete listing of interpretations from the verbal and written studies.

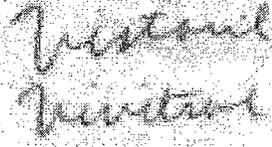
E. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name Vivitrol, the primary concerns identified from the Expert Panel related to look-alike and sound-alike confusion with Nicotrol, Levatol, Vivactil, Vistaril, Ovidrel, Limbitrol, Limbitrol DS, Visicol, and Imitrex. Upon further review of the names gathered from EPD, independent analysis, and POCA, the names Levatol, Limbitrol, Limbitrol DS, and Imitrex were not reviewed further due to a lack of convincing look-alike/sound-alike similarities with Vivitrol, in addition to numerous differentiating product characteristics such as the product strength, indication for use, frequency of administration, route of administration, and/or dosage formulation.

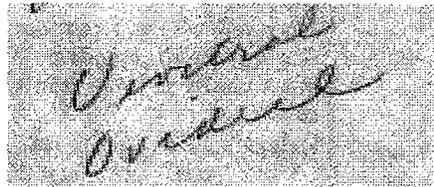
Additionally, DMETS conducted prescription studies to simulate the prescription ordering process. In this case, there was no confirmation that the proposed name could be confused with any of the aforementioned names. Negative findings are not predictive as to what may occur once the drug is widely prescribed, as these studies have limitations primarily due to a small sample size. The majority of misinterpretations were misspelled/phonetic variations of the proposed name, Vivitrol.

1. Vivitrol may look similar to Vistaril. Vistaril is an antihistamine with anxiolytic and sedative properties. Vistaril may also be used for the adjunct treatment of emotional disturbances associated with acute ethanol withdrawal. The two names have some orthographic similarities. Both names begin with "Vi-" which contributes to the look-alike properties. Additionally, the "-trol" in Vivitrol and the "-taril" in Vistaril can look similar when scripted. In addition to the orthographic similarities, there are overlapping product characteristics between Vivitrol and Vistaril, such as dosage form (injection), route of administration (intramuscular), and patient population (alcohol abusers). If the prescription is written as a one-time order, the dose on a prescription may be the only differentiating characteristic between the two names (380 mg vs. 25 mg to 100 mg for the IM dose). Since Vivitrol is available in only the one strength it is possible for the strength to be omitted on a prescription. However, Vistaril Injection is available in two strengths (25 mg/mL and 50 mg/mL) and has a wide dosage range of 25 mg to 100 mg

and thus, indication of the dose or strength will help to minimize confusion. Despite some orthographic similarities, distinguishing product characteristics such as the dose and strength will help minimize the potential for confusion between the two names.

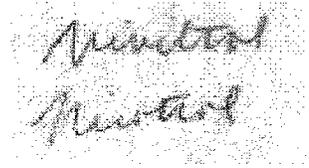


2. Vivitrol may look similar to Ovidrel. Ovidrel is injectable human chorionic gonadatropin, which is used for adjunctive treatment of anovulation in females with infertility. Ovidrel is used as part of a specific regimen in women after they have completed a typical ovulation induction protocol with Follicle Stimulating Hormone/Luteinizing Hormone (menotropins). The drug names Vivitrol and Ovidrel have some orthographic similarities. If the letter 'O' on Ovidrel is not closed when it is scripted, it may resemble the letter 'V'. Furthermore, the two names each end with similar suffixes (-rol vs. -rel) which contributes to the look-alike properties. However, the letters 't' in Vivitrol and 'd' in Ovidrel may remain distinguishable if scripted clearly and may help to differentiate the name. There are some overlapping product characteristics between Vivitrol and Ovidrel, such as dosage form (injection) and dosage frequency (monthly). It is possible that if the prescription is written as a one-time order, the dose on a prescription (380 mg vs. 250 mcg) and the route of administration (IM vs. SQ) may be the only differentiating characteristics between the two names. Since both Vivitrol and Ovidrel are available as only one strength and administered via one route it is possible for the strength and route to be omitted on a prescription. However, Ovidrel is typically administered as part of a specific regimen for ovulation induction in which the patient is first treated with menotropins, followed by a single dose of Ovidrel 250 mcg subcutaneously one day later. Therefore, additional prescription modifiers such as "give one day after final shot of Follitropin" may lessen the potential for confusion between the two products. Additionally, Vivitrol will be directly administered to the patient by a healthcare professional as part of a management program for alcohol dependence and thus, it will be ordered and administered by specialized practitioners for a specific patient population. Moreover, Vivitrol will not likely be distributed outside a clinic setting. Despite some overlapping product characteristics between Ovidrel and Vivitrol, orthographic differences and different context of use will help minimize the potential for confusion between the two names.

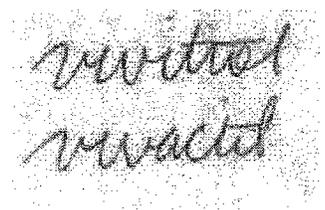


3. Vivitrol may look similar to Nicotrol. Nicotrol is an over-the-counter product line of nicotine replacement products to aid in smoking cessation. The two names have some orthographic similarities. The prefixes 'Viv-' in Vivitrol and the 'Nic-' in Nicotrol can look similar when scripted. Additionally, both names end with the suffix "-trol" which contributes to the look-alike properties. However, there are product characteristics that will help to differentiate the two products such as: dosage form (injection vs. nasal spray, inhaler, or patches), prescribed dose (380 mg vs. 0.5 mg, 5 mg, 10 mg, or 15 mg), and dosage regimen (once monthly vs. once daily or more often as needed for the inhaler or spray). Nicotrol is available in several dosage formulations and strengths, therefore the

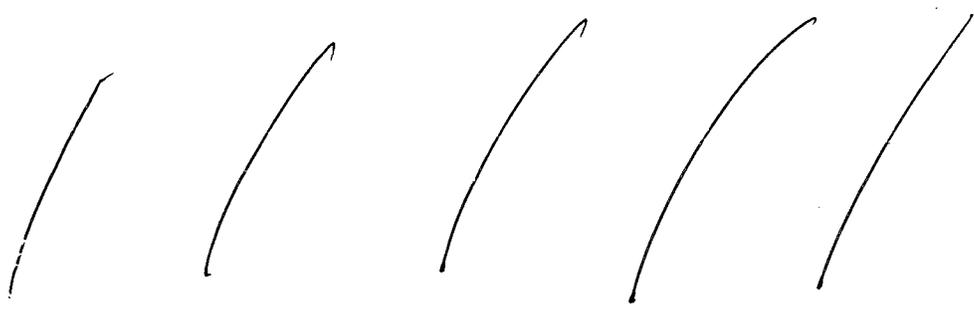
strength and formulation should be indicated on a prescription and will help distinguish it from a prescription for Vivitrol. Vivitrol is available in one dosage form and strength therefore the strength and formulation may be omitted on a prescription. Additionally, Nicotrol is available over the counter, whereas Vivitrol is a prescription and will be directly administered to the patient by a healthcare professional as part of a management program for alcohol dependence. Thus, despite some orthographic similarities, the different product characteristics of each drug such as the dosing regimen and dosage unit, and the management program for Vivitrol will help minimize the potential for confusion between the two names.



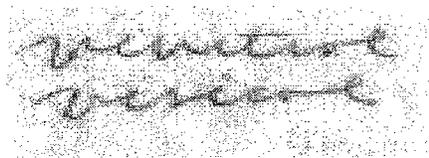
4. Vivitrol may look similar to Vivactil. Vivactil is an oral antidepressant prescription medication that is also used to treat apnea. The two names have some orthographic similarities. Both names begin with the prefix "Viv-" which contributes to the look-alike properties. Additionally, the '-trol' in Vivitrol and the '-til' in Vivactil can look similar when scripted, especially if the letter 'r' in Vivitrol is not prominent. Both names also have an upstroke from the letter 't', although the upstroke is in slightly different positions of the name. However, despite these look-alike similarities, there are product characteristics that will help to distinguish the two products such as: dosage form (injection vs. tablet), prescribed dose (380 mg vs. 5 mg or 10 mg), and dosage regimen (once monthly vs. three times a day). Vivitrol is available in one dosage form and strength, therefore the strength and formulation may be omitted on a prescription. Vivactil is available in two strengths, therefore the strength should be indicated on a prescription and will help distinguish it from a prescription for Vivitrol. Moreover, Vivitrol will be directly administered to the patient by a healthcare professional as part of a management program for alcohol dependence, therefore it will be ordered and administered by specialized practitioners for a specific patient population and will not likely be distributed outside a clinic setting. Thus, despite some orthographic similarities, the different product characteristics of each drug such as the dosing regimen, strength, and the management program for Vivitrol will help minimize the potential for confusion between the two names.



- 5.



6. Vivitrol may look and sound similar to Visicol. Visicol is a prescription bowel evacuant to clean the colon prior to colonoscopy (bowel preparation). Visicol has a 40-tablet regimen that is started the evening prior to the procedure. The two drug names sound-alike, as each is pronounced with three syllables (Viv-i-trol vs Vis-i-kol). However, the first syllables of the names sound distinct due to the second letter 'v' in Vivitrol and the letter 's' in Visicol. The last syllables of the names also sound distinct due to the sounds of the letters '-tr-' in Vivitrol and the hard letter 'c' in Visicol, which is pronounced as the letter 'k'. The two names also have some orthographic similarities due to shared letters in similar positions within the name (Vivitrol vs. Visicol). The letters 'v', 't', and 'r' in Vivitrol and the letters 's' and 'c' in Visicol are the only differences between the two names. If these letters are not clearly scripted, it may be difficult to differentiate between the two names. However, the letter 't' in Vivitrol contributes an additional upstroke that Visicol lacks and may help to differentiate between the two names. Additionally, the scripted appearance of Vivitrol is longer than Visicol. Moreover, there are product characteristics that may help to distinguish the two products such as: dosage form (injection vs. tablets), dose (380 mg vs. 2 tablets or 3 tablets), route of administration (IM vs. oral), dosing intervals (once monthly vs. every 15 minutes until tablets completed). Each of these names has a specific regimen (Visicol) or program (Vivitrol) where the drug is administered that decreases the possibility for confusion. Inpatient orders will require that a dose, route of administration, and dosing regimen be included. Although Visicol may be dispensed as an outpatient prescription, Vivitrol is to be administered only by a healthcare practitioner, minimizing the opportunity for outpatient dispensing. Thus, despite some orthographic similarities, DMETS feels that the product characteristics of each drug such as route of administration, dosing intervals, and the specific regimen or program for administering the drug will help to decrease the potential for confusion between the two names.

A rectangular area containing two handwritten signatures. The top signature is 'Vivitrol' and the bottom signature is 'Visicol'. Both are written in a cursive, handwritten style.

III. RECOMMENDATIONS:

- A. DMETS has no objections to the use of the proprietary name "Vivitrol." This is considered a final decision. However, if the approval of this application is delayed beyond 90 days from the signature date of this document, the name must be re-evaluated. A re-review of the name will rule out any objections based upon approval of other proprietary or established names from the signature date of this document.
- B. Revised container labels, carton and insert labeling were not submitted for review and comment. DMETS refers to ODS Consult 02-0071-1 for our previous label and labeling comments.
- C. DDMAC finds the proprietary name "Vivitrol" acceptable from a promotional perspective
- D. Consult Guiragos Poochikian, Acting Chair, of the CDER Labeling and Nomenclature Committee on the proper designation of the established name.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Diane Smith, project manager, at 301-796-0538.

Laura Pincock, Pharm.D.
Safety Evaluator
Division of Medication Errors and Technical Support
Office of Drug Safety

Concur:

Linda Kim-Jung, Pharm.D.
Team Leader
Division of Medication Errors and Technical Support
Office of Drug Safety

Voice	Outpatient	Inpatient
Visitrol	Vurtrol	Vivital
Visitrol	Virtrol	Vivitrol
Visitrol	Umtrol (or Vurtrol)	Vivitrol
Vivatrol	Uritrol	Vivitrol
Visitrol	Urtrol	Vivitrol
Vivitrol	Vurtrol	Vivitrol
Vivitrol	Untrol	Vivitrol
Vivitrol	Vistrol	Vivitrol
Visitrol	Vurtrol	Vivitrol
Vivitrol	Virtrol	Vivitrol
Visitrol	Virtrol	Vivitrol
Vivtal	Vurtrol	Vivitrol
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		Vivitrol
		Vivital

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/s/

Laura Pincock
10/26/2005 02:29:59 PM
DRUG SAFETY OFFICE REVIEWER

Linda Kim-Jung
10/26/2005 05:54:26 PM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
10/27/2005 09:59:53 AM
DRUG SAFETY OFFICE REVIEWER
Also signing for Carol Holquist, Director DMETS



NDA 21-897

INFORMATION REQUEST LETTER

10/21/05

Alkermes, Inc.
88 Sydney Street
Cambridge, MA 02139-4136

Attention: Priya Jambhekar
Global Vice President, Regulatory and Government Affairs

Dear Ms. Jambhekar:

Please refer to your March 31, 2005 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for naltrexone long-acting injection.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. [Redacted]
2. Clarity is needed in the description of the container closure system used for the bulk storage of [Redacted]

3. Provide the following stability updates for the [Redacted] batches at long term storage.

Lot # 402-1255AA
Lot # 402-0565AA
Lot # 402-3244BA
Lot # 402-3244BA
Lot # 402-3244CA

4. Expiration dating for the diluent is stated differently in the NDA and DMF. The DMF supports expiration dating of [Redacted] whereas the NDA claims it to be [Redacted]. Reconcile this discrepancy.

5. State clearly that the expiration dating period for the kit will be the shorter of the expiration dating periods for the drug product vial and the diluent.
6. During the Pre-NDA meeting dated February 2, 2005, it was stated that the kit would consist of _____ However, since no data on the _____ is provided in the NDA or in the DMF, they should not be included in the kits. Therefore, clarify that the kit will not contain _____
7. Provide a sample of the kit containing the drug product vial, the diluent, the syringe, and the needles.

If you have any questions, call Lisa E. Basham-Cruz, Regulatory Project Manager, at 301-827-7420.

Sincerely,

{See appended electronic signature page}

Sara Stradley, MS
Supervisory CSO
Division of Anesthesia, Analgesia and
Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Sara Stradley
10/21/2005 05:46:57 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-897

DISCIPLINE REVIEW LETTER

Alkermes, Inc.
88 Sydney Street
Cambridge, MA 02139-4136

Signed
9/23/05

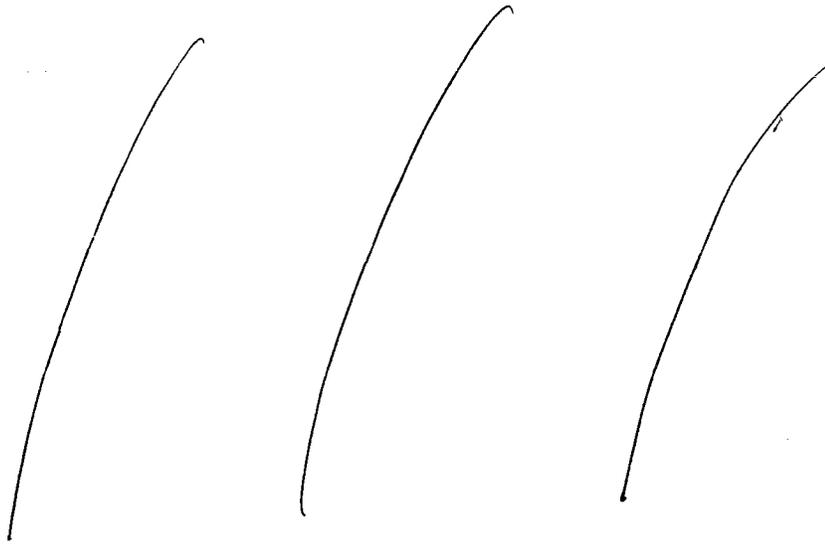
Attention: Priya Jambhekar
Global Vice President, Regulatory and Government Affairs

Dear Ms. Jambhekar:

Please refer to your March 31, 2005 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for naltrexone depot injection.

Our review of the Microbiology section of your submission is complete and we have identified the following deficiencies:

[Redacted content]



We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, call Lisa E. Basham-Cruz, Regulatory Project Manager, at 301-827-7420.

Sincerely,

{See appended electronic signature page}

Parinda Jani
Supervisory CSO
Division of Anesthesia, Analgesia and
Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Parinda Jani

9/23/2005 11:32:40 AM



PDUFA GOAL DATE EXTENSION

NDA 21-897

9/16/05

Alkermes, Inc.
88 Sidney Street
Cambridge, MA 02319

Attention: Priya Jambhekar
Global Vice President, Regulatory and Government Affairs

Dear Ms. Jambhekar:

Please refer to your March 31, 2005 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for naltrexone long-acting injection, 380 mg in 5 mL vials.

On September 12, 2005, we received your September 7, 2005, major amendment to this application. The receipt date is within three months of the user fee goal date. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is December 30, 2005.

If you have questions, call Lisa Basham-Cruz, Regulatory Project Manager, at (301) 827-7420.

Sincerely,

{See appended electronic signature page}

Lisa Basham-Cruz, MS
Regulatory Project Manager
Division of Anesthesia, Analgesia and
Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Lisa Basham-Cruz
9/16/2005 01:26:33 PM

MEMORANDUM

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

CLINICAL INSPECTION SUMMARY

DATE: 9/13/05

TO: Lisa Basham-Cruz, Regulatory Project Manager
Mwango Kashoki, M.D., Clinical Reviewer
Division of Anesthesia, Analgesia, and Rheumatology Products

THROUGH: Ni A. Khin, M.D., Chief
Good Clinical Practice Branch 1, HFD-46
Division of Scientific Investigations

FROM: Carolanne Currier, CSO
Good Clinical Practice Branch 1, HFD-46
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 21-897

APPLICANT: Alkermes, Inc.

DRUG: Vivitrex (Medisorb Naltrexone)

INDICATION: Treatment of alcohol dependence

CONSULTATION REQUEST DATE: 5/23/05

PDUFA DATE: 9/30/05

I. BACKGROUND:

Naltrexone has been shown to be effective as a maintenance agent in the treatment of alcohol dependence, however patient compliance has always been an issue limiting effectiveness of oral dosage forms. Vivitrex (medisorb naltrexone) was designed to address the patient compliance issue by using a slow-release drug delivery system. Vivitrex is microspheres of naltrexone in a matrix of a medical polymer which is administered IM every 4 weeks. The results of two protocols were included of this NDA:

1) ALK21-003: A Phase III, Multi-Center, Randomized, Double-Blind, Placebo-Controlled Study of the Efficacy and Safety of Medisorb Naltrexone in Alcohol Dependent Adults.

ALK21-003 was a 24-week, phase III, multi-center, randomized, double-blind, placebo-controlled study in adults with alcohol dependency. The primary objective was to compare 2 doses of Vivitrex, 190mg and 380mg, to evaluate the effectiveness of Vivitrex in reducing heavy drinking.

2) ALK21-006: A Randomized, Open-Label, Long-Term Multi-Center Study of the Safety of Medisorb Naltrexone.

ALK21-006 was a 52-week, randomized, open-label, long-term, multi-center study of the safety of Vivitrex in adults with alcohol and/or opiate dependency. Subjects were randomized to one of 2 regimens: 1) a 380mg dose of Vivitrex administered IM every 4 weeks or 2) oral naltrexone (50 mg) once a day.

The Division of Scientific Investigations (DSI) issued inspections at 4 clinical sites to verify data from both protocols. One of the 4 investigator sites conducted studies with both protocols. The inspection findings are summarized in the following table and described in detail in the RESULTS section below.

Site	Site Number	Protocol	City/State	Inspection Date	Classification
/ /	217	ALK21-003	/ /	8/15-22/05	Pending
	215	ALK21-003		8/1-11/05	Pending
Hisham Hafez, M.D.	214	ALK21-003 and ALK21-006	Nashua, NH	7/20-28/05	VAI
James M. Ferguson, M.D.	245	ALK-21-006	Salt Lake City, UT	8/8-16/05	Pending

II. RESULTS

Protocol ALK21-003

Site: _____

a. What was inspected: Fifty-five subjects were screened for the study, 9 failed screen, and 46 were consented. Seven subjects dropped out, terminated early or were lost to follow-up. Records for 15 randomized subjects were examined during the inspection. Records examined included consent forms; source documentation (such as medical histories, PEs, laboratory reports, and drug administration times); drug accountability records; correspondence with the IRB and sponsor; and CRFs (including TLFB and BRENDA evaluations). Records were checked for accuracy and completeness, subject eligibility, protocol violations, AE reporting, and proper consent.

b. Limitations of inspection: The EIR for this inspection has not been received by DSI. The summary of the findings at this site is based on the Form FDA 483, Inspectional Observations, issued at the conclusion of the inspection and correspondence with the field investigator.

c. General observations/commentary: The 483 indicated that in 8 instances for the 4 study subjects listed below, the site's research assistant performed both the Time Line Follow Back (TLFB) and the BRENDA assessments. This was in violation of the protocol which specified that the BRENDA therapist would not collect the TLFB data.

Subject	Visit(s)
010	Day 42
023	Screening visit, Day 0, Day 56, Day 70
030	Day 70
046	Day 42, Day 168

This finding suggests a potential bias in safety and efficacy data reporting. The protocol violation was found for 4 of 15 of the subjects whose records were reviewed

d. Recommendation: It is recommended that the Review Division consider excluding the data from these study subjects.

The 483 indicates that concomitant medications listed in the source documents for subject 028 were not reported on the corresponding CRFs, however, details are not available at this time.

Site: _____

a. What was inspected: Fifty subjects were screened for the study, 14 failed screen, and 36 were consented. Eleven subjects dropped out (reasons included dislike of injection/needles, incarceration, withdrew consent, "changed his mind," travel, loss of interest, etc.) and 25 subjects completed the study. Records for 12 subjects were examined during the inspection. Records examined included consent forms; source documentation (such as medical histories, PEs, laboratory reports, and drug administration times); drug accountability records; correspondence with the IRB and sponsor; and CRFs (including TLFB and BRENDA evaluations). Records were checked for accuracy and completeness, subject eligibility, protocol violations, AE reporting, and proper consent.

b. Limitations of inspection: None

c. General observations/commentary: The inspection revealed several protocol deviations. 1) The person who administered the study drug performed the safety physical exams; 2) that same person also performed some of the TLFBs; and 3) the person who performed the BRENDA assessments performed the majority of the TLFBs. The protocol prohibited all three of these situations. In addition, the inspection revealed that the person performing the safety physical exams was a foreign medical graduate not licensed to practice medicine in the US.

The inspection also revealed problems with obtaining proper informed consent. Twenty-one (subject numbers 215-001 through 215-021) did not sign all the available consent form revisions during their participation in the study. Several of the versions included updated safety and adverse event information.

d. The protocol violations represent a significant potential bias in safety and efficacy reporting. Data from this site is unacceptable. It is recommended that the Review Division consider excluding the data from the study subjects at this site.

Site: Hisham Hafez, M.D.

a. What was inspected: For protocol 003, 40 subjects were screened, 4 failed screen, 1 dropped out before randomization, 35 were randomized, 8 discontinued, and 28 completed. Source documents were compared to CRFs for 12 subjects during the inspection. For protocol 006, 22 subjects were screened, 6 failed screen, 16 were randomized, 7 discontinued and 9 completed. Source documents were compared to CRFs for 6 subjects during the inspection. Source records reviewed included: physician's notes, progress notes, screening records, dosing records, lab reports, ECG results, concomitant medications, AEs, and drug dispensing records.

b. Limitations of inspection: None

c. General observations/commentary: Records for the study were well organized and generally complete. Sponsor-provided data listings of efficacy endpoints for all subjects in were compared to source documentation and no discrepancies were noted. All subjects signed informed consents before entering the study. Dr. Hafez regarded all the AEs to be non-study related and AEs/SAEs were accurately reported to the sponsor on CRFs. However, SAEs where subjects were hospitalized, were not promptly reported to the IRB for assessment. The site reported the SAEs from 16 to 119 days after the SAE occurred. (The IRB had specifically requested in their approval letter for protocol 003, that all adverse events of grade 3 or above be reported within 48 hours. This was not done.) The SAEs included; hospitalization occurred for exacerbation of alcohol dependence (5 subjects), pleurisy (1 subject), and death (homicide – 1 subject). While the failure to promptly report SAEs to the IRB was a potential patient safety issue, it does not appear that this failure affected study data.

d. Recommendation: Overall, the data appear acceptable.

Protocol ALK21-006

Site: Hisham Hafez, M.D.

- a. What was inspected: For protocol 006, 22 subjects were screened, 6 failed screen, 16 were randomized, 7 discontinued and 9 completed. Source documents were compared to CRFs for 6 subjects during the inspection. Source records reviewed were the same as for protocol 003 above.
- b. Limitations of inspection: None
- c. General observations/commentary: Records for the study were well organized and generally complete. Sponsor-provided data listings of efficacy endpoints for all subjects in were compared to source documentation and no discrepancies were noted. All subjects signed informed consents before entering the study. Dr. Hafez regarded all the AEs to be non-study related and AEs were accurately reported to the sponsor on CRFs. However, 2 SAEs for one subject (012), (subject was hospitalized for scalp lacerations and exacerbation of alcohol dependence), were not promptly reported to the IRB for assessment. The site reported the SAEs 178 and 194 days after they occurred. While the failure to promptly report SAEs to the IRB could have been a patient safety issue, it does not appear that this failure affected study data.
- d. Recommendation: Overall, the data appear acceptable.

Site: James M. Ferguson, M.D.

- a. What was inspected: For protocol 006, 58 subjects were screened, 18 failed screen, 40 were randomized and 27 dropped out. Reasons for dropping out included: withdrew consent (10), lost to follow up (14), investigator decision (2), and AE/new or worsening lab abnormality (1). Thirteen subjects completed the study. An in-depth comparison of source documents (visit notes, subject history records, test and laboratory results, and medical records), and CRFs (including TLFB and BRENDA assessments), was performed for 8 subjects. In addition, drug accountability records, IRB approvals, consent documents, and correspondence with the sponsor were reviewed. Subject eligibility and adherence to the protocol was checked.
- b. Limitations of inspection: The EIR for this inspection has not been received by DSI. The summary of the findings at this site is based on the 483 issued at the conclusion of the inspection and communication with the field investigator.
- c. General observations/commentary: The inspection revealed 3 protocol deviations and numerous examples of inaccurate records.

The 3 protocol deviations are as follows:

1. The first 14 subjects enrolled in the study (subjects 001 – 014) received Medisorb Naltrexone or Oral Naltrexone before the results of the coagulation group test values were received and reviewed by the investigator. The coagulation group lab report documented prolonged prothrombin time which was an exclusion criterion for enrollment. Coagulation group lab reports were never received for two subjects (007 and 010); there was a notation in the study records that the samples were drawn but lost at the site. The field investigator has indicated that the coagulation group lab reports were received at the site approximately 3 weeks after the subjects were enrolled, however none of the subjects had prolonged prothrombin time. All subjects were eligible for the study. What is a little disconcerting is that the field investigator also indicated that these subjects were listed as protocol deviations on the firm’s electronic deviation log as “subjects randomized without coagulation results, and the “corrective action” listed on the electronic deviation log was “issue discussed with investigator; IRB notified.” However, the list of protocol deviations supplied to us by the sponsor does not contain these entries. This appears to be a sponsor issue, not a clinical investigator problem.

2. The Medisorb Naltrexone powder was stored outside of the protocol specified temperature range (2 – 8°C). Temperatures reached 13.7°. Per communication with Jila Boal, Chemist, HFD-170, stability testing indicated that the product is stable at controlled room temperature (25°C ± 2°C) for up to 4 weeks. It does not appear that the 13.7° would have affected stability, although the length of time the drug was stored is unknown.

3. The protocol specified the study drug injection site to alternate between right and left buttocks. Subject 008 received two consecutive injections in the left buttock. This does not appear to have any clinical significance.

The examples of inaccurate records found during the inspection area listed in the following table:

Subj No.	Start/Stop Date	Info in Source Doc	Info in CRF	Problem
032		Yes	No	Use of 3 concomitant medications (valium, benedryl, xanax) not recorded in CRF
008		Yes	No	Stop date for concom med use (orthocyclin) not in CRF
008		Yes	No	Stop date for concom med use (lexapro) not in CRF
014		Yes	No	Stop date for concom med use (prevacid) not in CRF
014		Yes	No	Stop date for concom med use (neurontin) not in CRF
014		Yes	No	Stop date for concom med use (phentramine) not in CRF
014		Yes	No	Stop date for concom med use (zyrtec) not in CRF
032		20 ultrams, PO, qd 12/23/03	Ultram, 20-unk units PO, 1x, 12/24/03	Day and amount of concom med differ
032		Cogentin, 2-mg, IM, tid	Cogentin, 6-mg, IM, 1x,	Dosage amount and times differ (although total dose is same)
032		Benedryl 50-mg, PO, qd	Benedryl, 1x 100- mg, PO	Dosage amount and times differ (although total dose is same)
032		Benedryl, 25-mg IM qd	Benedryl, IM, 25- mg, pm	Dosage times differ

028		"Continuous"	Blank	Reported frequency of the AE of anxiety differs
014				Stop date for concom med use (prednisone) differ
032				Date for concom med use (haldol) differ
032				Date for AE (agitation) differ
032				Date for AE (insomnia) differ
016		Blank	"No"	Question whether bilateral sciatic pain was an SAE
010		Blank	"No"	Question whether headaches was SAE
032		"Continuing"	"Resolved"	Question regarding outcome of insomnia AE
008		Blank	"Continuing"	Question regarding outcome of lower back pain AE
014		Blank	"Continuing"	Question regarding outcome of urticaria AE
014		Blank	"Continuing"	Question regarding outcome of fatigue AE
024	Screening visit			Date of screening visit differs

In addition, several instances were found where Data Clarification Forms from the sponsor resulted in the changing of concomitant medication use data or AE data on the CRFs but not on the original source.

To summarize the reported inaccurate data, it appears that with the possible exception of the first example (where 3 concomitant medications were not reported on the CRFs), the remaining data discrepancies (differing dates of concomitant med use, differing dates of AEs, differing record of drug administration regimens, and blank data fields) appear to be simple record keeping errors. Although the inaccuracies are numerous and would perhaps suggest poor record-keeping techniques, the problem does not appear to be serious enough to suggest that the validity of the data would be in question.

d. Recommendation: Overall the data appear acceptable.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

For protocol ALK21-003, the performance of the TLFs and BRENDA assessments by the same person at the [redacted] and [redacted] sites, and the performance of safety physical exams by an unlicensed person who also performed efficacy assessments at the [redacted] site, suggests significant potential bias in safety and efficacy reporting for these two sites. At the [redacted] site, study subjects were not re-consented with IRB approved informed consents which contained updated safety and adverse event information. DSI recommends that the Review Division consider removing data from these two sites in their evaluation of the Vivitrex NDA. After all unreliable data are eliminated from consideration, the remaining data from these inspected sites appear acceptable for use in support of the NDA. In addition, the Review Division should consider the possibility that similar deficiencies might exist at other study sites.

Note: The observations noted for the inspections of Drs. Ferguson and [redacted] are based on the Form FDA 483, Inspectional observations, and communications from the FDA field investigator. An inspection summary addendum will be generated if conclusions change upon complete review of the EIR.

Carolanne Currier
Good Clinical Practice Branch 1
Division of Scientific Investigations

CONCURRENCE:

Supervisory comments:

Ni A. Khin, M.D., Chief
Good Clinical Practice Branch 1
Division of Scientific Investigations

DISTRIBUTION:

NDA 21-897

HFD-170/ (through DFS)

HFD-45/Division File / Reading File

HFD-45/Program Management Staff

HFD-46/Khin/Currier

HFD-46/ GCPB1 Files # 11607, [redacted], #11587 (Hafez), Ferguson and [redacted] numbers to be assigned upon receipt.

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cac:9/9/05

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/s/

Carolanne Currier
9/13/2005 11:33:10 AM
MANGMNT ANALYST

Ni Aye Khin
9/13/2005 11:38:32 AM
MEDICAL OFFICER

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/s/

Dionne Price
12/16/2005 05:18:45 PM
BIOMETRICS

Thomas Permutt
12/16/2005 05:20:35 PM
BIOMETRICS
concur

S. Edward Nevius
12/16/2005 05:29:20 PM
BIOMETRICS
Concur with review.



NDA 21-897

INFORMATION REQUEST LETTER

Alkermes, Inc.
88 Sydney Street
Cambridge, MA 02139-4136

8/4/05

Attention: Priya Jambhekar
Global Vice President, Regulatory and Government Affairs

Dear Ms. Jambhekar:

Please refer to your March 31, 2005 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for naltrexone long-acting injection.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. DMF — for naltrexone base anhydrous is deficient. The Agency has conveyed the deficiencies to _____
2. Provide the following limits for the impurities in naltrexone base anhydrous drug substance:
 - a. Specified and identified impurities, _____ NMT — each. Alternatively, provide data supporting the safety of these impurities at the proposed level of — each.
 - b. Replace the statement "Each other related substance: NMT — with "Individual drug-related unspecified impurity or degradation product: NMT — each."

If you have any questions, call Lisa E. Basham-Cruz, Regulatory Project Manager, at 301-827-7420.

Sincerely,

{See appended electronic signature page}

Parinda Jani
Supervisory CSO
Division of Anesthesia, Analgesia and
Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

8/4/05

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/s/

Parinda Jani

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MEMORANDUM

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

DATE: July 11, 2005

TO: Bob Rappaport, M.D., Director
Division of Anesthesia, Analgesia, and Rheumatology
Drug Products, HFD-170

VIA: Lisa Basham-Cruz, Regulatory Project Manager
Division of Anesthesia, Analgesia, and Rheumatology
Drug Products, HFD-170

FROM: Jeanine Best, M.S.N., R.N., P.N.P.
Patient Product Information Specialist
Division of Surveillance, Research, and Communication
Support, HFD-410

THROUGH: Gerald Dal Pan, M. D., M.H.S., Director
Division of Surveillance, Research, and Communication
Support, HFD-410

SUBJECT: DSRCS Review of Patient Labeling for Vivitrex
(naltrexone long-acting injection), NDA 21-897

Background and Summary

The following is the revised patient labeling for Vivitrex (naltrexone long-acting injection), NDA 21-897. We have simplified the wording, made it consistent with the PI, and removed unnecessary information (the purpose of patient information leaflets is to enhance appropriate use and provide important risk information about medications). We have put this PPI in the patient-friendly format that we are recommending for all patient information, although, this format is not required for voluntary PPIs. Our proposed changes are known through research and experience to improve risk communication to a broad audience of varying educational backgrounds.

These revisions are based on draft labeling submitted by the sponsor, dated March 31, 2005. Patient information should always be consistent with the prescribing information. All future relevant changes to the PI should also be reflected in the PPI.

Comments and Recommendations

1. The sponsor's proposed PPI was submitted with a Flesch-Kincaid reading level of

10.9 and a Flesch reading ease of 45.4%. For optimal comprehension among a broad range of patients, including those with lower literacy levels, patient materials should be written at a 6th to 8th grade reading level and have a reading ease of at least 60%. We have recommended simplifying words and sentences to improve these readability scores.

Comments to the review Division are bolded, italicized, and underlined. We can provide marked-up and clean copies of the revised document in Word if requested by the review division. Please let us know if you have any questions.

B

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 / Draft Labeling

 Deliberative Process

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/s/

Jeanine Best
7/11/05 10:52:24 AM
DRUG SAFETY OFFICE REVIEWER

Toni Piazza Hepp
7/11/05 02:32:46 PM
DRUG SAFETY OFFICE REVIEWER
for Gerald Dal Pan



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-897

5/26/05

Alkermes, Inc.
88 Sydney Street
Cambridge, MA 02139-4136

Attention: Priya Jambhekar
Global Vice President, Regulatory and Government Affairs

Dear Ms. Jambhekar:

Please refer to your pending new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Vivitrex (naltrexone long-acting injection), 380 mg in 5 mL vials.

We also refer to our acknowledgment letter dated April 27, 2005, that stated the drug review priority classification for this application would be standard.

Our policy regarding determination of priority or standard review status is based on the proposed indication and alternative treatment marketed for the proposed indication. Upon further consideration of your application, we have concluded that this application should receive a priority review. The user fee goal date is September 30, 2005.

If you have any questions, call me at 301-827-7420.

Sincerely,

{See appended electronic signature page}

Lisa E. Basham-Cruz, MS
Regulatory Project Manager
Division of Anesthesia, Analgesia and
Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Lisa Basham-Cruz
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 61,138

Alkermes, Inc.
88 Sidney Street
Cambridge, MA 02139

Pre-NDA CMC Mtg

Attention: Priya Jambekar
Vice President, Regulatory Affairs

Dear Ms. Jambekar:

Please refer to the meeting between representatives of your firm and FDA on February 2, 2005. The purpose of the meeting was to discuss the Chemistry, Manufacturing, and Controls portions of your planned NDA for Vivitrex® (naltrexone long-acting injection).

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at 301-827-7420.

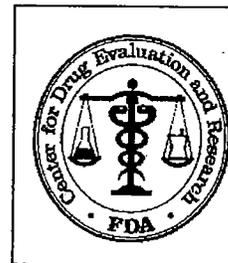
Sincerely,

{See appended electronic signature page}

Lisa E. Basham-Cruz, MS
Regulatory Project Manager
Division of Anesthetic, Critical Care, and
Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

3/4/05

Enclosure



MEETING MINUTES

Meeting Date: February 2, 2005

Location: Parklawn Building, Potomac Conference Room

IND/ Name: IND 61,138/Vivitrex® (naltrexone long-acting injection)

Sponsor: Alkermes, Inc.

Indication: alcohol dependence

Type of Meeting: Type B Industry Meeting; pre-NDA

Meeting Chair: Ravi Harapanhalli, PhD
Division of Anesthetic, Critical Care and
Addiction Drug Products, HFD-170

Attendees:

Alkermes	Title
Richard Batycky, PhD	VP, Research & Development
Lisa D'Attanasio	Manager, Regulatory Operations
Russ Doughty	Director, Quality Assurance
Elliot Ehrich, MD	VP, Science & Development, Chief Medical Officer
Matthew Gosnell, PhD	Associate Director, Analytical Development
George Grandolfi, PhD	Director, R&D
Dan LeBlanc	Manager, Process Development
Priya Jambhekar, MSc, MS, RAC	VP, Regulatory Affairs
Niall O'Leary	Associate Director, Regulatory Affairs
Gary Riley	VP, Toxicology
FDA	Title
Bob Rappaport, MD	Division Director
Eric Duffy, PhD	Director, DNDC II
Ravi Harapanhalli, PhD	Chemistry Team Leader
Dan Mellon, PhD	Supervisory Pharmacologist
Celia Winchell, MD	Medical Team Leader, Addiction Drug Products
Mamata De, PhD	Pharmacology Reviewer
Pramoda Maturu, PhD	Chemistry Reviewer
Mwango Kashoki, MD	Medical Reviewer
Arthur Simone, MD	Medical Reviewer
Lisa Basham-Cruz, MS	Regulatory Project Manager

Background: The IND was originally submitted on October 19, 2000. Type C meetings were held on April 10, 2001, and July 11, 2002. A Pre-NDA meeting was held on

October 7, 2004, to discuss the clinical/statistical aspects of the application. The purpose of this meeting is to discuss the Chemistry, Manufacturing and Controls portion of the planned NDA for Vivitrex® (naltrexone long-acting injection).

Note: Prior to the meeting, Lisa Basham-Cruz met with the sponsor and went over the Agency responses to the questions. The sponsor identified the responses for which they needed further clarification. The responses to Questions 1, 3, 6, 8, and 12 were discussed with the review team. The other responses were not discussed.

Meeting Minutes:

Following introductions, the discussion moved to the questions identified by the sponsor as needing additional explanation. The other questions/responses are shown below as well, but were not discussed. The questions are shown below in italics. Information presented on slides is bolded. Discussion is in normal typeface.

Dr. Harapanhalli led the discussions.

*Question 1 – Drug Substance
Does the Agency agree that
controlling and testing for
satisfactory?*

_____ proposal, including the timelines for
_____ in naltrexone drug substance, is

Response:

- As indicated in your submission, the expected date to accomplish the final specifications for the _____ impurity is March 2007.
- You may file the NDA in consonant with the DMF specifications effective at the time of filing with the understanding that you will follow the course of action taken by _____
- Ensure that the drug substance impurity specifications conform to ICH Q3A guidelines.
- Appendix 4 of the submission indicates that the impurities in naltrexone base are specified at _____ each. These may need additional data to support their safety as they exceed the qualification threshold of _____

The sponsor requested clarification on the fourth bullet. Dr. Harapanhalli explained that ICH Q3A specifies that for any drug substance used in quantities less than 2 g, the impurity specification should be less than 0.15%. The sponsor responded that their specification is the same as that of _____. Dr. Harapanhalli stated that this specification may be acceptable if there is adequate safety data in _____, DMF to support it. Dr. Mellon added that, if the specification exceeds that specified by ICH, then toxicity data is required to support the safety of impurity levels at the proposed specification. He stated that the general requirement is for two in vitro genotoxicity assays and a repeat-dose toxicology study. If available, the sponsor may submit literature references in lieu of animal data. In addition, if the impurity is a recognized human or

animal metabolite, then it would be considered qualified. Dr. Harapanhalli stated that this is a review issue, not one of filability. He suggested that the sponsor work with _____ to justify the levels of any impurity. This information may be present in _____, DMF. If so, the sponsor can refer to the DMF information in their application. If not, then the sponsor and _____ will have to address this issue together.

Question 2 – Drug Substance

Does the Agency agree that the resolution of this issue by _____ will not affect the timing of approval of the Vivitrex NDA?

Response:

- **This will not affect the timing of approval of the Vivitrex NDA provided you agree to time your change implementation according to _____ timelines on this issue.**

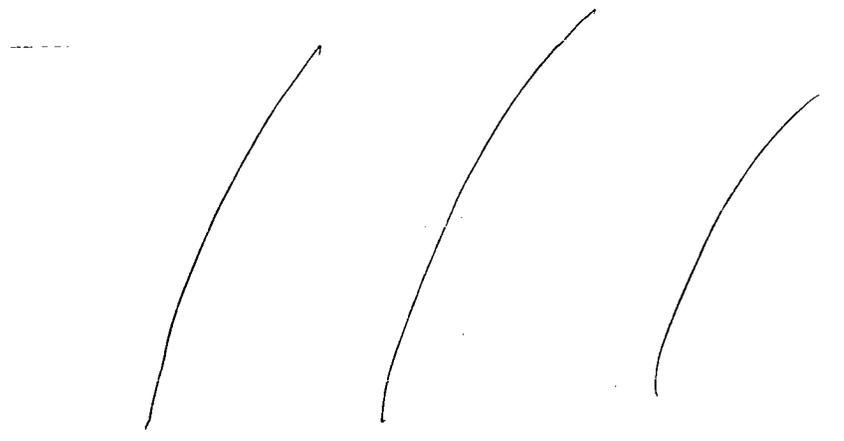
The sponsor required no further discussion of this response.

Question 3 – Scale Up

Does the Agency agree that the approach is sufficient to demonstrate comparability between the _____ and _____ batch scales, and therefore the approvability of the _____ batch scale?

Response:

The approach to demonstrate comparability between _____ and _____ batch scales should be supported by the following additional data:



Dr. Mellon referred the sponsor to the draft guidance relating to 505(b)(2) applications. He emphasized that the sponsor pay close attention to the right of reference and patent issues. He encouraged the sponsor to clearly delineate any reference listed drug in their application.

Post Meeting Note: The following reference is available on the CDER website: October 1999 DRAFT Guidance for Industry: Applications Covered by Section 505(b)(2). The following bullet points are highlights from that document and are provided for your information:

- For a 505(b)(2) application you must clearly identify those portions of the application that rely on information you do not own or to which you do not have a right of reference.
- A 505(b)(2) application that relays upon the Agency's previous finding of safety or efficacy for a listed drug must specifically identify any and all listed drugs by established name, proprietary name, dosage form, strength, route of administration, name of the listed drug's sponsor and the application number.
- A 505(b)(2) application relying upon literature must clearly identify the listed drug(s) on which the studies were conducted (if any).
- For a 505(b)(2) application you must provide a **patent certification** or statement as required under section 505(b)(2) of the Act with respect to any relevant patents that claim the listed drug and that claim any other drugs on which the investigations relied on by the applicant for approval of the application were conducted, or that claim a use for the listed or other drug (21 CFR 314.54(a)(1)(vi)). -- (Listed in the Orange Book)

- Patent certification should specify the exact patent number(s), and the exact name of the listed drug or other drug even if all relevant patents have expired.
- You must also submit a Bioavailability/Bioequivalence (BA/BE) study comparing the proposed product to the listed drug (if any).
- **Before submitting the NDA**, you are strongly encouraged to submit a plan to the Division specifically identifying the types of bridging studies that will be conducted. You should also identify those components of its application for which it expects to rely on FDA's finding of safety and effectiveness of a previously approved drug product. The Division will critique the plan and provide guidance.

Response contd...

- A description and justification of how the process critical control parameters presented in tables 4.5 – 4.9 of the pre-NDA package were scaled up including the _____ parameters.
- Data and justification for the _____ operations in the _____, and _____ processes.
- Material reconciliation data for the _____ and _____ processes describing _____ and final product yield.
- A justification for the following specific scale up changes described in Table 4.11 from the _____
 - _____
 - _____

Response contd...

- Data on the following additional critical process parameters:

C

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Lisa Basham-Cruz
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Pre-NDA P/T + CLINICAL

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 61,138

Alkermes, Inc.
88 Sidney Street
Cambridge, MA 02139

Attention: Priya Jambekar
Vice President, Regulatory Affairs

Dear Ms. Jambekar:

Please refer to the meeting between representatives of your firm and FDA on August 7, 2004. The purpose of the meeting was to discuss the clinical and nonclinical portions of your planned NDA for Vivitrex® (naltrexone long-acting injection).

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at 301-827-7420.

Sincerely,

{See appended electronic signature page}

Lisa E. Basham-Cruz, MS
Regulatory Project Manager
Division of Anesthetic, Critical Care, and
Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

8/11/3/04

Enclosure



MEETING MINUTES

Meeting Date: October 7, 2004

Location: Parklawn Building, Conference Room "C"

IND/ Name: IND 61,138/Vivitrex® (naltrexone long-acting injection)

Sponsor: Alkermes, Inc.

Type of Meeting: Type B Industry Meeting; pre-NDA

Meeting Chair: Celia Winchell, M.D.
Division of Anesthetic, Critical Care and
Addiction Drug Products, HFD-170

Attendees:

Alkermes	Title
Priya Jambhekar, MSc, MS, RAC	VP, Regulatory Affairs
Elliot Ahrich, MD	VP, Science & Development, Chief Medical Officer
Bernard Silverman, MD	Director, Clinical Development
John Loewy, PhD	Director, Biostatistics & Data Management
Pamela Higgins, MBA	Associate Director, Regulatory Affairs
Ryan Turncliff, PhD	Senior Scientist, Pharmacokinetics
Dan Deaver, PhD	Director, Life Sciences (Preclinical)
Geri Weeks	Associate, Regulatory Affairs
/ / /	Consultant;
	Consultant;
FDA	Title
Bob J. Meyer, MD	Director, ODE II
Bob A. Rappaport, MD	Division Director
Rigoberto Roca, MD	Deputy Division Director
Celia Winchell, MD	Team Leader, Addiction Drug Products
Suzanne Thornton-Jones, PhD	Acting Team Leader, Pharmacology/Toxicology
Thomas J. Permutt, PhD	Team Leader, Statistics
Mwango Kashoki, MD	Clinical Reviewer
Mamata De, PhD	Pharmacology/Toxicology Reviewer
David Lee, PhD	Biopharmaceutics Reviewer
Marty Pollock, RPh	Safety Evaluator, Office of Drug Safety
Lisa Basham-Cruz, MS	Regulatory Project Manager

Background: The IND was originally submitted on October 19, 2000. Type C meetings were held on April 10, 2001, and July 11, 2002. The purpose of this meeting is to discuss a New Drug Application for Vivitrex® (naltrexone long-acting injection).

Meeting Minutes:

During introductions, Priya Jambekar, of Alkermes, described the five issues that Alkermes would like to have clarified during the meeting: 1) the fileability of their proposed NDA submission, 2) the approvability of their proposed NDA submission, 3) the labeling and whether a boxed warning will be required, 4) the need for an Advisory Committee Meeting, and 5) any special considerations to make the review of their NDA more productive. Dr. Winchell responded that the Agency can answer some of these questions at this time; however, certain aspects of these issues must be evaluated at the time of the NDA review. Specifically, Dr. Winchell noted that it is too soon to determine whether an Advisory Committee meeting will be needed. Also, language for product labeling is developed throughout the review period, and is based on the data presented in the NDA and on discussions of how to best inform practitioners about the effect of the product and its appropriate use. The discussion then moved to the questions included in the September 16, 2004, meeting package. The questions are shown below in italics. Information presented on slides is bolded. Discussion is in normal typeface.

Dr. Kashoki addressed the clinical questions.

Clinical Question

- 1. Does the Agency agree that the clinical studies conducted would be sufficient to evaluate Vivitrex in terms of (a) safety and (b) efficacy, in order to gain marketing approval for an NDA submitted under Section 505(b)(2)?*

Response:

- **Yes, provided that there are sufficient exposure data to evaluate the safety of Vivitrex at the time of NDA filing.**
- **The safety database should include a sufficient number of subjects with the typical co-morbidities of the target population.**

Dr. Winchell added that, per the predicted enrollment in the on-going open label studies, it appears that the number of exposed subjects will be sufficient. However, it is not clear from the package whether there will be sufficient representation of patients with the full range of disease severity and comorbidities; this will be a matter for review.

Dr. Lee addressed the clinical pharmacology question.

- 2. Does the Agency agree that the clinical pharmacology studies conducted are sufficient to gain marketing approval for an NDA submitted under Section 505(b)(2)?*

Response:

**Your proposal appears to be adequate.
However, please provide:**

- **Rationale for not conducting a study in severe hepatic impairment population;**
- **Findings from in-vitro drug interaction, which may warrant in-vivo studies.**

The sponsor clarified that they have concerns regarding administering a large intramuscular dose of drug to individuals with severe hepatic impairment. Dr. Winchell emphasized that the sponsor should document this rationale in the NDA submission, rather than remaining silent on the subject of the use of Vivitrex in this population.

Regarding the second bullet, the sponsor said that they have observed no interactions with CYP450 in *in vitro* studies of Vivitrex. Since this intramuscular formulation of naltrexone is not hepatically metabolized, Alkermes has not conducted any *in vivo* drug-drug interaction studies. Dr. Lee reminded the sponsor that they must address the drug concentrations used in the *in vitro* studies, and how the concentrations compare to the relevant clinical concentrations. The sponsor agreed and noted that the clinical concentrations are very low compared to those utilized in the *in vitro* studies.

Clinical Question

3. *Does the Agency agree that the proposed text of the "Indications and Usage" and "Clinical Trials" sections of the label (Section 5.0) is consistent with the clinical data as summarized in this document?*

Response

- **It is premature to discuss the text of the label.**
- **However:**
 - **The proposed language for the "indications and usage" section appears reasonable.**
 - **Simpler and less specific language than that proposed is likely to be used for the "clinical trials" section. Specific numbers associated with the efficacy analysis are unlikely to be included.**

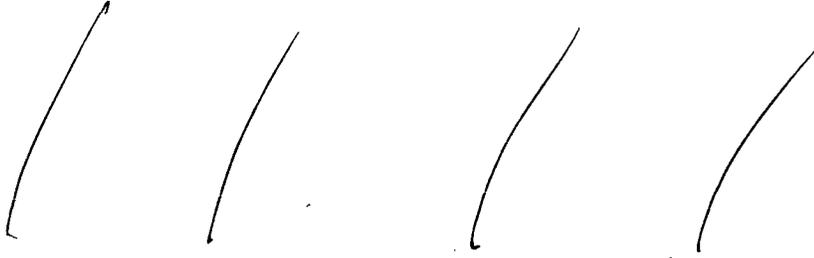
Clinical Question

4. *Does the Agency agree that the sponsor's approach based on route of administration, dose, and accumulated hepatic safety experience would support a label for Vivitrex 380 mg:* _____

Response

- _____ **s a**
- **matter for NDA review.**
- **The NDA safety data will be evaluated with respect to:**

(((



Clinical Question

5. *Based on the information provided in this document, does the Agency agree that Vivitrex meets the criteria for priority review?*

Response

- **Designation of priority or standard classification is done at the time of NDA filing.**
- **We do not currently expect that Alkermes will be able to demonstrate that they meet the criteria for a priority review.**

Dr. Winchell explained that, in order for a drug to qualify for priority review, superiority over current therapies for alcohol dependence must be demonstrated. The Division understands the rationale for a claim of Vivitrex's improvement over oral naltrexone based on comparative data. Since this is being planned as a 505(b)(2) application, however, Alkermes will rely on the Agency's previous findings of efficacy for oral naltrexone, while requesting a priority review determination based on a claim of

Lastly, there are no clinical trial data comparing Vivitrex to acamprosate, another available therapy. Therefore, it may be difficult to justify a priority review.

Dr. De addressed the preclinical question.

6. *Does the Agency agree that the proposed format and content of the nonclinical Pharmacokinetics Written Summary and the nonclinical Pharmacokinetics Tabulated Summary of the Common Technical Document are sufficient to support the evaluation of the Vivitrex nonclinical pharmacokinetics section of the NDA?*

Response:

- **The proposed CTD format for the written and tabulated summaries of the non-clinical PK is acceptable.**

The sponsor asked whether there was anything they should pay special attention to. Dr. De said to clearly compare the exposure between non-clinical species and humans at the maximum anticipated exposure.

Dr. De also added that all referenced literature publications and final complete study reports (not summaries of the results) characterizing the pharmacology and toxicology of the drug product need to be submitted as part of the NDA.

Post Meeting Note: Please note that not all studies reported in the literature are supported by data that exists within the public domain. Most studies in the literature are supported by proprietary data.

Dr. Kashoki continued with the clinical questions.

7. *Does the Agency agree that the initial NDA for Vivitrex is eligible for a waiver from conducting pediatric studies to support approval?*

Response

- **Pediatric studies may be deferred until after NDA approval.**

Clinical Question

8a. *Does the Agency agree that, upon approval, Vivitrex would be considered a Reference Listed Drug (RLD) in the Orange Book?*

Response

If Vivitrex is the first long-acting naltrexone product, it may be the RLD. It is premature to determine whether Vivitrex would block marketing of another long-acting naltrexone product, as this would depend on the specific characteristics of the 'second' drug compared to Vivitrex.

Clinical Question

8b. *Based on the information presented in this document and the labeling proposed by Alkermes, does the Agency feel that the Advisory Panel Review will be necessary to evaluate the approvability of Vivitrex?*

Response

- **The need for Advisory Panel review will be better assessed at the time of NDA filing, when the all the data will be available.**

Dr. Winchell explained that an advisory committee meeting would be requested if, for example, the data do not lead the Division to a firm conclusion regarding treatment efficacy, or there is uncertainty as to how to evaluate the risk: benefit ratio, or if additional expertise is necessary regarding the nature of the language for labeling. The sponsor inquired whether the issue of _____ product label would merit an advisory committee meeting. Dr. Winchell responded that this would be the case only if the Agency was unable to agree internally on _____ If this was the topic of discussion, the committee would likely be involved, rather than the _____ Committee. Dr. Winchell added that the Division will know whether or not an advisory committee meeting is indicated only as we proceed with the NDA review. Dr. Meyer noted that, for a ten-month review, we typically target month eight for an advisory committee meeting. For a priority review, the meeting could be held during month four or five.

Clinical Questions

8c. Given that this is the first NDA filing for Alkermes, would the Agency comment on the expected review timelines and future communication needs?

Response

- **The filing review will occur within 45 days of the NDA submission.**
- **Any filing review issues will be communicated in a letter no later than 14 days after the 60-day filing date.**
- **Discipline-specific review issues may also be communicated in separate letters.**
- **The Division will continue to communicate with Alkermes during the review period, as the need for further information arises.**

Additional Clinical Comments Regarding the NDA submission:

Data analysis: Missing data

- **Many of the analyses regarding treatment efficacy will have to deal with the issue of missing data. Methods used to handle missing data should be described, and will be important in the Division's review of the NDA.**

It was clarified that previous discussions with Agency biostatistics review staff regarding the handling of missing data for the primary analysis had occurred. However, Dr. Winchell reminded Alkermes that depending on the type of efficacy analysis applied (e.g. a responder analysis), different methods for handling missing data may be required. These methods should be clearly articulated in the NDA.

Data analysis: Responder analysis

- **As stated at the pre-IND meeting, a responder analysis should also be performed. Various definitions of treatment response may be used, including:**

- **abstinence from any drinking**
 - **abstinence from heavy drinking**
 - **abstinence from drinking above the NIAAA “safe” level (> 2 drinks/day for men, >1 drink/day for women)**
- **We do not agree with the definition of a treatment responder (clinical success) that you proposed in the ALK21-003 protocol:
Treatment with all doses and ≥ 50% decrease in the percent heavy drinking days, up to 30 days after treatment.**

The sponsor expressed concern regarding the definition of a treatment responder as only those patients who achieved abstinence. The Agency pointed out that the suggested definitions of a treatment responder allow for exploration of treatment effects involving drinking patterns other than complete abstinence.

Alkermes expressed concern about these analyses because the trial was designed based on a different primary. The Agency agreed that a finding of treatment efficacy would be based on the primary analysis because of the prior agreement with Alkermes; however, the Agency now has a strong interest in the responder analyses described.

Data regarding hepatic effects

- **Include LFT data showing shifts within patients from “normal” to “abnormal”, and from “abnormal” to “worse.”**
- **Include data regarding changes in LFTs associated with oral naltrexone treatment for comparison.**

Dr. Winchell explained that, when preparing shift tables for studies in this population, it is necessary to identify not only shifts from normal to abnormal, but also to identify what happens to laboratory values that were abnormal at baseline.

Adverse Event Coding

- **MEDRA and COSTART are generally inadequate to appropriately capture AEs associated with alcohol use.
e.g. “alcoholism” to code for hospitalization for detoxification**
- **Creation of sponsor-specified terms regarding alcohol-associated AEs is recommended to better capture what has occurred.**
- **Verbatim terms suggestive of any suicide-related AE should be flagged for follow-up.**

Required CRFs and Patient Narratives

- **All patient deaths, SAEs, discontinuations**
 - **CRFs for patients who met SAE criteria on the basis of being hospitalized for detoxification/alcoholism treatment *only* are not needed**

- **All attempted or completed suicides**
- **All patients with flagged AE verbatim terms suggestive of suicide**

Dr. Winchell added that the sponsor should include a thesaurus that defines all of the terms and how terms are grouped.

NDA Submission

- **You are encouraged to consult the following documents to assist you in understanding the Agency's approach to review of an NDA, the data that are sought, and the desired formats for tabular and/or graphical presentation of data:**
 - **Guideline for the format and content of the clinical and statistical sections of a New Drug Application**
<http://www.fda.gov/cder/guidance/statnda.pdf>
 - **Clinical Review Template (MaPP 6010.3)**

NDA Submission

- **Clarify how the you intend to submit the data electronically**
- **A follow-up meeting prior to NDA submission is recommended to provide:**
 - **An opportunity for a "test run" of the electronic data set with the review team**
 - **Recommendations regarding the NDA format that may not necessarily be described in the MaPPs and guidelines.**

The sponsor said that they prefer to submit in eCTD format, but that this depends on the timing of the submission, etc. The submission may ultimately be paper with electronic ISS and ISE.

The sponsor inquired whether the Division would like to have counting process type datasets in addition to the traditional datasets. Dr. Permutt responded that the sponsor should include the data sets used for the protocol-specified analyses, as well as the data that are used to provide supportive analyses and conclusions and data believed helpful in elucidating the drug's effect. Dr. Permutt added that it is very important, in these analyses, to provide a thorough explanation of how the derived data relate to data on the CRFs. The sponsor inquired whether source code should be submitted. Dr. Permutt replied that source code is sometimes very helpful to understand what was done.

Closing Comments

Dr. Permutt noted that the meeting package appeared to make assertions that might be difficult to reconcile. For example, the application might qualify for 505(b)(2) status based on similarity to approved products but also for priority review based on differences

from approved products. He suggested that the NDA explicitly state the applicant's views regarding these issues.

Dr. Roca noted that if the sponsor wishes to make an argument for priority review, then all of the critical safety data must be available at the time of NDA submission. A large safety update submitted 4 months into a 6-month review time would be undesirable.

Alkermes asked whether, to satisfy the Division's requirements regarding the safety database, there should be over-sampling of patients with psychiatric and medical conditions similar to the target population. In the current open-label trials, Alkermes is over-sampling for only opioid-dependent patients. Dr. Winchell responded it is desirable to have as large a safety database as possible which will then be evaluated with regards to comparability to the target population.

Dr. Winchell asked the sponsor to summarize their understanding of the meeting outcomes.

The sponsor summarized the following:

1. The proposed NDA appears to include enough studies to be submitted. Fileability will be determined after submission.
2. Determination of filing classification, priority or standard review, will be done at the time of NDA filing.
3. The proposed application appears sufficient to review.
4. The Agency is willing to consider the _____ for this product.
5. The need for an Advisory Committee meeting will be determined at a later date.

- Lisa E. Basham-Cruz/minutes recorder

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/s/

Lisa Basham-Cruz
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 61,138

Alkermes, Inc.
64 Sidney Street
Cambridge, MA 02139-4136

Attention: Don G. Burstyn, Ph.D.
Vice President, US Regulatory Affairs

Dear Dr. Burstyn:

Please refer to the meeting between representatives of your firm and FDA on July 11, 2002. The purpose of the meeting was to discuss the development plan for Medisorb® Naltrexone.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at 301-827-7420.

Sincerely,

{See appended electronic signature page}

Lisa E. Basham-Cruz 8/8/02
Regulatory Project Manager
Division of Anesthetic, Critical Care, and
Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

MEETING MINUTES

Meeting Date: July 11, 2002

Location: Parklawn Building, Conference Room "C"

IND/ Name: IND 61,138/ Medisorb® Naltrexone

Sponsor: Alkermes, Inc.

Type of Meeting: Type C Industry Meeting

Meeting Chair: Celia Winchell, M.D.
Division of Anesthetics, Critical Care and
Addiction Drug Products, HFD-170



Attendees:

Don G. Burstyn, PhD	VP, Regulatory Affairs
Elliot Ehrich, MD	VP, Medical Affairs
Dave Benzinger, PhD	Director, Pharmacokinetics
George Grandolfi, PhD	Director, Development
Pamela Higgins	Manager, Regulatory Affairs
Erin Kammann, PhD	Senior Biostatistician
Lionel Murray, PhD	Director, Quality Control
Bernard Silverman, MD	Director, Medical Affairs
Steve Wright	Associate Director, Process Development
Ari Illeperuma	Senior Biostatistician

Representing: Alkermes, Inc.

AND

Bob Rappaport, M.D.	Deputy Division Director
Celia Winchell, MD	Team Leader, Addiction Drug Products
Dale Koble, PhD	Team Leader, Chemistry
Michael Theodorakis, PhD	Chemistry Reviewer
Suliman Al Fayoumi, Ph.D.	Biopharmaceutics Reviewer
Vinayak Pawar, PhD	Microbiologist
Shaun Comfort, MD	Medical Reviewer
Ann Nguyen	Pharmacy Student
Jorge McDougall	Medical Officer Intern
Lisa Basham-Cruz, MS	Regulatory Project Manager

Representing: Division of Anesthetic, Critical Care, and Addiction Drug Products, FDA

Meeting Minutes:

Following introductions, the discussion moved straight to the questions submitted by the Sponsor in the meeting package, dated June 20, 2002. The Sponsor's questions are shown below in italics.

Question 1. As it relates to exclusivity under the Federal Food, Drug, and Cosmetic Act [505(c)(3)(D)(iii)], can you clarify what is meant by "...for the condition of approval?"

It was unclear to the Division what the Sponsor was asking with this question. The Sponsor clarified that they want to know what the criteria is for "same" versus "different" as it relates to exclusivity. Furthermore, the Sponsor wanted to know by what means exclusivity could be negated, e.g. an improved safety profile may override orphan drug exclusivity. As issues of exclusivity are handled by the Exclusivity Board and questions such as these are normally addressed by the Office of Generic Drugs, Dr. Winchell stated that the Division will look into this issue and provide a response in writing at a later date. The Sponsor was directed to the Federal Register citation relevant to the question (Vol. 54, No. 30, p. 28896), but was also encouraged to resubmit the question in writing for referral to the relevant agency personnel.

Question 2. If Alkermes decides to file a full NDA rather than a 505(b)(2) application, can the Agency confirm the following:

- *Only one Phase 3 trial is necessary*
- *Only toxicology studies on the final formulated product, and not the Naltrexone API, will be required.*

Dr. Winchell stated that two adequate and well-controlled clinical trials are necessary if the application is not submitted under 505(b)(2). The Sponsor inquired whether studies could be obtained through right of reference. Dr. Rappaport replied that a study for which right of reference is obtained will be evaluated as if it were conducted by the Sponsor, and added that the study must fit the requirements for an adequate and well-controlled trial. All the data must be submitted.

Dr. McGovern (Preclinical Pharmacology Team Leader) was not present at the meeting, but Dr. Winchell presented information, prepared by him and presented on a slide, addressing the second bullet of the question.

- Use of the final formulated product in toxicology studies is recommended.
- As indicated in the pre-IND meeting of June, 2000, reproductive toxicity studies, a genotoxicity battery, and carcinogenicity studies are required.
 - ✓ Portions of this information could be obtained from publicly available information or by obtaining a right of reference.
 - ✓ In vitro genotoxicity studies should assess the drug substance only.
 - ✓ The Sponsor is encouraged to submit carcinogenicity protocols for concurrence by the Carcinogenicity Assessment Committee (CAC).
- Additional studies could be requested should unexpected findings be identified with the drug product formulation compared to those associated with naltrexone.

Question 3. The manufacturing process used to produce material for the Phase 3 clinical study is at a _____ scale. For commercial supply, Alkermes plans to scale-up the manufacturing process to _____

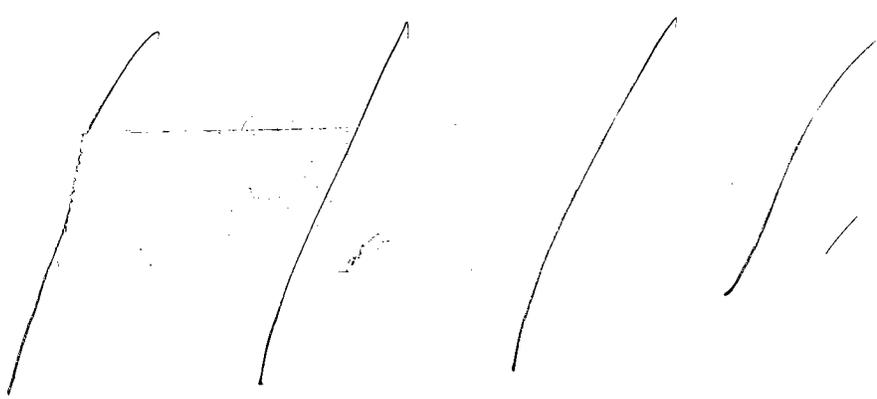
Is the proposal for demonstrating comparability of the clinical and commercial scale product acceptable to the Agency?

Dr. AlFayoumi inquired whether the _____ lot was available for use in the Phase 3 studies. The Sponsor replied that the _____ batches would not be available. Dr. AlFayoumi continued that a bioequivalency study will not be necessary if the Sponsor provides stability data as well as comparative multi-point dissolution testing data using a dissolution testing methodology accepted by the Agency. f2 criteria should be used to demonstrate similarity of batches. Depending on the reliability of the selected dissolution testing methodology, additional clinical data might be needed.

Question 4. Does the Agency agree that the planned clinical pharmacology studies are sufficient to gain marketing approval?

Dr. AlFayoumi displayed a slide showing that, for a 505(b)(2) application, PK in patients with moderate and severe hepatic impairment, and potential drug-drug interaction studies in the intended population will be required. Addressing the requirement for study of moderate to severe hepatic impaired patients, the Sponsor stated that study of such a moribund population will be difficult. Dr. Rappaport stated that the Sponsor should submit adequate justification for not evaluating PK in severe hepatic impaired patients and the Agency will consider it. Dr. AlFayoumi added that study of moderate hepatic impaired patients should be feasible, but a justification against conducting a PK study in this group would also be considered. Drug-drug interaction studies may also be required. Initial *in vitro* studies should be conducted. If there is an indication of drug-drug interactions in the *in vitro* assay, additional clinical studies may be required. Dr. AlFayoumi continued that a 505(b)(1) application will also require ADME studies, PK studies in the elderly, pediatrics, and renal impaired patients, as well as dose proportionality studies.

Question 5. Does the Agency agree that monitoring of the listed parameters is adequate to assess the long-term stability of Medisorb Naltrexone _____



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Post Meeting Note: The Sponsor is encouraged to take advantage of the information available on the FDA website and to consult "Frequently Asked Questions for New Drug Product Exclusivity" at www.fda.gov/cder/about/smallbiz/exclusivity.htm, for more information on exclusivity.

- Lisa E. Basham-Cruz/minutes recorder
- Celia Winchell, M.D./concurrence

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

/s/

Lisa Basham-Cruz
8/6/02 10:55:28 AM

Celia Winchell
8/8/02 12:12:03 PM

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