CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-431

Administrative/Correspondence

Item 13: Patent Information on any patent which claims the drug

To the best of Lipha Pharmaceuticals, Inc.'s knowledge, there exists no currently effective patent which claims acamprosate, or which claims a method of using acamprosate, with respect to which a claim of patent infringement could reasonably be asserted against any person engaged in the manufacture, use, or sale of the drug.

Anita M. Goodman

Dec. 21, 2001

Anita M. Goodman, M.D.
Chief Operating Officer and Vice President
Lipha Pharmaceuticals, Inc.

Date

EXCLUSIVITY SUMMARY FOR NDA # 21-431 SUPPL #_____

Trade Name Campral GenericName acamprosate calcium

Applicant Name Lipha Pharmaceuticals, Inc. HFD# 170

Approval Date If Known _____

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 question about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?
YES /_X_/ NO /___/

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

505(b)(1)

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 /_X_/ 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 /_X_/ NO /___/

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

_____5_____

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

YES /___/ NO /_X_/

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Writen 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 /_X_/

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 /_X_/

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 NDA'S 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:

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 /___/

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

_____ _____

_____ _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

_____ _____

_____ _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was

the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # _____ YES /___/ NO /___/ Explain: _____

Investigation #2

IND # _____ YES /___/ NO /___/ Explain: _____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

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: _____

_____

Signature Date

Title:

Signature of Office/ Division Director

Date

Form OGD-011347 Revised 05/10/2004

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA # : 21-431 **Supplement Type (e.g. SE5):** _____ **Supplement Number:**

Stamp Date: December 21, 2001 **Action Date:** To Be Determined

HFD 170 **Trade and generic names/dosage form:** CAMPRAL (acamprosate calcium delayed-release tablets)

Applicant: Lipha Pharmaceuticals, Inc. **Therapeutic Class:** 1

Indication(s) previously approved: NONE

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

Number of indications for this application(s): One

Indication #1: _____

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

- ☐ **Yes: Please proceed to Section A.**
- ■ **No: Please check all that apply:** X **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.

ection 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.** 18	**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): 08/04/09

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: Lisa Basham-Cruz

{See appended electronic signature page}

_____
Regulatory Project Manager

cc: **NDA 21-431**
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)

Item 16: Debarment Certification

In compliance with Section 306(k) of the Federal Food and Cosmetic Act, we hereby certify that Lipha Pharmaceuticals, Inc. and its corporate affiliates did not and will not use in any capacity the services of any person debarred under subsection 306(a) or (b) of the Act in connection with this application (NDA 21-431) for acamprosate.

Anita M. Goodman

Anita M. Goodman, M.D.
Chief Operating Officer and Vice President
Lipha Pharmaceuticals, Inc.

Dec. 21, 2001

Date

Office Director's Sign-Off Memorandum

Date:	Wednesday, July 28, 2004
NDA:	21-431
Sponsor:	Lipha Pharmaceuticals, Inc.
Proprietary Name:	Campra (acamposate calcium) Delayed-Release Tablets

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Introduction: This is the second cycle for this application. Campra (acamprosate calcium – *note my original memo of June 2002 incorrectly referred to the sodium salt*) is proposed for use as an oral treatment of alcohol dependence. The proposed dosage for this drug is 666 mg (two 333 mg tablets) three times daily, and it is intended to be started soon after detoxification and continued even during relapses.

At the time of the first action, there were a number of outstanding issues that led to a not-approvable action. First, there was an inadequate demonstration of efficacy, which led to an agency request for a further study along with a reanalysis of existing studies. Secondly, due to issues of organization and presentation, it was not clear from the submission of 2001 that there were sufficient safety data to support approval. There were also pharmacology/toxicology deficiencies, notably inadequate data to identify and characterize toxicity in the chronic dog model, inadequate mutagenicity testing and a failed carcinogenicity testing in mice. CMC was largely acceptable save for some DMF issues.

Current Submission: The sponsor resubmitted their application on February 3rd, 2004. In keeping with discussions with the FDA after the first action, Lipha did not report the results of any additional studies in this resubmission, but rather they did an extensive auditing of the data from their key European studies to address concerns the agency had as to whether these data were sufficiently robust and of sufficient integrity to allow for regulatory conclusions. Lipha performed a 100% audit of clinical trials material and redefined "complete abstinence" to account for all confirmatory data that would establish or refute abstinence. The results of their analyses from the key European studies based on this definition of complete abstinence and with the fully audited, quality assured data indeed showed clear efficacy for acamprosate vs. placebo in all three European trials (Pelc II, PRAMA, and Paille). The reorganized and clarified safety database is also adequate for supporting the safety of the proposed doses and the chronic administration of the drug. Overall the drug appears to be reasonably safe and fairly well tolerated. The most common adverse events reported in relation to active drug were GI in character, including diarrhea, nausea and flatulence. The only signals of note in the safety database are for allergic reactions and Stevens-Johnson, which have been rarely reported in the post-marketing databases and an apparent imbalance in suicidality and worsening depression. The overall rate of suicidal events (attempts, completions) was 1.8 % in acamprosate patients all controlled studies vs. 0.6% in placebo, though the actual rate of completions in the pivotal trials was more balanced. While this overall imbalance does not represent a clear enough causal signal to preclude approval, it does warrant precautions in the labeling and bears watching post-marketing. Finally, there are some post-marketing reports of acute renal failure temporally associated with Campral in post-

marketing use (which is extensive, since it has long been approved in Europe). These cases do not establish causality, but again deserve disclosure in labeling.

The Pharm/Tox issues were largely satisfactorily addressed with all the requested additional data other than a new mouse carcinogenicity study. Instead, Lipha presented an argument as to why the previous study was sufficient. Neither the primary review team nor the CAC accepted that argument, however. Therefore, the sponsor will need to perform a repeat mouse CA study. However, it is acceptable that this be a phase 4 commitment as this drug is not genotoxic in the adequate tests and showed no evidence of carcinogenicity in the sufficient rat study nor the flawed mouse study. Further, the chronic toxicity studies did not show evidence of premalignant changes.

Labeling: The proposed labeling was greatly revised by the Division and Office and we have reached agreement with the sponsor on a label sufficient to allow the safe and effective use of this product.

Regulatory Conclusions: This application will be approved. The company has agreed to the following phase 4 studies: a study of efficacy in 12 – 16 year olds under PREA; a study of the PK characteristics and appropriate dosing of the drug in severe renal impairment, .a study of the concomitant effects of the drug and alcohol in fetal development in animals, and the repeat mouse carcinogenicity study. Note that there is controversy as to whether the company can identify and study children in the above age range who are alcohol *dependant*, as would be necessary for this indication under PREA. The company believes they cannot. If they can provide us convincing data that either this population of alcohol dependant children is insignificant or the study is impracticable, we may waive it at a later date. However, we would issue a pediatric written request to get data in this age range for children with an alcohol *abuse* history.

/S/

Robert J. Meyer, MD
Director,
Office of Drug Evaluation II

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/s/

Robert Meyer
7/28/04 04:17:43 PM
MEDICAL OFFICER

Office of Drug Safety

Memo

To: Bob Rappaport, MD
Director, Division of Anesthetic, Critical Care, and Addiction Drug Products
HFD-170

From: Alina Mahmud, R.Ph.
Team Leader, Division of Medication Errors and Technical Support, HFD-420

Carol Holquist, R.Ph.
Director, Division of Medication Errors and Technical Support, HFD-420

CC: Lisa Basham-Cruz
Project Manager, Division of Anesthetic, Critical Care, and Addiction Drug Products
HFD-170

Date: July 21, 2004

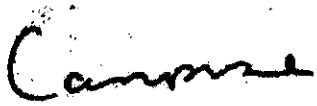
Re: ODS Consult 02-0104-3; Campral (Acamprosate Tablets), 333 mg; NDA 21-431.

This memorandum is in response to a July 20, 2004, request from your Division for a re-review of the proprietary name, Campral. In our previous reviews, dated June 11, 2002 and March 15, 2004 (ODS Consults #02-0104 and #02-0104-1, respectively), DMETS had no objections to the use of the proprietary name, Campral. Labels and labeling were reviewed in a consult dated June 15, 2004 (ODS consult 02-0104-2).

Since the completion of our last consult, DMETS has identified one additional proprietary name, Lamprene, with the potential for look-alike confusion with Campral. Lamprene contains clofazimine and is indicated for use in the treatment of leprosy. Campral is indicated for the maintenance of abstinence from alcohol in patients with alcohol dependence who have withdrawn from alcohol. The names Lamprene and Campral share the letters "ampr". Additionally, the first letter in each name "L" versus "C" may look similar when scripted (see below). The endings may also look similar if the letter "l" in Campral is not scripted with a prominent upstroke.

LAMPRENE

CAMPRAL



The products share a similar dosage form (capsule vs. tablets), route of administration (oral) and dosing quantity (2 tablets). Although the strengths do not overlap, a prescription for either Lamprene or Campral may written without a strength since each will be available in only one strength. The products differ in dosing frequency (once daily vs. three times daily). Additionally, Lamprene is indicated for use in combination with other antileprosy medications until negative skin smears are obtained. Furthermore, the manufacturer of Lamprene has changed the distribution of Lamprene as of July 1, 2004 whereby Lamprene will no longer be sold to pharmacies and will only be distributed under an Investigational New Drug (IND) application. To receive Lamprene for use in the treatment of Leprosy, physicians must be enrolled as an investigator under the IND. Despite the product and nomenclature similarities between Lamprene and Campral, DMETS believes that the potential for confusion between the drug products is minimal given the distribution changes implemented for Lamprene.

In summary, DMETS has no objections to the use of the proprietary name Campral. DMETS considers this a final review. However, if the approval of the NDA is delayed beyond 90 days from the date of this review, the name must be re-evaluated. A re-review of the name before NDA approval will rule out any objections based upon approvals of other proprietary/established names from this date forward.

If you have any questions or need clarification, please contact the medication errors project manager, Sammie Beam at 301-827-2102.

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/s/

Alina Mahmud
7/21/04 01:00:45 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
7/21/04 02:43:16 PM
DRUG SAFETY OFFICE REVIEWER

ADRA Review #2 of Action Package for NDA 21-431, Campral (acamprosate) Tablets

Reviewer: Lee Ripper, HFD-102
Date received in HFD-102: July 15, 2004
Date of Review: July 19, 2004

Date original NDA recd:	Dec 27, 2001	Date RS recd:	Feb 4, 2004
UF GOAL DATE:	July 29, 2004	PDUFA date:	Aug 4, 2004

Indication: [ ]

Action type: AP
RPM: Lisa Basham-Cruz, x7-7420
Drug Classification: 1P
505(b)(1) application

Patent Info: No current relevant patent
Clinical Inspection Summary: AC 6/7/02, 1 site in Germany and 1 site in France inspected
DDMAC review of PI: No review in pkg
Debarment statement: AC
DMETS Review of Trade Name: AC 3/19/04; 90-day update pending as of 7/19/04
EER: AC 6/24/04
EA: AC, CMC rev #1, p. 63
Financial disclosure information/review: AC
Safety Update: The 7/15/04 MOR is attached to the 5/28/04 SU.

1. I gave my comments on the draft letter to the RPM to incorporate into the next draft.

2. See comments on labeling.

/S/

Lee Ripper, ADRA

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/s/

Leah Ripper
7/20/04 04:35:38 PM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-431

DISCIPLINE REVIEW LETTER

7/14/04

Lipha Pharmaceuticals Inc.
10 Derby Square
Salem, MA 01970

Attention: Anita M. Goodman, M.D.
Executive Vice President, Chief Operating Officer

Dear Dr. Goodman:

Please refer to your December 21, 2001, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Campral (acamprosate calcium tablets).

We also refer to your submissions dated February 3 and April 29, 2004.

Our reviews of the Carton and Container sections of your submission are complete, and we have identified the following deficiencies:

1. BLISTER LABEL

   a. Professional Sample/Patient Starter Kit

   (1) The blister package describes its contents as a [redacted]" or "Patient Starter Kit," while the package insert describes the contents as a [redacted]" Revise the content description so that the descriptions are consistent.

   (2) It is unclear whether the blister package is perforated. If the blister card is perforated, there are safety concerns regarding the identification of the tablets should the "card" become separated from the section containing the proprietary name, established name, and strength. Include the product information (i.e., name, dosage strength, etc.) on the backside of each card.

   (3) Include a statement, "[redacted] – not for sale."

   (4) Add a warning regarding the presence of sulfites in the drug product.

b. Dose Pak

(1) See Comment 1.a(2)

(2) See Comment 1.a(4)

2. CONTAINER LABEL (180 and 1080 Tablets)

a. Increase the prominence of the product strength.

b. Relocate the quantity statement to appear away from the product strength.

c. See Comment 1.a(4)

3. PACKAGE INSERT (HOW SUPPLIED SECTION)

a. See Comment 1.a(1)

b. See Comment 1.a(4)

c. The descriptor "cards" in the statement "6 x 10 cards" and "6 x 7 cards" implies that the blister cards can be separated. If so, use another term to describe the perforated subsections.

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,

/S/

{See appended electronic signature page}

Parinda Jani
Supervisory CSO
Division of Anesthetic, Critical Care, and
Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Parinda Jani
7/14/04 12:35:32 PM

7/12/04

MEMORANDUM

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

DATE: June 25, 2004

TO: NDA File

FROM: Lisa Basham-Cruz

SUBJECT: **Clinical Requests/Questions Emailed to sponsor 6-30 through 7-1-04**

NDA 21-431, Acamprosate Calcium

The following emails were sent to Lipha on the dates specified at the request of Celia Winchell. Responses were received by email from the sponsor, also shown below. All attachments were submitted in hard copy to the NDA.

June 30, 2004; 2:12 PM:
Subject: Another Lipha question

Is there any followup information on any of the patients who became pregnant in any of the studies?

From: agoodman@[redacted] [mailto:agoodman[redacted]
Sent: Wednesday, June 30, 2004 4:46 PM
To: Basham-Cruz, Lisa
Cc: sylvie.chabac@merck.fr; [redacted] patrick.pechenart@merck.fr; cecile.pascaretti@merck.fr; mel.lewis@merck.fr
Subject: Pregnancy question
Importance: High

Dear Lisa:
In response to Dr. Winchell's question, [redacted] searched the databases for the terms "pregnancy", "unintended pregnancy", "abortion", "fetus" and "newborn". He was able to identify 4 pregnancies in the Group I studies and 1 pregnancy in the Group IV studies. Group I studies:

Paille Patient 469: This patient, randomized to acamprosate 1998 mg/day,was found to be pregnant at Day 60 of the study and was

terminated at that time. We do not have pregnancy outcome information. (See narrative on Page 225 of Vol. 21, Dec. 19, 2003 submission).
Poldrugo Patient 42: This patient, randomized to placebo, was found to be pregnant at Day 137 of the study and was terminated at that time. We do not have pregnancy outcome information and there was an indication she might have had her pregnancy terminated. (See narrative on Page 272 of Vol. 21, Dec. 19, 2003 submission).
UKMAS Patient 98: This patient, randomized to acamprosate 1998 mg/day, was found to be pregnant at Day 28 of the study and was terminated at that time. She had her pregnancy terminated 2 weeks later. (See narrative on Page 313 of Vol. 21, Dec. 19, 2003 submission).
UKMAS Patient 688: This patient, randomized to acamprosate 1998 mg/day, was found to be pregnant at Week 2 of the study and was terminated at that time. No pregnancy outcome information was available. (See narrative on Page 357 of Vol. 21, Dec. 19, 2003 submission--please note that Pages 322 through 378 of this volume were inadvertently omitted from the submission and are being sent today, via Fedex.). Group IV studies:
NEAT Belgium, Center 18, Patient 19: This patient, on acamprosate 1998 mg/day, had vaginal bleeding at Week 2 of the study and, at that time, was found to be approximately 10 weeks pregnant. Because of continued vaginal bleeding, she had a curettage and, thus, the pregnancy was terminated. She continued in the study. (See narrative on Page 562-563 of Vol. 22, Dec. 19, 2003 submission).
INTEGRAL, Center 77, Patient 1: This patient, on acamprosate 1998 mg/day, was identified as being pregnant at Week 20. No further information is available.

Although I am not optimistic about being able to get additional information on these cases, I will ask my colleagues in Lyon to see if there is anything more available. Best regards, Anita

June 30, 2004; 4:03 PM:
Subject: Request

I count about 19 pregnancies in the post-marketing line listings, plus four in the Group I studies and 2 in the Group IV studies--is there any outcome information on these cases at all? It would be helpful to have the pregnancy outcome information pulled together as much as possible.

From: agoodman@[redacted]
Sent: Wednesday, June 30, 2004 4:45 PM
To: Basham-Cruz, Lisa
Cc: sylvie.chabac@merck.fr; [redacted]
patrick.pechenart@merck.fr; mel.lewis@merck.fr;
cecile.pascaretti@merck.fr; [redacted]
Subject: Additional pregnancy question
Importance: High

Dear Lisa:
If Dr. Winchell has access to Volume 14 of the Dec. 19, 2003 submission, on Pages 97 to 99, the available information on pregnancy from the post-marketing reports is summarized and presented in tabular

form (16 pregnancies). In addition, there is information on 3 additional pregnancies, reported through post-marketing reports, in the May 28, 2004 amendment (Safety Update). If Dr. Winchell wishes, I can extract the table from Volume 14 and add in the additional 3 pregnancies from the recent safety update and the 3 pregnancies from Group I studies (1 of the 4 was on placebo) and the 2 pregnancies from the Group IV studies and re-do the summarized textual discussion. Best regards,

Anita

July 1, 2004; 5:14 PM:
Subject: One more for Lipha

Would it be possible to have tabulated, by study:
- patients with events of a suicidal nature by treatment group
- patients with an SAE of depression who didn't also have a suicide event by treatment group (If someone had a hospitalization for depression and ALSO had a suicidal event, he shouldn't be listed twice--in other words, any patient should only appear in the table once, and I should be able to add these two numbers together to get patients with severe affective symptoms).

I just want to see how the rates vary from study to study

From: agoodman@[ ]
Sent: Friday, July 02, 2004 12:25 PM
To: Basham-Cruz, Lisa
Cc: sylvie.chabac@merck.fr; [ ]
mel.lewis@merck.fr; patrick.pechenart@merck.fr;
cecile.pascaretti@merck.fr; [ ]
Subject: Suicidal events and serious depression
Importance: High

Dear Lisa:
[ ] has created 2 tabular displays for Dr. Winchell for the 11 Group I double-blind, placebo-controlled studies which captured spontaneous adverse events. One table provides the by-study information requested below, as an Excel spreadsheet, and the second provides further detail, showing by-patient information and including patients with suicidal events who also had depression and patients who had only serious depression.

The 2 Group I studies that were not included (Ladewig [Short-Term] and Lesch [Long-Term]) each had 1 suicidal event. In the Ladewig study, Patient 32 on placebo, committed suicide and in the Lesch study, Patient 106 on acamprosate, 1998 mg/day, committed suicide. [ ] indicates that there was only one SAE of depression in these 2 studies and this occurred in a patient on placebo in the Lesch study.

I hope this is what Dr. Winchell was looking for.
Best regards,
Anita
(See attached file: Suicidal events vs serious depression_bystudy list_July2.xls)
(See attached file: suicn_depnosuicn_bypatient list_July 2.doc)

July 1, 2004; 1:00 PM:
Subject: FW: Additional pregnancy question

Anita, See below...
L

-----Original Message-----
From: Winchell, Celia J
Sent: Wednesday, June 30, 2004 11:33 PM
To: Basham-Cruz, Lisa
Subject: Re: Additional pregnancy question

Thanks, that's just what I was looking for. An updated version would be most welcome. Don't really need the text--the table would be plenty.

Sent from my BlackBerry Wireless Handheld

From: agoodman@
Sent: Friday, July 02, 2004 3:34 PM
To: Basham-Cruz, Lisa
Cc: sylvie.chabac@merck.fr; patrick.pechenart@merck.fr; mel.lewis@merck.fr;
cecile.pascaretti@merck.fr;
Subject: Consolidated Pregnancy tables
Importance: High

Dear Lisa:
Attached is document which provides tables of all patients on acamprosate that we have identified as being pregnant (consistent with Dr. Winchell's numbers). In addition, I am adding some new or revised narratives and also PDF files for new CRFs for some of the cases which did not have CRFs submitted because they were Group IV patients where the pregnancy was considered a termination reason and not an AE. Best regards and have a happy 4th of July celebration! I will be back in the office on Tuesday. Anita (See attached file: Unintended Pregnancy.doc) (See attached file: Revised Narrative for NEAT BE CT 18 Pt19_July 2.doc) (See attached file: Revised Narrative for Paille 469_July1.doc) (See attached file: NEAT PO CT 6 Pt10_July 2new.doc) (See attached file: INTEGRAL CT 77 Pt1_July 2new.doc) (See attached file: NEAT BE CT 21 Pt5_July
2new.doc)
(See attached file: NEAT PO_Center 6 Patient 10.pdf) (See attached file: CRF 77_1_c.TIF) (See attached file: NEAT BE_Center 21 Patient 5.pdf)

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
7/12/04 03:50:12 PM
CSO

MEMORANDUM

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

DATE: June 25, 2004

TO: NDA File

FROM: Lisa Basham-Cruz

SUBJECT: **Clinical Requests/Questions Emailed to sponsor 6-14 through 6-17-04**

NDA 21-431, Acamprosate Calcium

The following emails were sent to Lipha on the dates specified at the request of Celia Winchell. Responses were received by email from the sponsor, who then followed up with a submission dated June 18, 2004, summarizing the email interactions initiated by the requests below.

June 14, 2004; 10:13 AM:
Subject: Efficacy analysis of Paille

This is probably in the submission somewhere but can you find out from Lipha how they came up with the efficacy numbers for Paille? I get 20, 20, and 10 completely abstinent and they get 26, 26, and 16. I used "RELFLAGU," I believe, for my analysis. What did they use?

June 14, 2004; 10:14 AM:
Subject: Another one

Is it the case that acamprosate has been on the market since 1989, but Lipha only has pharmacovigilance data since 1995? If so, what is the estimated exposure since 1995? I am seeing the figure [ ]but I think that is since 1989. If we only have pharmacovigilance information since 1995, any sales before then really don't help us much.

June 14, 2004; 10:15 AM:
Subject: More for Lipha

The table of for AE's in Group II Clin Pharm studies (8.8.24.6) includes 1 patient with "exfoliative dermatitis." However, in the discussion of SAE's, only one SAE, a seizure, was identified in Group II. Is there any more information about this case of exfoliative dermatitis?

June 14, 2004; 10:16 AM:
Subject: More on that last question

There is also one "vesicobullous rash." Is that the same patient?

June 14, 2004; 10:16 AM:
Subject: And yet more...

There are eight cases of exfoliative dermatitis and 4 of vesicobullous rash in the tabulation of incidence of adverse events for the Group IV studies. I don't remember seeing all of these in the list of SAEs. Is more information available on these cases?

June 14, 2004; 2:22 PM:
Subject: RE: Response to Paille Question of 6/14/04

I really do not understand this answer at all. I'm going to need someone to talk me through this. I thought they were constructing a variable that represented ALL of the available information--quantity, frequency, family report, labs etc., to assess abstinence. Is all of this taken into account in the variable QUANES1? And what variable should I be using to reconstruct the efficacy results of the other studies, while we're at it?

According to the ISE:
For the Paille study, the following data were used in this amendment to determine the patient's drinking status at each visit: . Blood alcohol; . Number of non-abstinent days since the previous visit; . Quantity of alcohol consumed; and . Relative's evaluation of abstinence. A patient was considered as "not abstinent" at a given visit if:
(1) Blood alcohol > 0.05 g/L; OR
(2) Number of non-abstinent days since the previous visit > 0; OR
(3) Quantity of alcohol consumed > 0; OR
(4) Relative's evaluation of abstinence = one of the following: 1 = has been drinking little and rarely 2 = is drinking less than before the treatment 3 = is drinking as much as or more than before the treatment. A patient was considered as "abstinent" at a given visit if:
(1) Blood alcohol is either missing or ?0.05 g/L; AND
(2) Number of non-abstinent days since the previous visit = 0; AND
(3) Quantity of alcohol consumed = 0; OR one of the values (of number and quantity) = 0 and the other value is missing; AND
(4) Relative's evaluation of abstinence is either missing or = 0 = has not been drinking at all.
A patient's status at a given visit was considered as "unknown" if the patient was not considered "not abstinent" using the algorithm above and:
(1) The number of non-abstinent days since the previous visit is missing; AND
(2) Quantity of alcohol is missing.

June 14, 2004; 5:39 PM:
Subject: RE: Response to Dr. Winchell's questions about Paille efficacy analysis

Thank you for this clarification. Let me probe a little further. It sounds as if the variable QUANES1 does, in fact, attempt to integrate the self-report of quantity/frequency, the family report, and the lab data. However, I need further clarification on the difference between QUANES1 and RELFLAGU, because it

seems to me that a SUBSTANTIAL number of the patients considered abstinent in the QUANES1 field are NOT coded as abstinent in the RELFLAGU field (6/26, 8/28, and 6/16--that's nearly 30%). Could I get a tabulation comparing the classification on these two variables for the 26, 28, and 16 patients who qualify as treatment successes in the QUANES1 field, showing how they are coded in RELFLAGU, and EXPLAINING why those who are coded as RELFLAGU = 1 are so coded, and why it isn't clinically relevant?

Sorry to be so persnickety.

June 16, 2004; 3:44 PM:
Subject: Pialle 448

Can I get more information on patient 448 in study Paille? He withdrew for adverse events including elevated creatinine, but I don't seem to have his creatinine in the database. Is there more follow-up information or anything to determine whether this creatinine elevation was drug-related?

June 17, 2004; 9:48 AM:
Subject: VERY important question

Can Lipha clarify whether the information in the "supplementary visits" files was or was not included in the adverse event database? I am finding people with adverse events described in the comments fields and I am not sure that the information was integrated into the adverse events data. Some hospitalizations and suicides, in fact.

June 17, 2004; 11:28 AM:
Subject: RE: FW: VERY important question

Patient 1500119, Paille 119, comment in PISUPVIS reads "Hospitalization for anxiety and depression and alcoholism (alcoholemia 3.33 gr upon inclusion); Smoking history (44 packs/year); Withdrawal treatment with delirium." No AE with this description is in the dataset. Is this a historical remark, or did it occur during treatment?

Paille 631 has the comment "Suicide attempt with drugs on 11 June 91 (benzodiazepines + alcohol). Was not hospitalized, was not examined." AE dataset documents a suicide attempt but doesn't give a date, and a hospitalization, but because there are no dates I can't tell if this is the same event (suicide attempt and hospitalization) which would make this a DIFFERENT suicide attempt than the one described in PISUPVIS

Pelc 137 has comment "hospitalised" listed in PE_ANCIL but no adverse event involving hospitalization in SS_AEs (only event is abdominal pain).

Just some examples--I haven't had a chance to find them all.

I would appreciate it if Lipha could read through the text in these ancillary/supplementary files and cross-check them with the AE database.

June 14, 2004; 1:48 PM:
Subject: RE: Response: General and two specific examples

It was not my intention to further audit these files if this information is included in the SS_AEs dataset. If you can confirm that all the information on all patients, no matter where it was in the CRF, was included in the integrated dataset, I won't devote more attention to the supplemental/ancillary comment datasets. I would like verification that:
- any adverse events mentioned in the ancillary/supplementary comment fields have been incorporated in the dataset SS_AEs
- any references to drinking/relapse in the ancillary/supplementary comment fields have been taken into consideration in classifying patients as drinking/abstinent.

APPEARS THIS WAY
ON ORIGINAL

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
6/25/04 02:21:12 PM
CSO

6/25/04

MEMORANDUM

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

DATE: June 25, 2004

TO: NDA File

FROM: Lisa Basham-Cruz

SUBJECT: **Clinical Request Emailed to sponsor 6/21/04**

NDA 21-431, Acamprosate Calcium

The following email was sent to Lipha on June 21, 2004 at Celia Winchell's request. Lipha' s response follows.

June 21, 2004; 11:17 AM:
Subject: Acamprosate again

I'm not spotting a section on experience in pregnancy in the ISS, or a section on overdose. Can Dr. Goodman point me to the right place?

RESPONSE: June 21, 2004; 12:07 PM
Subject: Overdose Pregnancy

Dear Lisa:
Dr. Winchell can find an updated section on acamprosate overdose in Volume 2 of the Dec. 19, 2003 NDA Amendment, Pages 43 to 48. There is no specific section devoted to pregnancy. However, in Volume 14 of the Dec. 19, 2003 NDA Amendment, Pages 97 to 99, the available information on pregnancy, obtained from Post-Marketing Pharmacovigilance, is provided. I hope this will be helpful in her review. Best regards, Anita

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
6/25/04 03:17:09 PM
CSO

6/16/04

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information			
NDA 21-431	Efficacy Supplement Type SE-	Supplement Number	
Drug: CAMPRAL (acamprosate calcium) Tablets		Applicant: Lipha Pharmaceuticals, Inc.	
RPM: Lisa Basham-Cruz		HFD-170	Phone # 301-827-7420

Application Type: (X) 505(b)(1) ( ) 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.) **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.** ( ) Confirmed and/or corrected	Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)): RECEIVED AUG 0 2 2004 FDR/CDER

❖ Application Classifications:	
• Review priority	( ) Standard (X) Priority
• Chem class (NDAs only)	1
• Other (e.g., orphan, OTC)	
❖ User Fee Goal Dates	August 4, 2004
❖ Special programs (indicate all that apply)	(X) None Subpart H ( ) 21 CFR 314.510 (accelerated approval) ( ) 21 CFR 314.520 (restricted distribution) ( ) Fast Track ( ) Rolling Review ( ) CMA Pilot 1 ( ) CMA Pilot 2
❖ User Fee Information	
• User Fee	(X) Paid UF ID number
• User Fee waiver	( ) Small business ( ) Public health ( ) Barrier-to-Innovation ( ) Other (specify)
• User Fee exception	( ) Orphan designation ( ) No-fee 505(b)(2) (see NDA Regulatory Filing Review for instructions) ( ) Other (specify)
❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	( ) Yes (X) No

• This application is on the AIP	( ) Yes ( ) No
• Exception for review (Center Director's memo)	
• OC clearance for approval	
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification & certifications from foreign applicants are cosigned by US agent.	(X) Verified
❖ Patent	
• Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	(X) Verified
• Patent certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) ( ) Verified 21 CFR 314.50(i)(1) ( ) (ii) ( ) (iii)
• [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	
• [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next box below (Exclusivity)).*	( ) N/A (no paragraph IV certification) ( ) Verified
• [505(b)(2) applications] For each paragraph IV certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation. Answer the following questions for each paragraph IV certification: (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? (Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))). *If "Yes," skip to question (4) below. If "No," continue with question (2).* (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? *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 (3).* (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?	( ) Yes ( ) No ( ) Yes ( ) No ( ) 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," 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)? *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? (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.*	( ) Yes ( ) No ( ) Yes ( ) No
❖ Exclusivity (approvals only)	
• 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
• 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)*	ADRA review July 20, 2004

General Information	
❖ Actions	
• Proposed action	(X) AP ( ) TA ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)	Not Approvable; June 27, 2002
• 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	( ) None ( ) Press Release (X) 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)	X
• Most recent applicant-proposed labeling	X
• Original applicant-proposed labeling	X
• Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	DMETS 6/15/04
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	NA
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	C & C DR letter 7/14/04
• Applicant proposed	X Response to DR letter 7/20/04
• Reviews	DMETS 6/15/04
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	Yes
• Documentation of discussions and/or agreements relating to post-marketing commitments	Pending
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	X
❖ Memoranda and Telecons	X
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	October 27, 1998
• Pre-NDA meeting (indicate date)	January 27, 2000
• Pre-Approval Safety Conference (indicate date; approvals only)	June 16, 2004
• Other	1st Cycle Post Action Meetings: October 9, 2002 & March 4, 2003
❖ Advisory Committee Meeting	
• Date of Meeting	May 10, 2004
• 48-hour alert	Flash Minutes
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	N/A

Summary Information	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)*	Pending
Clinical Information	
❖ Clinical review(s) *(indicate date for each review)*	7/15/04
❖ Microbiology (efficacy) review(s) *(indicate date for each review)*	NA
❖ Safety Update review(s) *(indicate date or location if incorporated in another review)*	In Clinical Review
❖ 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)	☒ Put into DFS
❖ Demographic Worksheet *(NME approvals only)*	NA
❖ Statistical review(s) *(indicate date for each review)*	7/10/04
❖ Biopharmaceutical review(s) *(indicate date for each review)*	7/13/04
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	6/4/04
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	First Cycle Only
• Bioequivalence studies	No
CMC Information	
❖ CMC review(s) *(indicate date for each review)*	4/20/04
❖ Environmental Assessment	
• Categorical Exclusion *(indicate review date)*	Adequate, See 6/7/02 CMC review
• Review & FONSI *(indicate date of review)*	
• Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Microbiology (validation of sterilization & product sterility) review(s) *(indicate date for each review)*	NA
❖ Facilities inspection (provide EER report)	Date completed: (X) Acceptable ( ) Withhold recommendation
❖ Methods validation	( ) Completed ( ) Requested (X) Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	6/16/04
❖ Nonclinical inspection review summary	NA
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	NA
❖ CAC/ECAC report	Consulted, No formal report

MEMORANDUM OF MEETING MINUTES

MEETING DATE:	June 15, 2004
TIME:	3:30-5 PM
LOCATION:	5600 Fishers Lane; Rockville, MD; Conference Room 17-5X
APPLICATION:	NDA 21-431
DRUG NAME:	Acamprosate Calcium, 333 mg Tablets
TYPE OF MEETING:	Office Level Briefing and Pre-Approval Safety Conference

MEETING CHAIR: Celia Winchell, MD

MEETING RECORDER: Lisa Basham-Cruz, MS

FDA ATTENDEES: (Title and Office/Division)

John Jenkins, MD	Director, Office of New Drugs (OND)
Sandy Kweder, MD	Deputy Director, OND
Robert Meyer, MD	Director, Office of Drug Evaluation II
Bob Rappaport, MD	Director, Division of Anesthetic, Critical Care, and Addiction Drug Products (DACCADP)
Rigoberto Roca, MD	Deputy Director, DACCADP
Eric Duffy, PhD	Director, Division of New Drug Chemistry II (DNDC II)
Celia Winchell, MD	Team Leader, Addiction Drug Products, DACCADP
Ravi Harapanhalli, PhD	Chemistry Team Leader, DACCADP
Dan Mellon, PhD	Supervisory Pharmacologist, DACCADP
Thomas Permutt, PhD	Statistics Team Leader, DACCADP
Suresh Doddapaneni, PhD	Biopharmaceutics Team Leader, DACCADP
David Lewis, PhD	Chemistry Reviewer, DNDC II
Adam Wasserman, PhD	Preclinical Pharmacology Reviewer, DACCADP
Brenda Marques	Division of Drug Marketing and Communications
Lisa Basham-Cruz, MS	Regulatory Project Manager

* The Office of Drug Safety was not represented at the meeting, but requested a copy of the minutes.

BACKGROUND:

The original IND was opened in June, 1996. The company's original intention was to market a 500-mg tablet. The development plan was to conduct a US study of 500 mg bid, and provide additional evidence of safety and efficacy from completed European studies at 1998 mg/day using the 333-mg tablet. The US study, however, failed, so the company decided to seek marketing approval for the 333-mg tablet based on the European studies alone. The NDA was submitted on December 27, 2001. A Psychopharmacologic Drugs Advisory Committee (PDAC) meeting was held on May 1, 2002, to discuss discrepant findings between the US and European studies. The efficacy of the drug was generally accepted by PDAC. The safety review, however, identified extensive deficiencies in safety data precluding the assessment of safety. An inspection by the Division of Scientific Investigation (DSI) identified "sloppiness" at clinical sites, calling into question the validity of both the efficacy and the safety data. A non-approval action was taken on June 27, 2002, requesting an additional efficacy study be performed, the safety data be recoded and reformatted, and pharm/tox deficiencies and CMC deficiencies be

addressed. Post-Action meetings were held on October 9, 2002, and March 4, 2003. The Agency agreed to accept 100% audited data from the pivotal studies, applying "complete abstinence" analysis, in lieu of a new efficacy trial. The response to the Non-approval action was submitted December 19, 2003.

MEETING OBJECTIVES:

To brief the Office of Drug Evaluation II, the Office of New Drugs, and the Office of Drug Safety on the pertinent issues associated with the review of and potential action for acamprosate calcium NDA 21-431.

PRESENTATION SUMMARY: Slides were presented summarizing the key issues for each discipline (attached). The presentation is summarized below, with key issues shown in italics.

Chemistry (slides 9-15):

David Lewis stated that the application is adequate from a chemistry standpoint, pending an outstanding compliance report. *The placement of a sulfite warning on the packaging will be recommended and the nomenclature for the drug product should be CAMPRAL (acamprosate calcium delayed-release tablets).* Post Meeting note: Melbourne site found acceptable on June 24, 2004.

Preclinical Pharmacology/Toxicology (slides 16-27): Adam Wasserman noted that, except for the repeat of the mouse carcinogenicity study requested in the first-cycle action letter, all other studies requested for resolution of outstanding nonclinical issues in the first cycle review were completed satisfactorily. *The sponsor will be required to repeat the mouse carcinogenicity study as a Phase IV Commitment. In addition, the positive teratogenicity observed in several species would require acamprosate to be labeled as Pregnancy Category "C," rather than "[redacted]" as suggested by the sponsor.*

Biopharmaceutics (slides 28-30): Dr. Doddapaneni noted that there are no approvability issues. Use of the drug is contraindicated in the severely renally impaired population. Dr. Meyer expressed concern that, if 10% of the population is alcoholic, then this would not preclude use in people on dialysis. *Dr. Doddapaneni responded that the he will recommend that the Division consider evaluation of the drug in those with severe renal impairment as a Phase 4 commitment.*

Clinical (slides 31-51): Dr. Winchell summarized that the problems with the database appear to have been adequately addressed with the 100% audit of the data. *Substantial changes will be proposed to the package insert, including rewording of the indication and inclusion of a suicide/depression warning.*

DISCUSSION POINTS:

- Dr. Jenkins recommended that Dr. Winchell consult with the Division of Neuropharmocologic Drug Products on the appropriate handling of the suicide/depression data.
- Dr. Kweder recommended that the sponsor further evaluate use of the drug during pregnancy.
- Dr. Meyer noted that approval of acamprosate will be newsworthy, and that the Press Office should be kept informed so that the appropriate communications may be composed.

Minutes Recorder: Lisa Basham-Cruz
Concurrence: Parinda Jani, Celia Winchell, Rigoberto Roca, Bob Rappaport

ATTACHMENTS/HANDOUTS: slides

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/s/

Lisa Basham-Cruz
7/16/04 12:49:00 PM

Office of Drug Safety

MEMO

To: Bob Rappaport, M.D.
Director, Division of Anesthetic, Critical Care, and Addiction Drug Products
HFD-170

From: Jinhee L. Jahng, Pharm.D.
Safety Evaluator, Division of Medication Errors and Technical Support
HFD-420

Through: Alina R. Mahmud, R.P.h.
Team Leader, Division of Medication Errors and Technical Support
HFD-420

Carol Holquist, R.Ph.
Director, Division of Medication Errors and Technical Support
HFD-420

CC: Lisa Basham-Cruz
Project Manager
HFD-170

Date: June 14, 2004

Re: ODS Consult 02-0104-2; Campral (Acamprosate Tablets); NDA 21-431.

This memorandum is in response to a request from the Division of Anesthetic, Critical Care, and Addiction Drug Products (HFD-170) for the Division of Medication Errors and Technical Support (DMETS) review the container labels and carton labeling for Campral. The blister label, container label, carton and insert labeling were reviewed in a previous consult (see ODS consult 02-00104). Campral will be available in bottles of 180 (1 month supply) and 1080 tablets (6 month supply) and in blister packages (Dose Pak) of 60 tablets and in [redacted] sample blister packages of 42 tablets.

DMETS has reviewed the proposed container labels and carton labeling for Campral in an attempt to focus on safety issues to prevent possible medication errors. We have identified the following areas of improvement, in the interest of minimizing potential user error and patient safety.

A. BLISTER LABEL (Blister Foil Label)

1. Professional Sample – Patient Starter Kit

   a. The blister package describes its contents as a [redacted] "Patient Starter Kit", while the package insert describes the contents as a [redacted] Revise content description so that the descriptions are consistent to minimize confusion.

   b. It is unclear whether the blister package is perforated. If the blister card is perforated, DMETS has safety concerns regarding the identification of the tablets should the "card" become separated from the section containing the proprietary name, established name, and strength. Please include the product information (i.e. name, dosage strength, etc.) on the backside of each card.

2. Dose Pak

   See Comment A.1.b.

B. CONTAINER LABEL (Bulk Shipping Labels – 180 and 1080 Tablets)

1. Increase the prominence of the product strength.

2. Relocate the net quantity statement to appear away from the product strength.

C. INSERT LABELING

1. See Comment A.1.b.

2. The descriptor "cards" in the statement "6 x 10 cards" and "6 x 7 cards", leads one to believe that the blister cards supplied by the sponsor can be separated. If this is the case, DMETS recommends that another term is used to describe the perforated subsections.

If you have any questions or need clarification with the recommendations, please contact the project manager, Sammie Beam at 301-827-3242.

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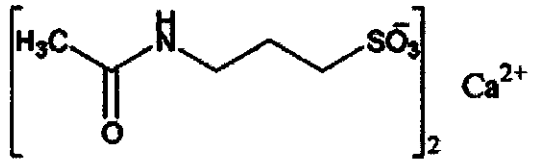
/s/

Jinhee Jahng
6/15/04 01:32:08 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
6/15/04 03:33:21 PM
DRUG SAFETY OFFICE REVIEWER

Acamprosate Calcium - (a kam proe' sate).

Date	[*2002*]
Molecular Info	$C_{10}H_{20}CaN_2O_8S_2$. 400.48.
Chemical Name	[Acamprosate is INN and BAN.] (1) 1-Propanesulfonic acid, 3-(acetylamino)-, calcium salt (2:1); (2) Calcium 3-(acetylamino)propane-1-sulfonate.
CAS Numbers	*CAS-77337-73-6; CAS-77337-76-9* [acamprosate].
Category	*Treatment of alcohol dependency.*
Manufacturer Info	Alcomed (Lipha); Aotal (Lipha); Campral (Lipha); Campral EC (Lipha); Sobriol (Lipha)



MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
CONTROLLED SUBSTANCE STAFF

Date: **June 4, 2004**

To: **Bob Rappaport, M.D., Director**
Division of Anesthetic, Critical Care and Addiction Drug Products
(HFD-170)

Through: **Deborah B. Leiderman, M.D., Director**
Michael Klein, Ph.D., Team Leader
Controlled Substance Staff (HFD-009)

From: **Katherine Bonson, Ph.D., Pharmacologist**
Controlled Substance Staff (HFD-009)

Consult on: **Review of resubmission of abuse liability package and draft labeling for**
Acamprosate
NDA 21-431
Lipha Pharmaceuticals, Inc.

Acamprosate is being developed as a treatment [redacted] This consult assesses the Sponsor's abuse liability package and draft labeling in support of their resubmitted NDA, which follows a Not Approvable action issued June 27, 2002.

I. Background

This consult is a review of the abuse potential of the resubmitted NDA for acamprosate. Acamprosate has been marketed in France since 1989 as a treatment [redacted] It was subsequently approved in 38 additional countries. The Sponsor estimates that [redacted] patients with alcohol dependence have been treated with acamprosate. The recommended therapeutic dose for the present indication is 3 divided doses of 666 mg, for a total daily dose of 1998 mg/day.

Acamprosate (calcium acetylhomotaurine) is a synthetic homologue of the amino acid taurine. Although homotaurine cannot cross the blood brain barrier, acamprosate is able to do so because of modified polarity. Acamprosate has structural similarity to the inhibitory amino acid neurotransmitter GABA, as well as to glycine and the excitatory amino acid neurotransmitters aspartate and glutamate. While acamprosate does not bind to any major central nervous system receptor or transporter, including those in the GABA

system, it does displace GABA from GABA-A and GABA-B receptors and increases GABA transporter sites and affinity. It also antagonizes glutamate and increases glutamate uptake, thus reducing excitatory transmission.

II. Recommendations

* Based on available epidemiological, clinical and preclinical data submitted by the Sponsor, CSS does not find evidence suggesting abuse liability for acamprosate. Thus, CSS does not recommend that acamprosate be scheduled under the Controlled Substances Act, following its approval for marketing

* The label should reflect this recommendation for unscheduled status.

* The assessment of the abuse potential of acamprosate is limited by the lack of a full data package from the COMBINE study that used the Addiction Research Center Inventory, an instrument that measures subjective responses indicative of abuse liability. However, given that the COMBINE study is a safety, efficacy and pharmacokinetic study in treatment-seeking alcoholics, not an abuse liability study with individuals who abuse drugs other than alcohol, the value of the ARCI data may be limited in predicting abuse liability of acamprosate. Additionally, CSS had requested the individual subject data from the COMBINE study, but the Sponsor did not provide these data.

III. Conclusions

* Available epidemiological data from the 39 countries in which acamprosate is currently marketed do not suggest that acamprosate has abuse liability.

* In clinical trials, acamprosate was not associated with symptoms of physical dependence or overdose.

* Subjective information collected from healthy volunteers during pharmacokinetic and dose-tolerance studies using Visual Analog Scales (VAS) related to abuse liability did not produce any data indicative of abuse potential of acamprosate. The VAS measures included assessment of Anxiety, Fatigue, Happiness, Relaxation, Sleepiness, Wooziness, Awkwardness, Fitness, Energy, Sadness and Depression, Alert/Drowsy, Muzzy/ Clearheaded, Tired/Energetic, and Withdrawn/Talkative.

* Pharmacokinetic studies show that acamprosate has a slow rise to peak plasma concentrations (4.5 hr) and a long terminal half-life (5.7 hr). This pharmacokinetic profile is not usually associated with high abuse potential. Oral acamprosate is not metabolized and the absorbed drug is primarily eliminated unchanged in the urine. The oral bioavailability of acamprosate is ~11%.

* Biochemical studies do not show that acamprosate has affinity for or action on central receptor systems implicated in abuse potential.

* Acamprosate does not induce self-administration, sedation, hypnosis, or analgesia in animals. However, it does reduce the hyperactivity induced by known drugs of abuse, suggesting that the drug may modulate the dopamine system. Acamprosate does not affect 5-hydroxytryptamine-induced head twitches, demonstrating it does not act at 5-HT2 receptors.

* Acamprosate does not generalize to the following Schedule II drugs in animal drug discrimination tests: d-amphetamine, phencyclidine (PCP), or pentobarbital. No data were submitted from a benzodiazepine drug discrimination study in rodents, as requested by CSS in February 2002.

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APPENDIX

I. Summaries of NDA Abuse-Related Data Reviewed by HFD-170 Staff

A. Epidemiology

The Sponsor states in the abuse liability narrative that acamprosate is not controlled under either the Single Convention on Narcotic Drugs or the Psychotropic Convention. The narrative also states that "in none of the countries where acamprosate is marketed are there any forms of specific drug abuse scheduling intended." However, no post-marketing data were submitted that support the claim that acamprosate has no abuse liability. In lieu of this lack of information, CSS attempted to obtain information from European drug abuse databases concerning the abuse liability of acamprosate. Databases available on the European Monitoring Centre for Drugs and Drug Addiction <www.emcdda.eu.int> website do not show any signals indicative of acamprosate abuse. However, the available reports do not specifically represent data on every marketed drug, and only discuss trends in drug abuse.

The June 2002 Medical Officer review of the original NDA notes the following epidemiological issues with relevance to an abuse liability assessment:

* Post-marketing adverse events (AEs) related to acamprosate administration were collected from worldwide sources (including case reports in medical databases) during the period September 1989 through July 2001.

* No case reports were found in the medical literature regarding abuse of acamprosate.

* It is difficult to estimate adverse drug reactions associated with acamprosate for the following reasons: there is a long treatment duration; detoxified alcoholics are known for compliance problems; single patients may receive successive courses of treatment which may then be counted as multiple patients; there is known underreporting to AE databases.

* Multiple reports of centrally-mediated AEs in the post-marketing data include: hallucinations, confusion, headache, psychosis, suicide attempts, somnolence, depression, confusion, and dizziness/ataxia. However, this can also be attributable to the use of concomitant medications, as well as to the sequelae of alcoholism or alcohol withdrawal or relapse.

* Multiply-reported and unusual singly-reported AEs in the post-marketing data do not include any terms that directly relate to abuse liability, including those from case reports of massive overdose.

B. Clinical Studies

The Sponsor states in the narrative of the abuse liability submission that no studies that directly evaluate tolerance or physical dependence have been conducted with acamprosate.

Subjective information collected from healthy volunteers during pharmacokinetic and dose-tolerance studies using Visual Analog Scales (VAS) related to abuse liability did not produce any data indicative of abuse potential of acamprosate. The VAS measures included assessment of Anxiety, Fatigue, Happiness, Relaxation, Sleepiness, Wooziness, Awkwardness, Fitness, Energy, Sadness and Depression, Alert/Drowsy, Muzzy/ Clearheaded, Tired/Energetic, and Withdrawn/Talkative.

The June 2002 Medical Officer review of the original NDA notes the following issues with relevance to an abuse liability assessment:

* Less than 1% of patients in the acamprosate clinical studies showed any symptoms of drug dependence or withdrawal. This was not statistically different from the response seen following placebo administration.

* Acamprosate by itself has not been associated with any cases of overdose in clinical trials. In 21 reported cases of overdose, none represented cases in which acamprosate was the only drug ingested. All but one of these cases involved suicide attempts in which other drugs, including alcohol, were consumed.

* Although acamprosate is a calcium salt, in 3 cases in which acamprosate ingestion was 26.6 gm, 28 gm and 30 gm, serum calcium levels were normal.

* The Integrated Summary of Safety does not mention or discuss any issues of relevance to an abuse liability assessment.

C. Clinical Biopharmaceutics and Chemistry Studies (reviews appear in Section II)

The Sponsor refers to 15 clinical pharmacokinetic studies submitted in the original NDA in which subjects received between 333 - 2664 mg acamprosate in oral or intravenous doses, given acutely or subchronically. These doses represent 0.5 to 4 times the recommended therapeutic dose. No adverse events were reported, including any centrally-mediated subjective effects.

The June 2002 Clinical Pharmacologist review of the original NDA notes the following issues with relevance to an abuse liability assessment:

* Peak plasma concentration occurs at ~ 4.5 hr following oral administration of acamprosate, suggesting a slow onset that is not typically associated with abuse liability.

Multiple dosing leads to increases in Cmax and AUC that are less than proportional. Steady-state levels are reached after 5 days of acamprosate administration t.i.d.

* The terminal half-life of acamprosate is reported in a broad range from 3-13.5 hr, with a mean of 5.7 hr.

* Oral acamprosate is not metabolized and the absorbed drug is primarily eliminated unchanged in the urine. The oral bioavailability of acamprosate is ~11%.

D. Preclinical Pharmacology/Toxicology Studies (reviews appear in Section II)

The June 2002 Clinical Pharmacologist review of the original NDA notes the following issue with relevance to an abuse liability assessment:

* Acamprosate's mechanism of action may be through modulation of the NMDA receptor, by acting as a partial co-agonist through allosteric interaction at the polyamine binding site. [This site increases binding at the modulatory glycine site and is not related functionally to the channel site where ketamine and phencyclidine (PCP) act.]

The June 2002 Pharmacologist review of the original NDA notes the following issues with relevance to an abuse liability assessment:

* Acamprosate displaces GABA from GABA-A and GABA-B receptors. It also increases GABA transporter sites and affinity, but reduces the rate of GABA uptake.

* Acamprosate does not displace MK-801 from NMDA channel sites but increases glutamate receptors in the brain.

* Acamprosate has no effect on motor activity or exploratory behavior. Conversely, it antagonizes hyperactivity induced by known drugs of abuse, including amphetamine, chlordiazepoxide and morphine and it reduces amphetamine-associated mortality. This suggests that acamprosate has dopamine antagonist activity. However, there were no interactive effects between acamprosate and the anti-dopaminergic antipsychotics, haloperidol, sulpiride or chlorpromazine.

* Acamprosate does not induce sedative, hypnotic, anxiolytic or muscle relaxation effects.

* Acamprosate has no effect on blood pressure and heart rate.

E. Preclinical Abuse Potential Studies

After review of studies with relevance to abuse potential that were submitted by the Sponsor, CSS has the following conclusions:

* Acamprosate does not have high affinity for DA, NE, 5-HT, GABA, NMDA, glycine, muscarinic or opioid receptors/transporters that are associated with abuse liability. However, acamprosate does produce 84% inhibition of control specific binding for the norepinephrine transporter, activation or blockade of which is not known to be associated with abuse potential.

* Monkeys do not self-administer acamprosate.

* In animals trained to discriminate pentobarbital, d-amphetamine or phencyclidine (PCP) from saline, there is no generalization between acamprosate and any of these 3 training drugs. However, no data have yet been submitted from a benzodiazepine drug discrimination study in rodents, as requested by CSS in February 2002.

* Acamprosate does not produce significant analgesia compared to saline, using morphine as a positive control. However, acamprosate was given via an oral (slower) route and morphine was given via an intraperitoneal (faster) route of administration.

* Acamprosate does not antagonize or potentiate 5-HTP-induced head twitches. However, acamprosate was not tested for its ability to induce head twitches by itself.

* Plasma levels produced by the doses selected for the animal studies are not correlated to plasma levels of acamprosate produced by therapeutic doses in humans. Abuse potential cannot be assessed by animal doses of the drug that produce plasma levels that are much lower than those produced in humans by therapeutic or supratherapeutic doses Thus, it is difficult to interpret whether the studies are valid in predicting the human abuse potential of acamprosate.

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II. Reviewed Clinical and Preclinical Studies Related to Abuse Potential

A. Clinical Behavioral Pharmacology

COMBINE Pilot Study #1

The purpose of this study was to evaluate safety, efficacy and pharmacokinetics. This is not an abuse liability study, although it utilizes some instruments that measure subjective responses indicative of abuse liability. However, the subjects were treatment-seeking alcoholics, who may or may not have had experience with other drugs of abuse, which may limit the usefulness of the data in assessing abuse potential. The Sponsor submitted only summaries of the data in narrative form and has not submitted primary data.

The study design was double-blind, double-dummy, placebo-controlled, randomized, 23-day, and 4-way crossover. Twenty-three individuals who were non-treatment seeking for their alcohol dependence served as subjects, assigned to 4 groups. There were 4 phases:

Phase 1: placebo washout

Phase 2: administration of acamprosate (2 or 3 g/day) or naltrexone (50 or 100 mg/day)

Phases 3 and 4: continuation of drug received in phase 2, plus low or high dose of the other drug to test the combination

A variety of subjective and psychomotor measures were used, including the Addiction Research Center Inventory (ARCI), Visual Analog Scales (VAS) questions related to abuse liability, the Profile of Mood States (POMS), the Rapid Visual Information Processing Task (RVIPT), the Digit Symbol Substitution Task (DSST), and the Hopkins Verbal Learning Test (HVLT).

Additionally, blood and urine were monitored for changes in urea, drug screens, pharmacokinetic parameters, as well as liver and renal functions. Gastrointestinal function and neurological function were assessed, as were all adverse events. Physiological safety measures included EKG, blood pressure and heart rate. Subjects were monitored for signs of alcohol and opioid withdrawal.

The Sponsor does not submit any data for the subjective measures. Instead, the Sponsor states that there were no changes in these measures that "met criteria for significant pathological change". However, in the Statistical Analysis section of the report, the Sponsor states that the criteria for behavioral or performance toxicity for the ARCI and POMS were a greater than two-fold change/subject in more than 3 subjects averaged over the study phase in total or factor scores. For the VAS, toxicity was defined as a two-fold change from baseline and the difference in score exceeded 5 mm. For the RVIPT, DSST and HVLT, toxicity was defined as a greater than 2 standard deviation change in score from baseline criterion scores. These criteria for significance are inadequate.

Significance should be assessed through statistical analysis comparing baseline to final score on each measure, using a p value of < 0.05.

Thus, the submitted materials from the COMBINE study are inadequate for evaluation of the subjective and psychomotor data.

"Jaillon" Study:
Clinical Tolerance Study of Intravenous Acamprosate in Healthy Volunteers

The primary purpose of this study was to evaluate the pharmacokinetics of acamprosate at 10, 20 and 30 mg/kg (equivalent to ~700, ~1400 and ~2100 mg/person), using a double-blind, randomized, placebo-controlled crossover design. Twelve healthy adults served as subjects. Physiological safety data were collected, including heart rate, blood pressure, and ECG.

Although this is not an abuse liability study, subjects also provided information on Visual Analog Scales for the following subjective measures that may be indicative of abuse liability: Anxiety, Fatigue, Happiness, Relaxation, Sleepiness, Wooziness, Awkwardness, Fitness, Energy, Sadness and Depression at baseline, 2 hr, and 8 hr after drug administration. However, the subjects in this study were healthy individuals without histories of drug abuse, which may limit the usefulness of the data in assessing abuse potential compared to data collected from drug abusers.

The Sponsor submitted primary data for all subjective measures. Two or three of the twelve subjects reported VAS change scores of greater than 2.0 for several of the scales for each of the three doses of acamprosate tested. However, there was no consistency in these responses across subjects for any particular scale and the overall mean for all subjects did not show a significant change.

Thus, acamprosate does not appear to be inducing any psychic changes that would be indicative of abuse potential.

"Dewland I" Study
A Rising Dose Tolerance Study of Acamprosate Following Single and Multiple Oral Doses to Adult, Healthy Volunteers

The primary purpose of this study was to evaluate the pharmacokinetics and dose tolerance of acamprosate at doses above 1332 mg/day, using a double-blind, placebo-controlled, ascending dose design. Eighteen healthy males served as subjects, divided into two groups. In Group A, 6 subjects received 666 mg of acamprosate orally and subsequent oral acamprosate doses of 1998 mg, with the 3 remaining subjects receiving placebo. In Group B, 6 subjects received 1332 mg acamprosate orally and subsequent acamprosate doses of 2664 mg, with the 3 remaining subjects receiving placebo. A single dose was given on Day 1, two doses on Days 2-6 and a single dose on Day 7. The total daily doses from Days 2-6 were: 1332 mg, 2664 mg, 3996 mg and 5328 mg. Physiological safety data were collected, including heart rate, blood pressure, and ECG.

Although this is not an abuse liability study, subjects also provided information on Visual Analog Scales for the following subjective measures that may be indicative of abuse liability: Alert/Drowsy, Muzzy/Clearheaded, Tired/Energetic, Withdrawn/Talkative on Days 1 and 7 at baseline, 0.5, 1, 2, 3, 4, 5, 7, 9 and 24 hr after acamprosate or placebo administration. However, the subjects in this study were healthy individuals without histories of drug abuse, which may limit the usefulness of the data in assessing abuse potential compared to data collected from drug abusers.

The Sponsor submitted primary data for all subjective measures. There were no consistent significant changes in VAS scores across doses or subjects compared to placebo. Thus, acamprosate does not appear to be inducing any psychic changes that would be indicative of abuse potential.

B. Preclinical Behavioral Pharmacology

* In the April 2003 consult from CSS to HFD-170, CSS responded to the Sponsor's statement that primary data from the morphine self-administration study and from the drug discrimination studies with pentobarbital and amphetamine were unavailable because they were generated in 1987 and the investigators have subsequently left their original institutions. In lieu of primary data, the Sponsor submitted the final study report with summarized data. These data were accepted by CSS as adequate to demonstrate that monkeys do not self-administer acamprosate and that there is no generalization between acamprosate and pentobarbital or d-amphetamine.

Reference 37:
Study D02.114/4
Interaction between acamprosate and morphine in the hot plate test in the mouse

Male mice were used to assess the ability of morphine and acamprosate to produce analgesia in the hot plate test, either alone or in combination. Notably, morphine (4 or 8 mg/kg) was given intraperitoneally, while acamprosate (200 and 400 mg) was given orally. Animals were all tested 30 min after drug administration, despite the use of two routes of administration (p.o., which produces a slower onset vs. i.p., which produces a faster onset). Thus, it is not possible to compare the two drugs for their ability to produce analgesia.

Primary data were submitted. Morphine at 8 mg/kg produced a statistically significant increase in foot-licking latency, while the 4 mg/kg dose did not. Acamprosate did not produce a statistically significant increase in foot-licking latency at either dose tested.

However, no information is provided about how the acamprosate doses were chosen. In the June 2002 NDA deficiency letter, CSS conveyed the following to the Sponsor:

> *Doses of acamprosate to be used in behavioral studies should represent plasma levels of drug that are within the range of plasma levels of drug that will be seen*

clinically, as well as plasma levels that are 2-3 times greater than therapeutic levels, if this can be done safely.

Thus, the lack of information about plasma levels and how they relate to the doses selected for the hot plate test makes it difficult to interpret this study in terms of the ability of acamprosate to produce analgesia in comparison to morphine.

Reference 39:
Study D02.116/4
Acamprosate evaluation in the 5-hydroxytryptophan (5-HTP) antagonism test (head twitches) in the mouse

Mice were injected with 5-HTP (400 mg/kg, i.p.) and observed 30 min later for head twitches over a 10 min period. The 5-HT2 antagonist cyproheptadine (16 mg/kg, p.o.) was used as a positive control that is known to antagonize 5-HTP head twitches.

Acamprosate (200 and 400 mg/kg, p.o.) was evaluated for its ability to antagonize the head twitch response from 5-HTP, using a 60 min pretreatment time prior to 5-HTP administration. Acamprosate was not tested for its ability to produce head twitches by itself.

Cyproheptadine significantly reduced 5-HTP-induced head twitches, but acamprosate at either dose did not. The report notes that 1 of 10 animals in the cyproheptadine/5-HTP group died, and that the 400 mg/kg dose of acamprosate in combination with 5-HTP produced sedation in 3 of 10 animals.

These data demonstrate that acamprosate does not have 5-HT2 antagonist properties, but they did not test any other serotonergic function.

Reference 42:
Study D02.115/4
Acamprosate evaluation in the 5-HTP potentiation test (head twitches) in the mouse

Mice were injected with 5-HTP (25 mg/kg, s.c.) and observed 30 min later for head twitches over a 10 min period. The MAO inhibitor nialamide (16 mg/kg, p.o.) was used as a positive control that is known to potentiate 5-HTP head twitches.

Acamprosate (200 and 400 mg/kg, p.o.) was evaluated for its ability to potentiate the head twitch response from 5-HTP, using a 60 min pretreatment time prior to 5-HTP administration. Acamprosate was not tested for its ability to produce head twitches by itself.

Nialamide significantly potentiated 5-HTP-induced head twitches, but acamprosate at either dose did not. The report notes that 1 of 10 animals in the cyproheptadine/5-HTP group died, and that the 400 mg/kg dose of acamprosate in combination with 5-HTP produced sedation in 3 of 10 animals.

These data demonstrate that acamprosate does not have the ability to potentiate a 5-HT2-mediated behavior, but they did not test any other serotonergic function.

Reference 56:
Drug discrimination testing of acamprosate in PCP-trained rats

Rats were trained to discriminate 2 mg/kg PCP (i.p.) from saline. Once rats were fully trained, they were tested with a range of PCP doses. Doses of PCP at 2, 4 and 8 mg/kg produced full generalization (defined as 80% of responses on drug lever), but reduced response rate to nearly zero at the highest dose tested. Doses of 0.5-1.0 mg/kg produced low partial generalization.

Acamprosate was then tested for its ability to produce generalization to the PCP cue. Doses of acamprosate from 30-560 mg/kg did not produce generalization different from that of saline. A rationale is provided for the selection of the acamprosate doses, based on plasma levels produced by the doses that are greatly in excess of those produced in humans by therapeutic doses. These data demonstrate that acamprosate does not produce an interoceptive cue that is similar to that of PCP.

C. Preclinical Pharmacokinetics

Reference 58:
Study 57709
GC-MS determination of acetylhomotaurine (acamprosate) in rat plasma samples

The plasma levels of acamprosate were assayed, using two sets of samples: 1) samples from rats that had received a single 100 mg/kg (i.p.) dose of acamprosate and 2) samples from rats that had received a single dose of acamprosate at 30, 100 or 560 mg/kg (i.p.). Calibration standards of acamprosate were also assayed to construct a standard curve.

In Sample Set #1, 3-4 samples were assayed at each time point (5, 10, 15, 20, 30 and 60 min). It is unclear from the data provided for Sample Set #2 when the samples were collected during the study.

The data are not averaged across samples, and there is no comparison between the two groups in terms of the 100 mg/kg dose. This is probably because there is no time frame given for the second set of samples that would allow comparison.

Additionally, no comparison to plasma levels resulting from human therapeutic doses are given that would allow an estimation of appropriate animal doses that should be used for behavioral studies.

D. Biochemical Pharmacology

Reference 4:
Study #892058
In vitro pharmacology study of acamprosate and calcium chloride

Acamprosate (and calcium chloride) were assayed for their binding affinity for DA, NE, 5-HT, GABA, and NMDA sites (including receptor subtypes and transporters). (Note that while no assays were conducted for opioid or acetylcholine receptor subtypes in this study, these assays were conducted in the study reviewed immediately below (Reference 22).)

Assay methodologies were based on published studies, using site-appropriate tissue from animal sources and appropriate radioligands and untagged ligands.

Individual data were submitted for each of the biochemical assays. Acamprosate does not have high affinity for DA, NE, 5-HT, GABA or NMDA receptors or transporters that are associated with abuse liability. However, 100 uM acamprosate does produce 84% inhibition of control specific binding for the norepinephrine transporter, a site not associated with abuse potential.

Reference 22:
Study 892060
In vitro pharmacology study of acamprosate and calcium chloride

Acamprosate (and calcium chloride) were assayed for their binding affinity for glycine, muscarinic and opioid receptor subtypes. Assay methodologies were based on published studies, using site-appropriate tissue from animal sources and appropriate radioligands and untagged ligands. Individual data were submitted for each of the biochemical assays.

Acamprosate does not have high affinity for glycine, muscarinic and opioid receptor subtypes.

Note that no binding studies were done to assess the ability of acamprosate to bind to nicotinergic acetylcholine receptors in either this binding study or the previous one.

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/s/

Katherine Bonson
6/4/04 12:09:56 PM
PHARMACOLOGIST

Michael Klein
6/4/04 12:14:02 PM
CHEMIST

MEMORANDUM

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

DATE: June 2, 2004

TO: File

FROM: Lisa Basham-Cruz

SUBJECT: **Clinical Info request**
NDA 21-431, Campral (acamprosate)

I emailed the following information request from Dr. Winchell to the sponsor on June 2, 2004:

> Could I get a tabulation similar to In-Text Table 8.8.7.2.5:1 but where the numerator is the number of patients with a severe/moderate/mild event and the denominator (for calculating percentage) is the number of patients who reported that event? I want to see for these terms how the frequencies break out. I'd like to see this for the terms that made the list in text table 8.8.7.1.3:1.
>
> Provide a summary table identifying the numbers of patients exposed to test drug who had baseline laboratory values and follow-up assessments, for each analyte.
>
> Why are only 4 of the studies included in the analysis of clinically significant abnormalities in clinical chemistry?
>
> Is there a shift table for hematology anywhere?
>
> In looking at the SAE tables, when I select all the rows where TESAE = 1, I get 624 events, which boils down to 594 when I eliminate duplicates of the same term within the same patient. However, if I add up the numerators across the in-text tables of SAE's, there are only 564 events. Is there an explanation for this? I got the right NUMBER of events when I used ANYTESAE = 1, but I didn't get all the right EVENTS.
>
> I have a table from the first cycle review, showing the international marketing status of acamprosate as of 11/01, which lists 39 countries, and now the submission says the product is marketed in 31 countries. Has it not been launched in some countries, or has it been withdrawn in any country?

If there are any changes from what was in-text table 3.3.1 of the original submission, I need an updated version of this table in electronic format.

In study APDT, how many of the 49 patients were assigned to each treatment arm? This study adds two more events of a suicidal nature to the controlled database and I need the proper numbers to add to the denominators.

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/s/

Lisa Basham-Cruz
6/2/04 04:46:49 PM
CSO

Please note our new address and telephone/fax information, as follows:
10 Derby Square
Salem, Massachusetts 01970
Telephone: 978-542-1904 Fax: 978-542-1950

LIPHA PHARMACEUTICALS INC
AN ASSOCIATE OF MERCK KGaA, DARMSTADT, GERMANY
1114 Avenue of the Americas • 41st floor • New York, NY 10036-7703
TEL: 212-398-4602 • FAX 212-398-5026

VIA Federal Express **April 29, 2004**

Food and Drug Administration
Center for Drug Evaluation and Research, HFD-170, Room 9B45
5600 Fishers Lane
Rockville, MD 20857

Attention: Bob Rappaport, M.D., Director
Division of Anesthetic, Critical Care, and Addiction Drug Products

Reference: Acamprosate Tablets, NDA #21-431,
Amendment #040
Revised Label Mock-ups and Revised Package Insert

Dear Dr. Rappaport:

Reference is made to New Drug Application #21-431 for acamprosate tablets. Reference is also made to Amendment #017 (**April 24, 2002**), which the current amendment supercedes.

We are enclosing updated color copies each of the product packaging and labeling for Campral™ as follows:

Attachment #1. Patient Starter Kit

Attachment #2. Dose Pak

Attachment #3. Bottle Label (1,080 tablet count)

Attachment #4. Bottle Label (180 tablet count).

We are also including, as **Attachment #5** to this letter, the current version of the acamprosate package insert with the name "Campral" substituted for "Tradename" and with a revised "How Supplied" section, reflecting the changes recommended by the Division in a telephone conference with Ms. Lisa Basham Cruz on April 14, 2004.

If there are any questions concerning this submission, please do not hesitate to contact us at 978-542-1904.

With best regards,

Sincerely,
LIPHA PHARMACEUTICALS, INC.

Anita M. Goodman, M.D.
Executive Vice-President and
Chief Operating Officer

Enclosed: Original, duplicate and 3 desk copies for Ms. Lisa Basham-Cruz

2 pages redacted from this section of the approval package consisted of draft labeling

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

4/20/04

DR

NDA 21-431

Lipha Pharmaceuticals Inc.
10 Derby Square
Salem, MA 01970

Attention: Anita M. Goodman, M.D.
Executive Vice President, Chief Operating Officer

Dear Dr. Goodman:

Please refer to your December 21, 2001 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Campral (acamprosate calcium) Tablets.

Our review of the Chemistry, Manufacturing, and Controls section of your submission is complete and we have identified the following deficiencies:

1. The acceptance criterion of acamprosate calcium release at [ ] should be further tightened. The proposed criterion of NMT [ ] is not supported by the supplied data. Provide the LOD and LOQ (limits of detection and quantitation) for determining acamprosate sodium in acid medium. Utilizing the available analytical data for acamprosate calcium release in acid medium, calculate the mean and standard deviation for acamprosate calcium release. All values listed as "not detected" should be treated as the LOD concentrations (*e.g.*, if the LOD was determined to be 0.1%, all values listed as "not detected" should be entered into the calculations as 0.1%). The acceptance criterion for acamprosate calcium release [ ] should be based on statistical analysis of the accumulated dissolution data (*i.e.*, mean plus three sigma).

2. Provide updated stability data for the primary stability batches 1500, 1501, and 1502 in support of the proposed 36-month expiration dating period.

We are providing these comments to you before we complete our review of the entire application to give you preliminary montice 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}

/S/

Ravi Harapanhalli, PhD
Chemistry Team Leader
Division of Anesthetic, Critical Care, and
Addiction Drug Products
DNDC II; Office of New Drug Chemistry
Center for Drug Evaluation and Research

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/s/

Ravi Harapanhalli
4/20/04 04:47:46 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-431

4/13/04

Lipha Pharmaceuticals Inc.
10 Derby Square
Salem, MA 01970

Attention: Anita M. Goodman, M.D.
Executive Vice President, Chief Operating Officer

Dear Dr. Goodman:

Please refer to your December 21, 2001 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Campral (acamprosate calcium) Tablets.

We also refer to your submission dated September 11, 2003.

We have completed our review of the suggested tradename Campral and we find it acceptable at this time. This tradename will be reevaluated approximately 90 days prior to the action date to rule out any objections based upon approval of other proprietary/established names from this date forward.

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
Chief, Project Management Staff
Division of Anesthetic, Critical Care, and
Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Parinda Jani
4/13/04 10:12:05 AM

Office of Drug Safety

Memo

To: Bob Rappaport, MD
Director, Division of Anesthetic, Critical Care, and Addiction Drug Products
HFD-170

From: Charlie Hoppes, R.Ph., M.P.H.
Safety Evaluator, Division of Medication Errors and Technical Support
HFD-420

Through: Alina Mahmud, R.Ph.
Team Leader, Division of Medication Errors and Technical Support
HFD-420

Carol Holquist, R.Ph.
Deputy Director, Division of Medication Errors and Technical Support
HFD-420

CC: Lisa Basham-Cruz
Project Manager, Division of Anesthetic, Critical Care, and Addiction Drug Products
HFD-170

Date: March 15, 2004

Re: ODS Consult 02-0104-1; Campral (Acamprosate Tablets), 333 mg; NDA 21-431.

This memorandum is in response to a September 11, 2003, request from your Division for a re-review of the proprietary name, Campral. In our last review, dated June 11, 2002, (ODS Consult #02-0104), DMETS had no objections to the use of the proprietary name, Campral.

DMETS has not identified any additional proprietary or established names that have the potential for confusion with Campral since we conducted our initial review on June 11, 2002. Therefore, we have no objections to the use of this proprietary name.

DMETS considers this a final review. However, if the approval of the NDA is delayed beyond 90 days from the date of this review, the name must be re-evaluated. A re-review of the name before NDA approval will rule out any objections based upon approvals of other proprietary/established names from this date forward.

If you have any questions or need clarification, please contact the medication errors project manager, Sammie Beam at 301-827-3242.

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/s/

Charles Hoppes
3/19/04 07:12:05 AM
DRUG SAFETY OFFICE REVIEWER

Alina Mahmud
3/19/04 02:05:13 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
3/19/04 03:19:34 PM
DRUG SAFETY OFFICE REVIEWER

5/02

3 PAGES REMOVED. SEE THE ADVISORY COMMITTEE MEETING INFORMATION LOCATED ON THE FDA WEBSITE BELOW:

http://www.fda.gov/ohrms/dockets/ac/

[FLASH MINUTES]

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-431

3/4/04

Lipha Pharmaceuticals, Inc.
10 Derby Square
Salem, MA 01970

Attention: Anita M. Goodman, MD
Executive Vice-President and COO

Dear Dr. Goodman:

We acknowledge receipt on February 4, 2004, of your February 3, 2004, resubmission to your new drug application for Acamprosate Tablets.

We consider this a complete, class 2 response to our June 27, 2002, action letter. Therefore, the user fee goal date is August 4, 2004.

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 acknowledge receipt of your request for a waiver of pediatric studies in children from 0 through 11 years of age. We are granting a waiver for studies in that age group for this application. We also acknowledge your request for a deferral of pediatric studies in children from 12 through [illegible] years of age. We defer the pediatric study requirement for that age group for this application until August 4, 2009, at which time, completed study reports must be submitted to the Agency. However, this date may be amended as necessary in relation to the actual approval date of the application.

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

Sincerely,

{See appended electronic signature page}

/S/

Lisa 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

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/s/

Lisa Basham-Cruz
3/4/04 12:09:08 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-431

1/26/04

Lipha Pharmaceuticals, Inc.
10 Derby Square
Salem, MA 01970

Attention: Anita Goodman, MD
COO & Vice President

Dear Dr. Goodman:

We acknowledge receipt on December 19, 2003, of your December 19, 2003, submission to your new drug application (NDA) for Acamprosate Tablets.

We do not consider this a complete response to our June 27, 2002, action letter. Therefore, the review clock will not start until we receive a complete response. The following deficiencies still need to be addressed:

1. Provide a single, comprehensive Table of Contents for the submission, providing volume and page location for document sections, tables, and figures, down to the level of fifth-level subheadings (e.g. section 8.7.11.2.1).

2. Provide reviewer guidance to substantive changes listed among the edits made during the database audit of Studies PRAMA, Paille, and Pelc-II (section 8.7.11.2).

3. Provide additional information on subjects for whom the text in the Case Report Form raises the possibility of suicide, but for whom the narrative does not list suicide as an adverse event, or states that suicide has been ruled out.

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 June 27, 2002, for the pediatric study requirement for this application for patients under 12 years of age. We also reference the deferral granted on June 27, 2002, for the pediatric study requirement for this application for patients 12- years of age until two years following the ultimate approval of this product.

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

Sincerely,

{See appended electronic signature page}

/S/

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

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/s/

Lisa Basham-Cruz
1/26/04 01:25:23 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-431

8/5/03

Lipha Pharmaceuticals Inc.
10 Derby Square
Salem, MA 01970

Attention: Anita M. Goodman, M.D.
Executive Vice President, Chief Operating Officer

Dear Dr. Goodman:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Acamprosate Tablets.

We also refer to your May 22, 2003 submission, containing your rationale for not repeating the carcinogenicity study in mice, as requested in our June 27, 2002, not approvable letter.

We have performed a preliminary review of the referenced material and have the following comments.

A definitive determination regarding your response concerning the adequacy of the mouse carcinogenicity study will be made following formal review of the two recently conducted *in vitro* genetic toxicology studies, the 28-day mouse toxicokinetic study and the supporting Expert Report (with references). The issues in question will be presented to CDER's Executive Carcinogenicity Assessment Committee for recommendations once this review has been completed. This review will be conducted in as timely a fashion as is possible in conjunction with other Division priorities.

Should the issues related to adequate evaluation of tissue histopathology from the low- and mid-dose groups and nematode infestation be resolved, the inadequacy of the dosing is likely to remain of concern as the maximum tolerated dose was not achieved and kinetic comparisons between mice and humans indicate that the highest administered dose in the mouse carcinogenicity study provided only a 3- to 6-fold mouse:human exposure ratio. Of note, dosing based upon systemic exposure criteria should achieve at least a 25-fold animal:human exposure ratio as per ICH recommendations. Additionally, protein binding and metabolism data in mice should be available to adequately determine systemic exposure ratios.

Should the previously conducted mouse carcinogenicity study be deemed an inadequate assessment of the carcinogenic potential of acamprosate, a decision to accept a second study in mice as a condition for approval or as a post-approval commitment will be made by the Division.

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

Sincerely,

{See appended electronic signature page}

Bob Rappaport, M.D.
Acting Director
Division of Anesthetic, Critical Care, and
Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Bob Rappaport
8/5/03 06:10:47 PM

3/21/03

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-431

Lipha Pharmaceuticals, Inc.
10 Derby Square
Salem, MA 01970

Attention: Anita Goodman, MD
Executive Vice President and Chief Operating Officer

Dear Dr. Goodman:

Please refer to the meeting between representatives of your firm and FDA on March 4, 2003. The purpose of the meeting was to discuss your plan for data validation, quality assurance and re-analysis of your Phase 3 clinical trials for resubmission of your NDA for acamprosate tablets.

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

Also enclosed are the reviewer notes that you requested during the meeting. Understand that some of these discrepancies may have been included in the action letter or may already have been addressed. Furthermore, some of the discrepancies noted may be based on misunderstandings due to the manner in which the data was presented. The inclusion of these notes are intended only as an aid to assist you in your reconstruction of the datasets for resubmission.

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

Enclosure

SPONSOR MEETING ATTENDEES

Meeting Date: March 4, 2003

Location: Parklawn Building, Conference Room 17-05(1:30-3:00pm)

IND/ Name: NDA 21-431 (Acamprosate)

Sponsor: Lipha Pharmaceuticals, Inc.

Type of Meeting: 2nd Post Action Meeting

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

Lipha	Title
Anita Goodman, MD	Executive VP & COO
Bruce Goddard, RAC	Sr. Director of Regulatory Affairs
Sylvie Chabac, MD	International Product Manager
[redacted]	
[redacted]	
Robert Ashworth, PhD	Senior Director, Regulatory Affairs
Robert Jackson	Project Manager, Forest Laboratories
FDA HFD-170	**Title**
Bob Meyer, M.D.	Director, ODE II
Bob Rappaport, MD	Acting Division Director
Celia Winchell, MD	Team Leader, Addiction Drug Products
S. Edward Nevius, PhD	Director, Division of Biometrics II
Tom Permutt, PhD	Mathematical Statistician, Team Leader
Sue Jane Wang, PhD	Sr. Mathematical Statistician
Mwango Kashoki, MD	Medical Reviewer
Lisa Basham-Cruz, MS	Regulatory Project Manager

Meeting Minutes:

Following introductions, the discussion moved straight to the questions presented by the sponsor in their February 12, 2003, meeting package.

Note: The sponsor's questions are presented below in bolded text. Agency responses, prepared prior to the meeting and presented on slides are shown in italics. Discussion is presented in normal text.

Question 1. Does the Division agree with the proposed methodology described in the proposed Data Validation and Quality Assurance Plan?

- *The proposed re-audit of CRFs against electronic datasets appears suitable and should include both efficacy and safety variable.*

Question 2. Does the Division agree that the appropriate primary endpoint is the rate of complete abstinence?

- *The rate of complete abstinence is an appropriate primary endpoint.*

Other Comments re: Efficacy Analyses

- *The plan to report the "abstinence rate at each visit...to illustrate the evolution of this outcome over the course of the study" is unclear, as these rates will include different subjects at different times.*

- *The use of CCAD and survival analyses as secondary endpoints is the sponsor's option, but inclusion in labeling is not envisioned.*

- *Consideration should be given to the use of a term other than "corrected cumulative abstinence duration" if the variable calculated is a percent rather than a number of days (a duration).*

Question 3. Will a reanalysis, as proposed in this document and using this primary endpoint, which demonstrates a statistically significant treatment difference between acamprosate (1998 mg/day) and placebo, be sufficient for approval?

- *We are willing to reconsider the data from the original application, with new analyses and new assurances about the integrity of the data. We are mindful of the advisory committee's provisional recommendation of a favorable finding on efficacy, unless problems arose later in the review. The most important problems that did arise related to data quality, so that results from an audited database might lead to different conclusions.*

  This question subsumes five issues:

1. *Will an audit and regeneration of the datasets for the already-submitted studies, with reanalysis, suffice for filing, in lieu of the requested additional efficacy study?*
2. *Can a two-way comparison between acamprosate 1998 mg/day vs placebo be substituted for the protocol-specified comparisons?*
3. *Are the proposed definitions of abstinence acceptable?*
4. *Is the primary analysis (complete abstinence, with dropouts treated as failures) acceptable?*
5. *Will a statistically significant p-value guarantee an approval decision?*

There was some discussion of the definition of abstinence. Dr. Winchell inquired about the inconsistencies allowed between an investigator's note of abstinence and laboratory values. The Sponsor explained that the MCD and GDT values may not change as rapidly as behavior changes, therefore, that discrepancy is allowed, but no other discrepancies, i.e., breathalyzer, urinalysis, etc. Dr. Winchell encouraged the sponsor to consider accepting an abstinence report only if it is fully supported by laboratory values or to analyze the data with both definitions of abstinence. The sponsor understood, in principle, the Division's position, but expressed concern over issues of multiplicity. Dr. Winchell asked the Sponsor to let the Division know how many subjects fall into this category of conflicting data.

- *A reanalysis of fully audited, revised datasets for the existing trials will be acceptable for filing in lieu of the requested additional study.*

- *A two-way comparison between acamprosate 1998 mg/day vs placebo is clearly relevant to the proposed labeling, but it is still post hoc, so that the issue of multiple comparisons still needs to be dealt with. It will be necessary to clarify how subjects treated with 1332 mg/day (or subjects <60 kg treated with placebo) will be handled in the PRAMA data.*

- *The definition of abstinence in the PRAMA study should not include subjects for whom the investigator feels the subject is abstinent "although not all the findings above support this"; otherwise, the definitions proposed are acceptable.*

- *The primary analysis proposed (complete abstinence with dropouts treated as failures) is acceptable.*

- *The division cannot guarantee that "a statistically significant treatment difference between acamprosate (1998 mg/day) and placebo [will] be sufficient for approval." Evaluation of statistical significance is only a part of the review of clinical trial data.*

- *Although we are primarily interested in the rate of complete abstinence, it cannot properly be termed a "primary endpoint," and we will remain interested in whether other analyses support the conclusion of efficacy.*

- *If questions remain, on review, concerning whether the studies submitted can be considered adequate and well-controlled, or whether the data are reliable, this will affect the decision regarding the application.*

Dr. Permutt commented on simplifying the acceptability of a study to statistical significance, saying there are bigger issues to contend with. One must keep in mind that this is an old study, reanalyzed. Therefore, one cannot discuss a primary endpoint in the same sense as one does when the primary endpoint is defined prior to conducting a study. Issues of multiplicity must be dealt with. The Sponsor must provide a reasoned argument about what data from all the various endpoints are telling us. The Sponsor replied that, although the Division has issues with the primary endpoints selected, i.e., time to first drink, and CCAD, the data is all going in the direction of significance. Dr. Permutt responded that that information should be included as part of the argument, e.g., expressing the results as original primary endpoints and reevaluated primary endpoints.

The Sponsor proposed a summary statement of the Division's opinion of their resubmission approach: "The approach seems reasonable, but you reserve all of your review rights as you would with any other application." Dr. Winchell agreed with the basic concept of this statement.

Question 4. Does the Division agree that the proposals contained herein for revision to the safety data presentation in NDA 21-431 are sufficient to address the Division's concerns regarding the collection and presentation of safety data for acamprosate?

- *The proposal to construct a new integrated summary of safety with accompanying data tables is in general appropriate*

Specific Comments on ISS Proposal

- *Hospitalizations for alcoholism treatment may (and should) be reported separately from other hospitalizations.*

- *An appropriate term for intoxication/relapse to alcohol use should be proposed* (rather than alcohol intolerance).

- *Narratives and CRFs for both related and "unrelated" SAEs from non-Group I studies should be submitted.*

The Sponsor stated that they will supply what they have, although the CRFs differ from the various categories of studies. Dr. Winchell clarified that both related and unrelated SAEs should be submitted. The Sponsor inquired whether the Division required CRFs for alcohol hospitalizations. Dr. Winchell responded that CRFs are not required for subjects who were rehospitalized for alcoholism treatment.

- *Clarify why intentional overdose will not be coded as suicide attempt.*

There was some discussion about coding of suicides. It was agreed that intentional overdoses will be encoded to suicide attempt or death, or both. Where it is not known whether the overdose was intentional, the overdose will be encoded as an intentional suicide attempt.

- *Examples of errors and discrepancies will be provided; it is anticipated the proposed revision of the dataset will resolve these issues.*

- *Please provide blank CRFs for all studies (translated).*

Comments on Text Strings for SAE Search

- *anaphyl* would be more sensitive than anaphylaxis*

- *similarly, hepat* is preferable to hepatitis*

- *Comments on Proposed Re-Mapping of Reasons for Discontinuation*

  - *During review of CRFs in the original NDA, examples were identified of subjects who reported unwillingness to continue because of adverse effects, coded as "patient decision," "patient refusal," etc.*

  - *Careful attention should be given to the category of patient refusal/patient decision to identify these cases, which should be coded as discontinuations due to AE.*

Dr. Winchell provided examples of discrepancies found in the datasets that confounded the prior review. The discrepancies were various, e.g., hypertension coded as a CNS event, bruising coded as hemorrhage, rather than ecchymosis; positive urine tox coded as drug dependence. Dr. Winchell expressed confidence that reconstructing the datasets should rectify these discrepancies. The Division will provide other examples of difficulties encountered with the review of the datasets in the NDA in writing, upon approval of Dr. Rappaport
Listings of adverse events (AEs) should include one tabulation of all events that were reported spontaneously prior to administration of the AE checklist. Checklist-derived AEs should also be reported, but the details should allow for generation of tables of spontaneously reported AEs integrated across the studies in which spontaneous AEs were collected first.

The Sponsor will consider the Agency recommendations and either resubmit or request another meeting for further clarification.

/S/

Lisa E. Basham-Cruz, MS

Attachment

Redacted 4

page(s) of trade secret and/or confidential commercial information (b4)

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/s/

Lisa Basham-Cruz
3/21/03 12:17:44 PM

11/7/02

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-431

Lipha Pharmaceuticals, Inc.
10 Derby Square
Salem, MA 01970

Attention: Anita Goodman, MD
Executive Vice President and Chief Operating Officer

Dear Dr. Goodman:

Please refer to the meeting between representatives of your firm and FDA on October 9, 2002. The purpose of the meeting was to discuss the FDA's Not Approvable action on your NDA for Acamprosate Tablets, and requirements for resubmission.

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}

/S/

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

Enclosure

SPONSOR MEETING ATTENDEES

Meeting Date: October 9, 2002

Location: Parklawn Building, Potomac Conference Room (1:30-3:30pm)

IND/ Name: NDA 21-431 (Acamprosate)

Sponsor: Lipha Pharmaceuticals, Inc.

Type of Meeting: Post Action Meeting

Meeting Chair: Cynthia G. McCormick, M.D.
Division of Anesthetics, Critical Care and
Addiction Drug Products, HFD-170

Lipha	Title
Anita Goodman, MD	Executive VP & COO
Bruce Goddard, RAC	Sr. Director of Regulatory Affairs
Sylvie Chabac, MD	International Product Manager
[redacted]	
[redacted]	
[redacted]	
Robert Jackson	Project Manager, Forest Laboratories
FDA HFD-170	**Title**
Bob Meyer, M.D.	Director, ODE II
Cynthia G. McCormick MD	Division Director
Celia Winchell, MD	Team Leader, Addiction Drug Products
S. Edward Nevius, PhD	Director, Division of Biometrics II
Tom Permutt, PhD	Mathematical Statistician, Team Leader
Sue Jane Wang, PhD	Sr. Mathematical Statistician
Lisa Basham-Cruz, MS	Regulatory Project Manager

Meeting Minutes:

Following introductions, Dr. McCormick provided a summary of reasons for the Division's not approvable action on the Acamprosate NDA. In brief, problems with safety data seemed to indicate a systematic problem that might carry over into the efficacy data. Further, the DSI inspection results led to concerns about the reliability of the efficacy data. Therefore, the Division is not confident in the efficacy results from the European trials and would like to see new data generated in an adequate and well-controlled trial conducted by today's standards.

Ms. [ ] said that Lipha plans to address items 2-13 of the action letter which relate to the safety database by correcting the errors, inconsistencies and mistakes mentioned in items 3-13, and resubmitting this corrected safety data. The PK, preclinical toxicology and abuse liability issues mentioned in deficiencies 14-19 and 21 will also be addressed. Item 20, regarding the need for a repeated carcinogenicity study in mice will be addressed through a request for discussion with the Carcinogenicity Assessment Committee. Dr. McCormick suggested providing a scientifically sound rationale for not repeating the study, which the Division will take into consideration. Ms. [ ] continued that the chemistry items, 20 through 25, will also be addressed. Item 26, regarding significant payments of other sorts has already been addressed in a prior submission.

Ms. [ ] commented further on the Division's requirement for an additional adequate and well-controlled clinical trial by stating that it is not Lipha's intention to conduct an additional trial and may appeal the Division's and Office's decision. Dr. McCormick acknowledged the Sponsor's right to an appeal of the decision.

Dr. Winchell provided an overview of the discrepancies identified by Dr. Malek during his inspection of one site from the Paille study and one site from the PRAMA study. Each site had examples of subjects whose status as abstinent/non-abstinent were incorrectly recorded. She noted that the results from the Paille study were marginal to begin with, and this inspection finding cast further doubt on the ability of the study to support the drug's efficacy. Exploration of the dataset also revealed discrepancies between documented blood alcohol levels and assessments of abstinence at sites that were not inspected. For the PRAMA study, some discrepancies were also noted on inspection. Although the specific problems identified upon inspection of the PRAMA site were not as significant as the problems at the Paille site, Dr. Winchell noted that the results of the study were driven by a very small number of successful subjects, and that a single miscoded subject at each site would have the potential to invalidate the results. The sponsor indicated their confidence in the quality of the PRAMA study. The need for more complete auditing of the study to ensure validity of the results was discussed.

The Sponsor will attempt to provide information to convince the Division of the acceptability and validity of data from the European studies. Dr. McCormick reminded the Sponsor that the regulatory clock for their resubmission will not start until all deficiencies listed in the letter have been addressed and received by the Agency.

/S/

Lisa E. Basham-Cruz, MS

/S/

Celia Winchell, MD/concurrence

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/s/

Lisa Basham-Cruz
11/7/02 05:12:01 PM

Celia Winchell
11/7/02 05:15:04 PM

Office Director's Sign-Off Memorandum

Date:	Thursday, June 27, 2002
NDA:	21-431
Sponsor:	Lipha Pharmaceuticals, Inc.
Proprietary Name:	Acamposate sodium

Introduction: This is a first-cycle application for this drug product, proposed for use as an oral treatment of alcohol dependence. The drug – acamprosate – has been marketed in Europe for a number of years, but received priority status in the U.S. because of the dearth of products available in this country for this indication. The proposed dosage for this drug is 666 mg (two 333 mg tablets) three times daily, and it is intended to be started soon after detoxification and continued even during relpases.

I refer the reader to the summary memorandum of Dr. Cynthia McCormick, Director of DACCADP, for a very fine and detailed synopsis of this application. I am in substantial agreement with Dr. McCormick's observations and recommendations. I will summarize selected important points, nonetheless, from my review of the action package.

CMC: There are a number of reasonably minor outstanding CMC issues, largely having to do with needing acceptable DMFs (including the DMF for drug substance) and the need for additional stability data. These issues should be easily addressed by the sponsor.

Pharm/Tox: There are more serious deficiencies with the pre-clinical toxicology data. Of note, the sponsor has already been informed that the chronic dog toxicity data are not sufficient since the toxicology was not adequately characterized. The sponsor was previously informed of this problem and is currently conducting a 1-month study in dogs to better define the target(s) of toxicity. Since this study is still outstanding, this deficiency is noted in the action letter. The sponsor also did not provide adequate genotoxicity/mutagenecity data and will be asked to repeat the gene mutation assay in Chinese hamster V79 cells and the chromosome aberration assay using adequate dosing and procedures. Unfortunately, one of the two submitted carcinogenicity studies (the mouse study) was inadequate both in terms of achieving an MTD and because a parasitic infection in the animal cohort confounded the interpretability of the resulting histopathology. This study or some other acceptable carcinogenicity study in the mouse will need to be repeated.

Biopharmaceutics The low proportion of Acamposate that is absorbed (11%) is almost entirely eliminated via the renal route. Yet, the effects of renal failure and aging on the PK of this drug have been less than well defined. There are a number of additional PK studies needed that would have been appropriate phase-4 commitments if these were the only deficiencies. These deficiencies include the need for better PK/dosing data in geriatric patients and renal-failure patients. Given the multiple other problems with this application, these deficiencies will be included in the letter rather than allowing for them to be considered as phase-4 commitments.

Clinical / Stastical: There are two very large problems with the clinical dataset provided by the sponsor. The first is that the only apparently positive efficacy data are derived from non-US studies, as the US trial failed when proper analyses were conducted. When two of these European sites were audited by DSI, there were a number of instances of "sloppy" record keeping that call into question the ability to rely on these data. For instance, there are a few instances where patients called "abstinent" in the CRF but in fact had high blood alcohol levels on their laboratories. While such instances were relatively infrequent, the results from the European trials – while nominally positive – were sufficiently modest such that the results could easily have been affected by poor patient data accounting, if in fact these two sites were typical of the record keeping at all sites. Therefore, solely relying on these data for approval cannot currently be justified. Therefore, the sponsor will need to submit another study of adequate design **and**, if possible, rectify the sloppiness in the non-US studies for there to be sufficient efficacy data to allow for approval. It should be noted that while the advisory committee recommended approval 8 to 2, many of the members cited that this recommendation was contingent on being able to verify the European data and was contingent on the safety findings, which were not discussed with the committee.

The safety database is the other large problem with the clinical dataset. The safety database was poorly put together, incomplete and insufficient in substance and presentation to allow for any firm conclusions on the safety of this drug. One concern that did arise from the data available was a seeming excess in suicides (along with depression) in acamposate treated patients, compared with placebo patients. In addition to many comments in the action letter asking for new presentations of the safety data and additional safety data, the sponsor will need to clarify the issues related to a possible effect on suicides, as well.

Labeling: No major labeling comments are being provided this cycle, due to the broad and serious deficiencies in this application.

Regulatory Conclusions: This application will be given a "not approvable" action. The company will be encouraged to meet with DACCADP to go over the letter and deficiencies, so that a path forward can be reached. Clearly, an effective and safe drug to help alcoholics maintain abstinence would be of great therapeutic benefit. Right now, it cannot be stated that acamposate is either safe nor effective for that purpose.

/S/

Robert J. Meyer, MD
Director,
Office of Drug Evaluation II

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/s/

Robert Meyer
6/27/02 09:45:42 AM
MEDICAL OFFICER

6/19/02

NDA 21-431

Campral (acamprosate calcium) 333 mg tablets

CHEMISTRY DIVISION DIRECTOR REVIEW

Applicant:

Lipha Pharma
10 Derby Square
Salem MA

Indication: [redacted]

Presentation: HDPE Bottles 180 and 1080 count; [redacted] tablet blisters

EER Status: Final overall recommendation form Compliance is pending.

Consults: ODS – Tradename: [redacted] acceptable 12-JUN-2002
Statistics – none
EA – no consult - waiver requested – granted

Phase IV Commitments: none

The original NDA was received 21-AUG-2001

The **drug substance** is manufactured by:

Lipha S.A.
Meyzieu, FR.

Manufacturing and controls information was reviewed in DMF [redacted] - a deficiency letter was issued 12-JUN-2002. Acamprosate calcium is manufactured at Meyzieu, GFR and Calais,FR. [redacted]

[redacted], so a product comparison has been requested. Some deficiencies were noted in the impurities specifications.

Structural characterization of the drug substance was satisfactory. The manufacturing process and controls were found generally acceptable with a few

comments being offered. Other specifications were found acceptable. [ ] The stability testing protocol is considered adequate

Conclusion
Drug substance deficiencies need resolution.

The **drug product** is an enteric coated 333 mg tablet equivalent to 300 mg of acamprosate.

Manufacturer:

Merck Lipha SAS

The manufacturing method is [ ] process. Adequate in-process controls are in place. Test methods for some of the product components are tested to EP standards – the approved specifications must be USP, however alternate methods may be proposed, with demonstration of equivalence. The proposed regulatory specifications are acceptable except for dissolution. The dissolution test and acceptance criteria were not found acceptable by OCPB – see review dated 10-JUN-2002. The [ ] months of submitted stability data do not support the proposed 36 month expiry – additional data have been requested. Supporting data from the European product (different formulation) have been provided. Additional should be requested. The stability testing protocol is considered adequate. The established name acamprosate calcium is pending USAN approval. No labeling comments in this review cycle.

Minor deficiencies have been cited.

The overall Compliance recommendation is pending as of 18-JUN-2002.

All associated DMFs are unacceptable. The firm should be notified that DMF [ ] was not reviewed due to its late submission.

Deficiencies
For the the excipients, where a USP monograph exists, the specification (test, procedure, acceptance criteria) should be USP. If alternate methods are proposed provide a demonstration of equivalence (or superiority).

Please provide additional stability data to support the proposed 36 month expiry.

Please be aware that all manufacturing and testing facilities should have a satisfactory GMP compliance status for approval.

Note that DMF [ ] was not reviewed due to its late submission.

Overall Conclusion
From a CMC perspective the application is approvable.

Eric P Duffy, PhD
Director, DNDC II/ONDC

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/s/

Eric Duffy
6/19/02 05:02:34 PM
CHEMIST

MEMORANDUM OF TELECON

DATE: May 24, 2002

APPLICATION NUMBER: NDA 21-431, acamprosate

BETWEEN:

Name:	Anita M. Goodman, MD, Executive Vice President and COO	
	Bruce Goddard, Sr. Director of Regulatory Affairs	
Phone:	978-542-1904	
Representing:	Lipha Pharmaceuticals, Inc.	

AND

Name:	Cynthia G. McCormick, MD	Division Director
	Bob Rappaport, MD	Deputy Division Director
	Eric Duffy, PhD	Director, DNDC II
	Celia Winchell, MD	Team Leader, Addiction Drug Products
	Tom Permutt, PhD	Biostatistics Team Leader
	Tim McGovern, PhD	Supervisory Pharmacologist
	Sue Jane Wang, PhD	Statistics Reviewer
	David Lewis, PhD	Chemistry Reviewer
	Mike Sevka, MD	Medical Reviewer
	Chuck Cooper, MD	Medical Reviewer
	Lisa E. Basham-Cruz, Regulatory Project Manager	
Representing:	Division of Anesthetic, Critical Care, and Addiction Drug Products, HFD-170	

SUBJECT: To communicate status of NDA reveiw to Applicant.

The Applicant was informed that their pending NDA 21-431 for acamprosate will not be approved, due to extensive deficiencies with primarily the safety database and chemistry. The deficiencies will be communicated in detail in the action letter to be issued no later than June 27, 2002. It has not been decided whether the action will be APPROVABLE or NOT APPROVABLE.

Lisa E. Basham-Cruz
Regulatory Project Manager

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/s/

Lisa Basham-Cruz
6/7/02 06:19:48 PM
CSO

MINUTES OF TELECON

DATE: February 14, 2002

APPLICATION NUMBER: NDA 21-431, Acamprosate

BETWEEN:

Name:	Anita M Goodman, M.D., Executive Vice President and COO Bruce Goddard, Sr. Director of Regulatory Affairs Craig McMillan, Project Manager, Regulatory Affairs
Phone:	(212) 398-4602
Representing:	Lipha Pharmaceuticals

AND

Name:	Judit Milstein, Regulatory Project Manager Cynthia G. McCormick, M.D., Division Director Celia Winchell, M.D., Medical Team Leader Cathy Haberny, Ph.D., Pharmacology reviewer Tim McGovern, Ph.D., Pharmacology team leader Sue Jane Wang, Ph.D., Statistician Tom Permutt, Ph.D., Statistics Team Leader Judit Milstein, Regulatory Project Manager Division of Anesthetic, Critical Care, and Addiction Drug Products

SUBJECT: Review of issues identified at the filing meeting

BACKGROUND:
NDA 21-431 was submitted on December 27, 2001.

The purpose of this telecon was to communicate with the sponsor the review issues identified during the filing meeting held on February 8, 2002.

DISCUSSION:

1. The Division raised the possibility of a Psycopharmacology Advisory Committee meeting in early June to discuss the efficacy of acamprosate. The cumulative abstinence duration analysis appears to have been calculated from data which was largely imputed. More conservative analysis may be necessary.
2. No filing issues were identified to this point, however the Division is still waiting for the Controlled Substance Staff's (CSS) filing review.
3. The Division noted the lack of pre-clinical data to characterize the toxicity in nonrodents following a preliminary review of the studies. Formal review of the studies will determine if a 4-week study in dogs, with doses that will induce toxicity, will be needed.
4. Review will determine if the excipient "Eudragit 30" needs further qualification. This might happen if the total daily dose of the excipient exceeds the total daily dose within currently

approved products with the same ingredient. Qualification will require chronic toxicity studies in 2 species.

5. The Division noted that interval data from EKGs are missing in the submission and that, overall, there is very little information on the effect of acamprosate on the EKG. Lipha indicated that they will review their studies and submit any information they have for EKG's.
6. The initial clincial and statistical reviews of the dataset revealed inconsistencies that require clarification. The inconsistencies and information required are clarified below:

The reviewing medical officer has the following comments and requests for information (grouped by study site):

Paille

The Paille dataset and the report in section 8.4 offer four possible sets of data for determining how many subjects were continuously abstinent through the treatment period.

The in-text table 8.4.2.3.3. lists subjects abstinent through various time points. The last time point listed as "treatment phase" is day 340. Note that there is no category corresponding to this in the dataset. The dataset includes categories of continuous abstinence of "280-<340" and "340-<400"

There are four columns in the dataset that purport to identify continuously abstinent subjects. These are "Cont Abstinence thru Trt Period (Yes/No)" (CABSTYN); "Cont Abst thru Obs Period (Yes/No" (CABSTOYN), "Relapse to drinking" (RELFLAGC, RELFLAGU).

While it would be reasonable to expect these numbers to match, they do not.

Representations of continuous abstinence:

	Placebo	Acamprosate	Acamprosate
In-text table 8.4.2.3.3: Number (%) of Patients with Continuous Abstinence from Alcohol since day 0— Line adjacent to time period 340 days	20 (11%)	34 (18%)	33 (19%)
Dataset PI_EFFPT + PI_POP, Patients listed as having CAD of 340-<400, 400-<460, 460-<520, OR 520+	20 (11%)	34 (18%)	32 (18%)

CABSTYN = yes	40 (22%)	50 (27%)	52 (30%)
CABSTOYN = yes	35 (20%)	40 (21%)	46 (27%)
RELFLAGU = 0	12 (7%)	26 (14%)	25 (14%)

In the dataset, the flag for relapse does not match continuously abstinent columns. For example, the matrix below shows that 17 subjects listed as "no" for CABSTOYN (were NOT continuously abstinent) were coded as 0 (NO RELAPSE). 75 subjects listed as "yes" for CABSTOYN (were continuously abstinent) have a code of 1 for the relapse flag (DID RELAPSE).

Yes/No = continously abstinent during observation period. 1 = Relapse, 0 = no relapse

		0	1
No	416	17	399
Yes	121	46	75

1. Explain the difference between CABSTYN and RELFLAG, and explain why the sum of the subjects having CAD of 340 days or more does not equal the number of subjects coded as continuously abstinent on treatment. Explain how the derived variables were derived.

PRAMA

There are four columns in the PR_EFFPT dataset that could represent continuous abstinence. These include RELAPITT (Relapse to drinking ITT, Yes/No), RELAPOT ("Relapse to Drinking OT, Yes/No") (note that there is no explanation of the term OT anywhere), RELFLAGC and RELFLAGU, "Relapsed to Drinking for ISE" censored and uncensored analyses, 1=relapse.

	Placebo	Acamprosate
Text, page 29 sec 8.4[1]	25%	45%
CADITT at least 360 days	13%	29%
RELAPITT = no	40%	51%
RELAPOT = no	42%	52%
RELFLAGU	12%	29%
RELFLAGC	40%	51%

[1]"Forty-five percent of patients on acamprosate remained abstinent over the 48 week treatment phase compared with 25% of patients on placebo."

The figures 25% and 45% given in the text appear consistent with the survival curve presented in the text, but there is no way to reconstruct these numbers from the dataset.