2. Explain the difference between RELAPITT and RELAPOT. Clarify how the abstinence survival of 25% and 45% can be reconciled with the data in the CADITT column. Explain how the derived columns (those coded yes/no or 0/1) were derived.

Pelc-II/US study

3. Examine the datasets for these two studies and determine which columns represent continuous abstinence, identify the methods of calculating any derived variables, and identify how any calculations of continuous abstinence in the study reports/ISE summaries may be replicated.

The reviewing statistician has the following request:

4. Explain how the variable RELAPITT, defined as Relapse to Drinking ITT ('Yes', 'No') in the patient efficacy file, was determined (was it obtained from patient's self-report? Was it based on physician's assessment?)

/S/

Lisa E. Basham-Cruz
Regulatory Project Manager

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/s/

Lisa Basham
2/27/02 05:29:59 PM

FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANESTHETIC, CRITICAL CARE, AND ADDICTION DRUG PRODUCTS
HFD-170, Room 9B-45, 5600 Fishers Lane, Rockville MD 20857
Tel:(301) 827-7410

DIVISION DIRECTOR REVIEW AND BASIS FOR APPROVAL ACTION

DATE: June 18, 2002

DRUG: Acamprosate Calcium

NDA: #21-431

NDA Code Type 1 P NDA

SPONSOR: Lipha Pharmaceuticals, Inc.

INDICATION: [redacted]

Summary

Lipha Pharmaceuticals has submitted a New Drug Application for acamprosate, a product that has been available in Europe for the treatment of chronic alcoholism for nearly 15 years. It was assigned a priority review status because of the high morbidity and mortality associated with the disorder and the lack of effective treatments available.

Early in the review cycle concerns about disparate efficacy results between the US and European efficacy trials emerged. Therefore the application was brought before the Psychopharmacologic Drugs Advisory Committee for a discussion of the drug's efficacy. While overall the committee felt that the failed US study should not be considered to weigh against the approval, several members of the Committee stipulated that assurance of the reliability of the European data should be obtained before any approval decision was made.

The safety reviewers assigned to this NDA and indirectly the DSI investigator have cast considerable doubt about the integrity of the data, and thus, have led to the review team's overall recommendation for a nonapprovable action.

Efficacy

The efficacy database on which this application relies includes a single U.S. multicenter trial completed recently and number of older European clinical trials, three of which are considered "pivotal" studies. The sponsor conceded that the US study was a failed trial, while the European studies, performed over the last approximately 15 years, were interpreted as successful. The review team has attempted to explore the apparent contradictions between these studies by evaluating their differences through a variety of analyses. Drs. Winchell and Wang's review of efficacy and statistics carefully detail the analyses undertaken.

The three pivotal European trials, Pelc II, Paille, and PRAMA, were of similar design, methodology and outcomes. The trials have been considered successful by the sponsor and by the review team based on a very conservative analysis of the data, albeit *post hoc*. The trials all were characterized by a lack of prospective plan for analysis of efficacy data. The reviewers made the assumption that the only reliable approach was that of a responder's analysis in which success was defined as complete abstinence. This endpoint and analysis method was not preordained. The precision of the result rests squarely on the likelihood that drinking data was accurately collected and recorded.

In the case of Pelc II, visits took place every 1-2 weeks over the course of the brief 90-day study. Urine ethanol, signs of withdrawal, serum transaminases, and recall of alcohol use were obtained at each visit. On the *post hoc* FDA defined outcome measure of responder rate based on complete abstinence from alcohol, acamprosate was shown to be superior to placebo. This study was not inspected, and the quality of efficacy data was not verified. The study was not capable of contributing safety data to the NDA because of the nature in which the safety information was collected.

In the case of Paille, visits took place every month for the first half of the 1-year study, then every two months for the remainder of the year. Patients were asked to recall any non-abstinent days and if non-abstinent, to recall the amount imbibed. Dr. Winchell points out that accuracy based on a categorical assessment of drinking vs. abstinence would have been a more accurate approach, and the data were converted accordingly. The results of this study based on the *post hoc* responder analysis described above were only very weakly positive and not sustained. Inspection of only one site, 36 patients, reveled two patients who were coded as abstinent who were recorded with high levels of blood alcohol. Other sites were not inspected, however this alone sheds considerable doubt on whether the underlying data are credible.

PRAMA was also a long study, lasting 48 weeks, with visits occurring monthly at first, then every three months. This study is expected to have the same difficulty with accurate

ascertainment of data, relying on recall and patient reliability to provide accurate drinking data over 3 months at a time. At visits, attempts were made to verify history with biological measures of drinking such as a breathalyzer test, history of drinking obtained from patient and family, and hepatic transaminases. These objective measures are obviously not accurately reflective of 3 months' drinking history, and probably reflect the only immediate drinking behavior. The DSI inspection reported at one site a patient was classified as nonabstinent due to missing data, when indeed, the patient's data were present in the CRF.

The review team considered the European trials successful by using the most conservative of outcome measures, complete abstinence defining a responder, one would be hard pressed to disagree, unless the data on which the calculations and analyses rested was inaccurate. This is now in question.

It should be pointed out that if the three efficacy studies from Europe were to be accepted as evidence for efficacy, the drug will have been shown effective only in patients who have undergone detoxification, not a practice used in the United States at this time.

The U.S. study was not successful in demonstrating superiority over placebo on the primary outcome and most secondary measures, and indeed on some measures, the drug appeared to perform less well. Some differences between the European and U.S. studies can be clearly delineated. The European population was primarily one of pure alcoholics; the U.S. population was largely polysubstance abusers. The European patients had either recently undergone detoxification or were abstinent prior to randomization; the U.S. patients were generally not abstinent prior to randomization. The ascertainment of drinking data in the European studies was essentially retrospective and not diary-based; it was very methodical and rigorous in the U.S. study, using the timeline follow-back method of collecting drinking data, which relied on daily drinking diaries, calendar recall, and tight follow-up provisions in place. Finally, the studies differed in terms of the formulation of acamprosate that was used and the regimen of administration, although the total daily dose (TDD) was essentially the same, the US study dosed BID and the European studies dosed TID. Given the long half-life of this drug (21 hours), it is not expected that the dosing regimen would have played a significant role in efficacy from a pharmacokinetic perspective. However the psychological effect on efficacy of frequent dosing versus less frequent dosing cannot be ruled out.

Advisory Committee Meeting

A meeting of the Psychopharmacologic Drugs Advisory Committee was convened to discuss the conflicting results between the US and European studies. The committee made a number of points about the possible lack of relevance of the older European data to the modern US alcoholic and substance abuser, pointing out that even in Europe the demographics of alcoholism have changed over 15 years. There was discussion about the lack of rigor of the European methodology by three members, and reservation in accepting the data unless they could be verified. Overall, however, the majority of the vote was to accept the efficacy data. Two members voted not to accept the European

studies. One member concluded that another study should be conducted using modern methodology and prospectively defined endpoints and statistical methods. The committee was informed that the inspections had not yet taken place and that the safety review had also not been completed. Therefore advice about final approval of the product was not being sought.

Safety—Nonclinical

Nonclinical chronic safety studies of acamprosate calcium in rats and dogs were significant for increased urine calcium and cardiac abnormalities (myocarditis). In rats tubular distension with evidence of coagulum accumulation at high doses, renal vacuolation, renal calculi, tubular ectasia, and pelvic distention were described. Other target organs were brain and GI tract. Chronic safety in nonrodent species was found to be inadequate early in the review of this application, and the sponsor was invited to initiate a chronic dog study. This study is currently being undertaken.

The sponsor was required to perform neurotoxicologic evaluation of acamprosate because of its effect at the NMDA receptor site. These studies showed no evidence of neuronal vacuolation (Olney lesion) or necrosis in the posterior cingulate and retrosplenial cortices at doses of 2000 mg/kg.

Genotoxicity has not been fully characterized. The in vitro chromosome aberration assay and point mutation assay using CHO V79 cells with proper dosing criteria and incubation times will be required.

Carcinogenicity has not been adequately studied. The results of the carcinogenicity studies in mice and rats were presented to the executive CAC on March 19, 2002. The doses used in the rat were marginally adequate. The carcinogenicity study in mice was rejected due to inadequate dose selection based on lack of evidence for an MTD and furthermore histopathology was confounded by a systemic parasitic infestation.

Reproductive toxicology revealed evidence of teratogenicity in animals. Rat pups demonstrated ocular, renal and vascular anomalies at doses of 300 mg/kg. In peri- and postnatal studies, an increase in fetal death was noted at higher doses of 960 mg/kg and 2400 mg/kg. Because of the lack of human teratogenicity data, a Pregnancy Category C is warranted. The ultimate labeling for this product if it were to be approved should caution the balance between treatment with this agent and the risks of exposure to alcohol *in utero*.

Safety—Clinical

The clinical safety review team was not able to perform an adequate review of the safety of acamprosate because of the many systemic problems with how the safety data were collected, stored and reported. This will be discussed below as ***Data Integrity***.

There were only five studies in the NDA database which were thought to be capable of contributing safety data for evaluation. These were the US 96.1, Paille, PRAMA, UK MAS, and ADISA. The evaluations of serious adverse events, dropouts due to adverse events and treatment emergent adverse events were derived from these 5 placebo-controlled trials. Deaths were contributed from all acamprosate studies.

There were estimated to be 22 deaths associated with acamprosate treatment. These were evaluated and with the exception of suicide, the majority appeared to be associated with complications of alcoholism. There was no pattern in the deaths that could be considered a signal.

Serious adverse events were reviewed and again, the numbers were estimated due to problems of ascertainment. Some of the concerning events, which emerged from this group included depression, suicide, overdose, and myocardial infarction. Withdrawals due to adverse events followed a similar pattern. An emerging concern which could not be fully evaluated due to data quality issues is the higher incidence of suicide and myocardial infarction in the acamprosate treated groups compared with the placebo groups.

Treatment emergent adverse events raised further concerns about the renal toxicity of acamprosate, but again, this could not be verified. Reports included urinary tract abnormalities, frequency and renal colic. Eosinophilia, ulcerative colitis and thrombocytopenia were also not fully evaluated.

Overall the safety review, conducted by two independent reviewers working on two sections of the ISS, was hampered by issues of inconsistent coding, lack of coding, and data inconsistencies that prevented a thorough review. These must be corrected before any analysis of risk can be entertained.

Abuse liability assessment

The sponsor has provided only a limited abuse liability assessment of acamprosate. The consultation from the Controlled Substances Staff has outlined what will be necessary for a complete assessment of this drug as a new chemical entity. This includes receptor binding studies in the CNS, drug liking and drug discrimination studies in animals, and possible further additional studies if these are positive. These will be requested again at the time of the action letter. However, it must be noted that there has been no signal of abuse of acamprosate in the 15 years of postmarketing experience in Europe.

Biopharmaceutics

Acamprosate is not metabolized and is excreted renally; it is not protein bound and has a half-life of 21 hours. There is clearly an effect on clearance of acamprosate with decreased urine function and the sponsor has recommended that in the presence of severe renal impairment, acamprosate should not be used.

Acamprosate has no identified interactions with disulfiram, a drug to treat alcoholism, or with alcohol itself. There was no demonstrable effect of acamprosate on the kinetics of naltrexone, but naltrexone was shown to increase the rate of absorption of acamprosate with resultant increases in Cmax and AUC of 33% and 25% respectively.

There is also a significant food effect with a decrease in absorption of acamprosate with resultant decreases in Cmax and AUC of 45% and 23% respectively. During clinical trials, patients were instructed to take acamprosate with meals.

Chemistry, Manufacturing and Controls

The formulation of the drug product consists of an enteric coated (eudragit) formulation containing 333 mg of acamprosate, making up [ ] of the tablet. Acamprosate is very soluble in water.

Deficiencies in the DMFs for acamprosate and homotaurine have been identified and deficiency letters have been sent.

Minor deficiencies in the drug substance ([ ] and drug product, and information on packaging materials have been identified by the chemistry review team. These should be easily remedied.

The drug product is highly stable and data have been provided to support a 36 month shelf life.

Inspection

The cGMP inspection has not been completed. Since an approval action is not contemplated this cycle, the results of this inspection will be incorporated into the next review cycle, if the sponsor chooses to resubmit this application.

Data Integrity

The five studies that were highlighted as contributing safety data for the NDA were US 96.1, Paille, PRAMA, UK MAS, and ADISA. It was only in these studies where there was spontaneous reporting and recording of adverse events.

Only in US 96.1 were serious adverse events collected prospectively, and in the remainder these studies, spontaneously reported events were retrospectively classified as serious based on the US regulatory definition of serious using a very narrow search definition. This process was imperfect and as detailed in both safety reviews, not reliably adhered to. The electronic data confirmed that at least 47 hospitalizations were not coded as serious adverse events.

There was unreliable reporting of deaths as described in the medical officers' safety reviews, and therefore an exact number of fatalities associated with acamprosate cannot be accurately determined. There is lack of consistency of the reporting of deaths in this NDA.

The reviewing medical officers were unable to confirm the results of safety data presented in the ISS. This included withdrawals due to adverse events, adverse events, serious adverse events and deaths. Discrepancies between patient narratives, adverse event datasets and the ISS report were common. The reviewers were unable to reconcile these differences.

DSI Inspection

An inspection of two clinical study sites from the PRAMA and Paille studies revealed a certain level of carelessness. Of concern were errors directly relating to the reporting of efficacy data, for example, coding two patients in the Paille study as abstinent when there was evidence in the record of elevated blood alcohol levels. If any of the European studies are resubmitted in response to the action letter, a more in-depth inspection of the clinical sites should be carried out.

Discussion:

This NDA has deficiencies in almost every aspect of its data collection, presentation and analysis.

The preclinical evaluation will require new studies in three areas including chronic dosing in nonrodents, carcinogenicity and genotoxicity. The completion of these will take several years to accomplish.

The clinical data, both safety and efficacy are a problem. Clearly the integrity of the safety data has been examined most closely by two reviewers who concur that the data in the ISS cannot be verified, and that there were errors in collection, coding, and presentation, both electronically and on paper that render the information unreliable. In addition, certain essential analyses of adverse event patterns were not performed. The sponsor should undertake a careful and thorough audit of the safety data from the five Group I studies in which spontaneous reporting was done, and should recode and reanalyze the data for deaths, serious AEs, withdrawals due to AEs, and treatment emergent AEs, ensuring that important adverse events are not miscoded and not overlooked.

The efficacy data could not be examined with the same precision as the safety data. It is very difficult for the FDA to assess the data quality and reliablity of data reporting and gathering particularly during the long intervisit intervals of up to 3 months when no documentation of drinking was obtained. The DSI inspection raised some questions, and coupled with the data integrity problems that plagued the safety data, one cannot assume that these problems do not also exist in the efficacy data from the same trials. Given the

imperative from the advisory committee to confirm the quality of the efficacy studies before considering approval, the efficacy data should be more carefully audited by the sponsor and provided to the FDA.

While it is not uncommon for an NDA database to have both successful results and results which are not considered "positive", this data set raises special concerns. In general, the approach to such a situation is to consider the totality of the evidence, giving consideration and weight to such factors as the quality of the data, strength of the effect size, statistical significance, and assessment of whether the effects, even in the negative trials, are supportive, trend in the same direction, and are not contradictory. If a trial has truly failed, that is, demonstrated an effect that contradicts the remainder of the evidence, an attempt is made to understand the reason for the contradiction, and to determine, on balance, which results are more credible. In this case, the US study is truly a failed study. The credibility of the European data is in question. In order for this product to be approved, these two problems must be addressed head on. It will be recommended that the sponsor undertake to salvage the PRAMA study, as the study of adequate duration, and which, if the data quality were found to be acceptable, would be considered positive. The Paille study results are already borderline and given the questions about data quality, may not be worth the effort to try to salvage it. The Pelc II study is far too brief to stand on its own as a pivotal trial. The sponsor currently has a large multicenter US study underway. This study should be completed, and if positive, submitted in support of efficacy. This taken together with the PRAMA study (if salvaged) should provide assurance of the efficacy of this product. If the PRAMA study cannot be salvaged, then the sponsor should perform an additional adequate and well-controlled trial.

The safety data should be salvaged, accordingly. Additional safety experience from the ongoing US trial should provide adequate exposure to acamprosate to fulfill the recommendations of the ICH E1A guidelines.

Action recommended by the Division: NonApproval

/S/

Cynthia G. McCormick, MD,

Director
Division of Anesthetic, Critical Care and Addiction Drug Products
Office of Drug Evaluation II, CDER, FDA

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/s/

Cynthia McCormick
6/18/02 11:12:32 AM
MEDICAL OFFICER

6/14/02

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-431

Lipha Pharmaceuticals Inc.
1114 Avenue of the Americas, 41st floor
New York, New York 10036-7703

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

Dear Dr. Goodman:

Please refer to the meeting between representatives of your firm and FDA on February 14, 2002. The purpose of the meeting was to communicate review issues identified during the filing meeting held on February 8, 2002, for your NDA 20-431 for Acamprosate, received December 27, 2002.

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,

/S/

{See appended electronic signature page}

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

Enclosure

ADRA Review #1 of Action Package for NDA 21-431, Campral (acamprosate) Tablets

Reviewer: Lee Ripper, HFD-102
Date received in HFD-102: June 11, 2002
Date of Review: June 14, 2002

Date original NDA received: December 27, 2001
UF GOAL DATE: June 27, 2002

Indication: [ ]

Action type: AE
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: Deferred until response to action letter
Debarment statement: AC
DMETS Review of Trade Name: AC. Trade name will need to be re-evaluated prior to AP.
EA: AC, CMC rev #1, p. 63

1. Financial disclosure information/review: The European studies were completed a number of years ago. The U.S. study was completed 1/28/99. The NDA, page 441, says "Disclosure statements are not applicable to this NDA. The clinical studies submitted in support for this NDA were conducted and completed prior to 2/2/99. However, reporting of SPOOS payments does apply to any payments between 2/2/99 and 1/28/00. The applicant needs to submit forms for this time period.

2. EER: Pending as of 6/12/02, two facilities in France, inspections scheduled for 6/5/02 and 6/18/02.

3. Safety Update: The electronic C&H listing doesn't show a SU submission. For several obvious reasons, it doesn't matter in this case, but we do need to remember to make sure that these are always submitted and reviewed.

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

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/s/

Leah Ripper
6/14/02 05:59:06 PM
CSO

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

6/12/02

CONSULTATION RESPONSE
DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(ODS; HFD-420)

DATE RECEIVED: 4/29/02	DUE DATE: 6/14/02	ODS CONSULT: 02-0104

TO:

Cynthia McCormick, MD
Director, Division of Anesthetic, Critical Care, and Addiction Drug Products
HFD-170

THROUGH:

Lisa Basham-Cruz
Project Manager
HFD-170

PRODUCT NAME:	**NDA SPONSOR:**
Campral (Acamprosate Tablets) 333 mg **NDA #:** 21-431	Lipha Pharmaceuticals

SAFETY EVALUATOR: Nora Roselle, PharmD

SUMMARY: In response to a consult from the Division of Anesthetic, Critical Care, and Addiction Drug Products (HFD-170), the Division of Medication Errors and Technical Support (DMETS) conducted a review of the proposed proprietary name "Campral" to determine the potential for confusion with approved proprietary and established names as well as pending names.

DMETS RECOMMENDATION:
DMETS has no objections to the use of the proprietary name, Campral. This name must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary and established names from the signature date of this document. In addition, DMETS recommends implementation of the labeling revisions outlined in section III of this review to minimize potential errors with the use of this product.

/S/

Carol Holquist, RPh
Deputy Director
Division of Medication Errors and Technical Support
Office of Drug Safety
Phone: 301-827-3242 Fax: 301-443-5161

/S/

Jerry Phillips, RPh
Associate Director
Office of Drug Safety
Center for Drug Evaluation and Research
Food and Drug Administration

Division of Medication Errors and Technical Support
Office of Drug Safety
HFD-420; Rm. 15B32
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: June 11, 2002

NDA NUMBER: 21-431

NAME OF DRUG: Campral (Acamprosate Tablets) 333 mg

NDA HOLDER: Lipha Pharmaceuticals

I. INTRODUCTION:

This consult was written in response to a request from the Division of Anesthetic, Critical Care, and Addiction Drug Products (HFD-170), for assessment of the tradename "Campral", regarding potential name confusion with other proprietary/generic drug names.

PRODUCT INFORMATION

Campral is the proposed proprietary name for Acamprosate Tablets. Campral is indicated for the [redacted]

[redacted] The usual dose of Campral is two tablets three times a day. Campral will be supplied in a 333 mg strength in bottles of 180 (1 month supply) and 1080 tablets (6 month supply) and in packages of [redacted] unit dose tablets. The use of Campral is contraindicated in patients who have exhibited hypersensitivity to acamprosate or any of its components. In addition, Campral should not be used for the treatment of the acute symptoms of alcohol withdrawal.

II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of several standard published drug product reference texts[1,2] as well as several FDA databases[3] for existing drug names that sound-alike or look-alike to "Campral" to a degree where potential confusion between drug names could occur under the usual clinical practice settings. The Saegis[4] Pharma-In-Use database was searched for drug names with potential for confusion. An expert panel discussion was conducted to review all findings from the searches. In addition, DMETS conducted three prescription analysis studies consisting of two written prescription studies (inpatient and outpatient) and one verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

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[1] MICROMEDEX Healthcare Intranet Series, 2002, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes the following published texts: DrugDex, Poisindex, Martindale (Parfitt K (Ed), Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic version.), Index Nominum, and PDR/Physician's Desk Reference (Medical Economics Company Inc, 2002).
[2] Facts and Comparisons, 2002, Facts and Comparisons, St. Louis, MO.
[3] The Division of Medication Errors and Technical Support [DMETS] database of proprietary name consultation requests, New Drug Approvals 98-02, and the electronic online version of the FDA Orange Book.
[4] Data provided by Thomson & Thomson's SAEGIS™ Online Service, available at www.thomson-thomson.com

A. EXPERT PANEL DISCUSSION

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

Several product names were identified in the Expert Panel Discussion (EPD) that were thought to have potential for confusion with Campral. These products are listed in Table 1 (see below), along with the dosage forms available and usual FDA-approved dosage.

DDMAC did not have concerns about the name with regard to promotional claims.

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

Product Name	Dosage form(s), Generic name	Usual adult dose*	Other??
Campral	Acamprosate Tablets, 333 mg	2 tablets three times a day	
Compro	Prochlorperazine Suppositories, 25 mg	Insert one rectally one to three times a day as needed	L/A, S/A
Cantil	Mepenzolate Bromide Tablets, 25 mg	25 mg to 50 mg four times daily with meals and at bedtime	S/A
Cartrol	Carteolol Hydrochloride Tablets, 2.5 mg, 5 mg	2.5 mg to 5 mg once daily	S/A
Campath	Alemtuzumab, 30 mg/ 3 mL solution for injection	3 mg administered as a 2 hr IV infusion daily then increase to 10 mg	L/A, S/A
Captopril (generic name for Capoten)	Captopril Tablets, 12.5 mg, 25 mg, 50 mg, 100 mg	Initial: 12.5 mg - 25 mg 2-3 times/day Maximum: 150 mg 3 times/day	S/A

*Frequently used, not all-inclusive.
**L/A (look-alike), S/A (sound-alike)

B. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

Three studies were conducted by DMETS and involved 108 health professionals comprised of pharmacists, physicians, and nurses within FDA to determine the degree of confusion of Campral with other drug names due to similarity in handwriting and verbal pronunciation of the name. Inpatient order and outpatient prescriptions were written, each consisting of marketed and unapproved drug products and a prescription for Campral (see page 4). These prescriptions were scanned into a computer and were then delivered to a random sample of the participating health professionals via e-mail. In addition, the outpatient orders were recorded on voice mail. The voice mail messages were then sent to a random sample of the participating health professionals for their interpretation and review. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

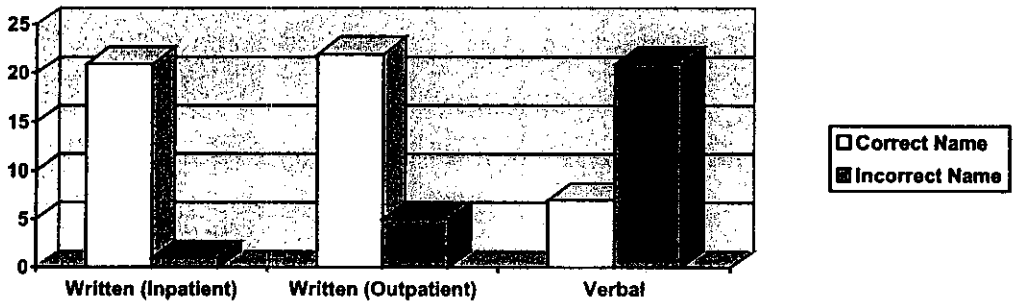
HANDWRITTEN PRESCRIPTIONS	VERBAL PRESCRIPTION
Outpatient RX: Campral Sig: ii po TID	Campral Take two tablets three times a day.
Inpatient RX: Campral 2 tid	

2. Results:

The results are summarized in Table I.

Table I

Study	# of Participants	# of Responses (%)	Correctly Interpreted Campral	Incorrectly Interpreted
Written Inpatient	36	22 (61%)	21 (95%)	1 (5%)
Written Outpatient	33	27 (82%)	22 (81%)	5 (19%)
Verbal Outpatient	39	28 (72%)	7 (25%)	21 (75%)
Total	108	77 (71%)	50 (65%)	27 (35%)



Among the verbal outpatient Campral prescriptions, 21 of 28 (75%) respondents interpreted the name incorrectly. Many of the incorrect name interpretations were misspelled variations of "Campral". Incorrect interpretations included Camprel, Kamprel, Cambprell, Campril, Camprell, Kempra, Camprow, Campril, Caprel, and Kinpral. One respondent commented that the name was "too much like captopril".

When examining the interpretations from the written inpatient prescriptions, 1 of 22 (5%) respondents interpreted the name incorrectly. One respondent incorrectly interpreted the name to be Compral.

In addition, 5 of 28 (19%) respondents from the written outpatient prescriptions interpreted the name incorrectly. Incorrect interpretations included Campial, Capral, Camial, and Canpral.

C. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name "Campral", the primary concerns raised were related to sound-alike, look-alike names that already exist in the U.S. marketplace. The products considered having the greatest potential for name confusion with Campral were Compro, Cantil, Cartrol, and Campath. One respondent from the verbal outpatient prescription study responded that the name was "too much like captopril".

Compro (Prochlorperazine) is a prescription medication used in the management of nausea and vomiting. Compro is available as 25 mg rectal suppositories. Compro is administered as one suppository given rectally one to three times a day as needed. Compro can sound-alike and look-alike to Campral in that each name contains similar letter combinations and two syllables. Both drug names contain "compro" vs. "campra" where an "a" and "o" can look and sound similar. The proposed tradename ends in the letter "l" which can easily be overlooked in a written prescription if there is interference from the above line or if the letter is written in the same height as the neighboring letter "o" as identified below.

Even though Compro and Campral are available in different dosage forms (suppository vs. tablet) there are several similarities between the two drug products that increase the risk for error. Compro and Campral are each only available in one strength increasing the potential for confusion since a corresponding strength does not have to be specified on a prescription. Frequently, physicians prescribe prescription drugs with the directions "use as directed". Confusion may occur if a prescription for either drug is written "use as directed", because of the imprecise directions and the look-alike and sound-alike similarities of each name. In addition, Compro and Campral may each be prescribed three times a day. IMS data was retrieved for the drug name "Compro" to determine the amount of prescriptions written and sold for "Compro" since its approval in the year 2000. IMS data revealed no information on sales by this name, and based on this and the fact that the name "Compro" is a generic name with little market share, DMETS believes that the potential risk is reduced.

Cantil (Mepenzolate Bromide) is an anticholinergic used in the treatment of ulcers. Cantil is a prescription medication available as 25 mg tablets. The usual dosage of Cantil is 25 mg to 50 mg given four times a day. Cantil and Campral have sound-alike similarities to one another. Cantil and Campral each have two syllables and contain similar sounding prefix letter combinations ("can" vs. "cam"). Likewise, the two name endings also have similar rhyming sounds ("til" vs. "pril") which may aid in confusion. However, Cantil and Campral have different directions for use. Cantil is usually prescribed as one to two tablets four times a day and Campral is prescribed as two tablets three times a day. In addition, both drugs have different strengths and indications for use. Thus, the potential for confusion between these two drug names is minimal.

Cartrol (Carteolol Hydrochloride) is a beta-blocker used in the treatment of hypertension. Cartrol is available in 2.5 mg and 5 mg tablet strengths. The initial daily dose of Cartrol is 2.5 mg once daily with a maintenance dose of 2.5 mg to 5 mg once daily. Cartrol and Campral have similar sound-alike characteristics. Both drug names contain two syllables and have similar prefix and suffix letter combinations ("car" vs. "cam" and "rol" vs. "ral"). Cartrol and Campral are both oral tablets but do not share overlapping dosing schedules or drug strengths. In addition, Cartrol is available in two strengths (2.5 mg and 5 mg) while Campral will only be available in one strength (333 mg). Thus, a strength will need to be specified on a prescription

for Cartrol which may help to decrease the risk for confusion between the two drug names. The risk of confusion between Cartrol and Campral is minimal.

Campath (Alemtuzumab) is indicated for the treatment of B-cell chronic lymphocytic leukemia (B-CLL) in patients who have been treated with alkylating agents and who have failed fludarabine therapy. Campath therapy should be initiated at a dose of 3 mg administered as a 2 hour IV infusion daily. When the Campath 3 mg daily dose is tolerated, the daily dose should be increased to 10 mg and continued until tolerated. When the 10 mg dose is tolerated, the maintenance dose of Campath 30 mg may be initiated. The maintenance dose of Campath is 30 mg/day administered three times per week on alternate days for up to 12 weeks. Campath is supplied in single-use clear glass ampules containing 30 mg of Alemtuzumab in 3 mL of solution. Campath and Campral have similar sound-alike and look-alike characteristics. Each name contains two syllables with the prefix "camp". Campath and Campral have completely different indications for use, dosage forms, dosage strengths, dosing schedules, and routes of administration. The likelihood of confusion between the two drug products is minimal.

Captopril is the generic name for Capoten, an angiotensin-converting enzyme (ACE) inhibitor used in the treatment of hypertension and congestive heart failure. Captopril and Campral have similar sounding letter combinations. Each drug name contains similar endings ("pril" vs. "pral") which can sound alike. In addition, both medications can be prescribed for use three times a day, and are oral tablets. However, Captopril is available in four strengths while Campral is available in only one strength. A prescription for Captopril would have to specify a strength in order for a prescription to be filled for a patient. Also, Captopril and Campral contain different numbers of syllables (three vs. two) which may help to differentiate the two names when spoken. DMETS believes that the likelihood of confusion between the two names is low based on the differentiating strengths of Captopril.

III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES

In review of the blister label, container label, carton and insert labeling and has attempted to focus on safety related issues relating to possible medication errors. DMETS has reviewed the current blister label, container label, carton and insert labeling and has identified several areas of possible improvement which might minimize potential user error.

A. BLISTER LABEL (Blister Foil Label)

1. The proprietary and established names should be the most prominent information on the label. We recommend increasing the size of the established name on the blister foil label. The established name should be at least ½ the size of the proprietary name per 21 CFR 201.10(g)(2).

2. Revise the established name to read "tablet" rather than "tablets" as there is one tablet contained in each blister.

3. In order to reduce the potential for confusion, we recommend relocating the company name lower on the label so that it appears away from the proprietary and established names.

B. CARTON LABELING (Blister Box - [ ]

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

2. [ ]

3. [ ]

4. Include a statement '[ ] – not for sale".

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

See comment B1.

D. INSERT LABELING

1. The statement [ ]' should be removed from the "HOW SUPPLIED" section of the package insert as this packaging is for Physician Sample.

APPEARS THIS WAY
ON ORIGINAL

IV. RECOMMENDATIONS:

A. DMETS has no objections to the use of the proprietary name, Campral.

B. This is considered a tentative decision and the firm should be notified that this name with its associated labels and labeling must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary and established names from the signature date of this document.

C. DMETS recommends the labeling revisions as outlined in section III of this review that might lead to safer use of the product. We would be willing to revisit these issues if the Division receives another draft of the labeling from the manufacturer.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Sammie Beam, project manager, at 301-827-3242.

/S/

Nora Roselle, PharmD
Safety Evaluator
Division of Medication Errors and Technical Support
Office of Drug Safety

Concur:

/S/

Alina Mahmud, RPh
Team Leader
Division of Medication Errors and Technical Support
Office of Drug Safety

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/s/

Alina Mahmud
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PHARMACIST

Carol Holquist
6/12/02 01:29:28 PM
PHARMACIST

Jerry Phillips
6/12/02 02:42:42 PM
DIRECTOR

MEMORANDUM

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

Date: **June 10, 2002**

To: **Cynthia McCormick, M.D., Director**
Division of Anesthetics, Critical Care and Addiction Drug Products
(HFD-170)

Through: **Deborah B. Leiderman, M.D., Director**
Controlled Substance Staff (HFD-009)
(signed by Corinne Moody, acting director)

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

Consult on: **Abuse Liability of Acamprosate**
NDA 21-431
Lipha Pharmaceuticals, Inc.

Acamprosate is being developed as a treatment [redacted] CSS was first consulted to assess the abuse potential of acamprosate on December 21, 2001. A separate and complete abuse liability package was not submitted when the NDA was filed.

Material Reviewed:

date submitted	*contents of submission*
March 12, 2002	protocols for receptor binding assays, hot plate assayss, serotonin systems assays
April 17, 2002	protocols for drug discrimination studies (benzodiazepine cue and PCP cue)
May 3, 2002	response from Sponsor to CSS comments on protocols protocols for cell biology assays

CSS Summary of Acamprosate Protocol Review

At the present time, no data from completed abuse liability studies have been submitted to CSS for review. The Sponsor submitted protocols for abuse liability studies that it intends to conduct. These studies include:

* receptor binding assays to evaluate the affinity of acamprosate for all major central nervous system neurotransmitter systems

* cell biology assays for dopamine, norepinephrine and serotonin transporter sites

* drug discrimination behavioral tests to determine if monkeys identify acamprosate as being similar to a benzodiazepine or to PCP

The protocols have been evaluated by CSS and the biochemical assays (receptor binding and cell biology assays) have been deemed acceptable.

In the CSS review of the discrimination studies, CSS noted that flunitrazepam has a very fast onset and is very potent relative to other benzodiazepines. The Sponsor agreed to substitute either lorazepam or chlordiazepoxide for flunitrazepam. The benzodiazepine drug discrimination study is not currently acceptable because the Sponsor has not yet identified which benzodiazepine will be used, the dose of the benzodiazepine to be used, and when peak plasma levels of the chosen benzodiazepine and acamprosate occur following intramuscular administration, to guide selection of appropriate discrimination testing times.

The PCP drug discrimination study is currently unacceptable because the Sponsor has not yet identified what percent responding on the PCP lever constitutes full generalization during the acamprosate challenge tests, how percent responding will be calculated, and how response rate will be calculated and assessed for significance.

The Sponsor submitted three additional protocols: one to evaluate the interactions between acamprosate and morphine in the hot plate test in mice, and two others that evaluate whether acamprosate acts as a partial agonist at 5-HT2 receptors. CSS responded to these protocols with the following on May 29, 2002:

Hot Plate Test

In the original NDA submission, the Sponsor states in Section 5.2.5.1 (Effects on Central Nervous System, pg. 65) that "Acamprosate produced significant analgesic activity at 400 mg/kg" and that "Acamprosate potentiated morphine analgesia, with an ED50 of 210 mg/kg." This study is listed in the Summary of Safety Pharmacology (Table 5.2.3:3) as reference 71. If this study has been completed, it is unclear why the Sponsor submitted a new protocol in March 2002 to assess acamprosate potentiation of morphine analgesia in the hot-plate test.

In the CSS consultation of February 25, 2002, we requested that the Sponsor submit all primary data for the study showing that acamprosate can potentiate morphine analgesia. We request again that the Sponsor send these data for review.

Serotonin System Tests

In the original NDA submission, the Sponsor states in Section 5.1.1 (Nonclinical Pharmacology, pg. 11) that "Acamprosate interacted with the serotonergic system in a complex fashion. At high doses it appeared to be inhibitory when the serotonergic system was stimulated, but was agonistic when the activity in the serotonin system was low." While there does not appear to be a reference to this study in the Summary of Safety Pharmacology (Table 5.2.3:3), if this study has been completed, it is unclear why the Sponsor submitted new protocols in March 2002 to assess the ability of acamprosate to either induce or block head-twitches induced by administration of 5-HTP.

In the CSS consultation of February 25, 2002, we requested that the Sponsor submit all primary data for the study showing that acamprosate acts as a partial agonist in serotonin systems. We request again that the Sponsor send these data for review.

Summary

If the hot plate and serotonin system studies have not been conducted, CSS is willing to prioritize self-administration studies and drug discrimination studies in monkeys over the need for new studies addressing the effect of acamprosate on analgesia or serotonin systems.

Conclusions for Sponsor:

CSS is presently unable to assess the abuse potential of acamprosate because no data from abuse liability studies have been submitted for CSS review.

The biochemical pharmacological experiment protocols submitted by the Sponsor are adequate. The Sponsor should submit additional information on the proposed protocols and should submit data on completed studies, as detailed below:

* The benzodiazepine drug discrimination study is currently unacceptable because the Sponsor has not yet identified whether lorazepam or chlordiazepoxide will be used, the dose of the benzodiazepine to be used, and when peak plasma levels of the chosen benzodiazepine and acamprosate occur following intramuscular administration, to guide selection of appropriate discrimination testing times.

* The PCP drug discrimination study is currently unacceptable because the Sponsor has not yet identified what percent responding on the PCP lever constitutes full generalization during the acamprosate challenge tests, how

percent responding will be calculated, and how response rate will be calculated and assessed for significance.

* The Sponsor should submit primary data from behavioral studies investigating acamprosate self-administration and the ability of acamprosate to generalize to pentobarbital in drug discrimination studies.

* The Sponsor should submit primary data from behavioral studies showing acamprosate potentiation of morphine analgesia and the ability of acamprosate to act as a partial agonist in serotonin systems, as mentioned in the NDA submission. If these studies have not been conducted, CSS is willing to prioritize drug discrimination and self-administration studies in monkeys over the need for new studies addressing the effect of acamprosate on analgesia or serotonin systems.

* Doses for acamprosate to be used in all 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.

Review of submitted protocols

* In vitro pharmacology -- study of acamprosate and chlorure de calcium

Receptor binding assays will be conducted to evaluate the affinity of acamprosate for all major central nervous system neurotransmitter systems. Cell biology assays will also be conducted for NE, DA and 5-HT transporter sites, using rat brain synaptosomes. The conditions listed in these protocols appear to be appropriate for each assay.

* Benzodiazepine-like discriminative stimulus effects of acamprosate

Four adult squirrel monkeys will be trained to respond under a fixed ratio 10 (FR10) schedule of stimulus-shock termination. Once responding is stable, monkeys will be trained to discriminate 0.3 mg/kg midazolam from saline, such that 10 responses on one of two levers will terminate a mild tail shock under midazolam conditions while 10 responses on the other lever will terminate the shock under saline conditions. It is not stated what route of administration will be used, nor the pre-treatment timing.

Following stable discriminative responding, training sessions will be expanded. There appears to be saline components followed by a final drug or saline component. The protocol states that "training sessions will be expanded to comprise 1-4 components, each consisting of a 10-min timeout period followed by 10 presentations of the FR10 schedule." Saline or midazolam are to be given at the onset of the 10-min timeout periods, with midazolam injected only during the final component if drug is to be given. Not all sessions will be drug sessions, though, so that on some days, only saline will be

given to preclude association of the final component with drug administration. Following these extended training sessions, drug sessions with acamprosate or flunitrazepam will begin, with drug trials occurring no more than twice a week. Training sessions will occur on non-drug days.

The doses of acamprosate to be used are 3-100 mg/kg, i.m. Although the protocol states that these doses are based on behaviorally active doses of 3-10 mg/kg, i.v., there are no data provided indicating similarities in plasma levels from these doses between i.v. and i.m. routes of administration. There is no information given on what sort of behavior is produced at 3-10 mg/kg, i.v. or why it might suggest appropriate doses for benzodiazepine-like behavior. The protocol notes that doses above 100 mg/kg, p.o., produce "mild untoward effects" in monkeys, but no data are provided showing what dose of acamprosate given i.m. is equivalent to 100 mg/kg, p.o. Additionally, mild untoward effects are not necessarily detrimental in abuse liability testing, and may indicate doses that are equivalent to those that humans or lesser animals may find reinforcing.

The positive control in this study was originally proposed to be flunitrazepam, at doses of 0.01-0.30 mg/kg, i.m. Following CSS comment that flunitrazepam has a very rapid onset and is very potent, the Sponsor volunteered to substitute either lorazepam or chlordiazepoxide as the positive control. This is acceptable to CSS, as long as the Sponsor notifies CSS of its choice of benzodiazepine and submits proposed doses for review. Full substitution from the positive control benzodiazepine or acamprosate will be considered to have occurred when drug lever responding is 90% or greater.

Cumulative dosing procedures will be used at first to determine the effects of acamprosate and the positive control benzodiazepine. When a dose is found that substitutes for midazolam, that dose will be given in a single injection, with a pretreatment time of 10 or 30 min to compare onset of behavioral effects. This presumably occurs on another session day, but this is not stated. A day after this confirmatory session, the effects of acamprosate will be "examined" to see if there are any prolonged effects from acamprosate. It is not described how the dose will be examined, although this presumably means animals will be tested to see if they chose the midazolam lever.

* Drug discrimination testing of acamprosate in rats

Male rats (n = 6-8) will be trained to discriminate 2.0 mg/kg PCP from saline in a two-lever behavior box. No route of administration or pretreatment time is given for PCP. Rats will be trained on an FR32 schedule of reinforcement. Generalization tests will be conducted two days a week with acamprosate at doses of 30, 100, 170, and 300 mg/kg, i.p., with a pretreatment time of 30 min. If necessary, a dose of 560 mg/kg, i.p., will also be tested if lower doses have no observable effects.

No information is given regarding the analysis of data in terms of what percent responding on the PCP lever constitutes full generalization during the acamprosate challenge tests, nor how percent responding will be calculated. Additionally, response rate is mentioned, but is not detailed in terms of how it will be calculated or assessed for significance.

* Interaction between acamprosate and morphine in the hot plate test in the mouse

Mice will be tested in the hot plate test (at 54 degrees Celsius) to see if acamprosate increases latency to first foot-lick, either alone or in combination with morphine. There will be seven groups: vehicle; acamprosate 200 mg/kg, p.o.; acamprosate 200 mg/kg, p.o. + morphine 4 mg/kg, i.p.; acamprosate 400 mg/kg, p.o.; acamprosate 400 mg/kg, p.o. + morphine 4 mg/kg, i.p.; morphine 4 mg/kg, i.p.; and morphine 8 mg/kg, i.p. Drugs will be administered 30 min prior to each session.

It is unclear how doses of acamprosate were chosen, and why acamprosate is to be given p.o. when morphine is given i.p.

* Evaluation of acamprosate in the 5-HTP head-twitches potentiation in the mouse

The number of head-twitches in mice will be counted following administration of vehicle, 5-HTP (25 mg/kg, s.c., 10 min pretreatment time), acamprosate (200 and 400 mg/kg, p.o., 60 min pretreatment time) or nialamide (16 mg/kg, p.o., 60 min pretreatment time). All sessions are presumably 10 min but this is not stated.

It is unclear how doses of acamprosate and pretreatment times were chosen, and why acamprosate and nialamide are to be given p.o. when 5-HTP is given s.c.

* Evaluation of acamprosate in the 5-HTP head-twitches antagonism in the mouse

The number of head-twitches in mice will be counted following administration of 5-HTP (400 mg/kg, i.p., 30 min pretreatment time). Acamprosate (200 and 400 mg/kg, p.o., 60 min pretreatment time) or cyproheptadine (32 mg/kg, p.o., 60 min pretreatment time) will be administered prior to 5-HTP administration to see if these drugs can block the head-twitch response. All sessions are presumably 10 min but this is not stated.

It is unclear how doses of acamprosate and pretreatment times were chosen, and why acamprosate and cyproheptadine are to be given p.o. when 5-HTP is given s.c.

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

/s/

Katherine Bonson
6/10/02 04:08:07 PM
PHARMACOLOGIST

Corinne Moody
6/10/02 04:12:02 PM
CSO

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINSTRATION	**ODS POSTMARKETING SAFETY REVIEW**

TO:	**FROM:**	**ODS PID #**
Cynthia McCormick MD Director Division of Anesthetics, Critical Care and Drugs to Treat Substance Abuse HFD-170	Martin Pollock Pharm. D. Safety Evaluator Division of Drug Risk Evaluation Office of Drug Safety HFD-430	D020216

DATE REQUESTED: 6/7/02	**REQUESTOR/Phone #:** Lisa Basham, Project Manager 301-827-7420	
DATE RECEIVED: 5/3/02		
DRUG (Est): Acamprosate	**NDA/IND** 21-431	**SPONSOR:** Lipha Pharmaceuticals
DRUG NAME (Trade): Not applicable	**THERAPEUTIC CLASSIFICATION:** C J	
EVENT: all events		

Executive Summary:

Division 170 has been reviewing the NDA for acamprosate for treatment of alcohol abstinence. Acamprosate is approved outside of the United States. In preparation for a pre-approval safety conference on 6/14/02, the Division has asked ODS for a summary of all post-marketing events submitted in AERS.

Ten foreign (France, n=7, United Kingdom, n=3) cases were found. Sex was evenly distributed for male and female. Mean age was 40 years (range 30-67 years). Cases were received from 1998 to 2002. There were no deaths (of the patient) and where known, most (6/9) patients recovered. Two cases had overdoses ranging from 2.5 to 5 times the recommended dose. There was one congenital anomaly that resulted in a therapeutic abortion, with no reported harm to the mother. In the sponsor's proposed labelling, acamprosate 's pregnancy-risk-classified as ' — ' however the particular case of the congenital anomaly was confounded by co-administration of xazepam (classified as "D"),[1] as well the mother's history of alcoholism.[2]

All cases had at least one concomitant medication; for cases where medical history was known (n=6), four had a history that may have contributed to the event (Table 2). Excluding the congenital anomaly, there were nine patients who had a total of 38 different events. Of these 38 events (Table 3), 18 were not mentioned in the sponsor's proposed labelling. The most common type of labelled and unlabelled event was neurologic-related.

In this case series, acamprosate was not associated with any deaths and where known, most patients recovered. The ten reports retrieved in AERS are too small a number to allow for any further assessment concerning the post-marketing safety profile of acamprosate.

Results:

Demographics and Dose

All cases were foreign (France, n=7; United Kingdom, n=3). Sex was male (n=5) and female (n=5); for nine patients, the mean age was 40 years and range was 30-67 years. Cases were received by FDA in the following years: 1998 (n=2); 1999 (n=2); 2000 (n=3); 2001 (n=2); 2002 (n=1). Eight cases had a history of alcohol addiction. Dosage information was reported for five cases. Two of these cases were overdoses (see below) and the remaining three cases had doses of 1, 1.3 and 2 grams/day, respectively.

Overdose

There were four cases that had "overdose" as one of the event terms. Two of these cases were acute overdoses (hyperventilation, hypertension; tremor, agitation) and the amounts ingested were 4.66 and 9.99 grams respectively. One of these patients was also concomitantly using alcohol. Both of these cases also had reported concomitant overdoses of venlafaxine. The proposed normal recommended acamprosate dose is 2 grams per day. The proposed labelling also states that with acute acamprosate overdoses (as much as 56 gram per day), the only associated adverse event was diarrhea.

In another overdose case, one patient took an unknown amount of acamprosate along with eight other medications in a suicide attempt which resulted in coma and respiratory depression (patient recovered). In the remaining overdose case (convulsion, dyskinesia, syncope), the overdose was not acamprosate, but Mucilar (carbocisteine), however, the patient also had taken a recommended dose of acamprosate.

Outcome and Duration of Therapy

A listing for all events in each case is given in Table 1 below. There were no deaths in any of the ten cases. Six patients recovered; three did not and in one, recovery was unknown. Outcome was hospitalization for all the cases. Duration of therapy was known for four cases. One case resulted in a congenital anomaly (see below). The other three cases had durations of therapy of 43, 45, and 97 days, respectively.

Congenital Anomaly

In one case, a congenital anomaly was seen after 118 days exposure of an unknown dose of acamprosate and 86 days exposure to oxazepam. This resulted in a therapeutic abortion, with no reported harm to the mother. Details of the anomalies are given in Table 1 below. This case was further confounded by the concomitant exposure of the fetus to oxazepam, for which human congenital malformations have been reported,[1] as well the mother's history of alcoholism.[2]

Concomitant Medication and Medical History

All patients were receiving at least one other concomitant medication as follows: one medication (n=3); two medications (n=2); three to four medications (n=2); five medications (n=2); nine medications (n=1). Because acamprosate is not yet a marketed product in the U.S., all of the reports in this case series were submitted to FDA based upon the concomitant medication that was a marketed U.S. product by the respective sponsors. The case with nine concomitant medications was a multi-drug intoxication and suicide attempt that resulted in coma and respiratory depression (patient recovered). Two patients (one an overdose case, mentioned above) were drinking alcohol while taking acamprosate; two other patients were taking disulfiram. Four cases had unknown medical history. In the remaining six cases, four had medical history that may have contributed to one or more of the adverse events (Table 2). One of these four cases also had taken an overdose of carbocisteine (mucolytic).

Labelled vs. Unlabelled Events

Excluding the congenital anomaly, there were nine cases that had 38 different adverse event terms. Of these 38 terms, 20 were mentioned in the proposed labelling and 18 were not (Table 3). For labelled events, the system Organ Classes (SOC) that had two or more events were Dermatologic (n=6), Neurologic (n=6), Metabolic (n=2), and Psychiatric (n=2). For unlabelled events, SOC's that had two or more events were Neurological (n=4), Respiratory (n=3), Psychiatric (n=2), Renal and Urinary (n=2), and General (n=2).

Discussion and Conclusion

The limited number of all-foreign cases in AERS of acamprosate-associated post-marketing adverse events was expected because sponsors are not required to report postmarketing adverse events to FDA for products not marketed in the United States. The ten acamprosate reports in AERS were submitted by different sponsors pertaining to drugs that they market in the U.S.

In this case series, acamprosate was not associated with any deaths and where known, most patients recovered. The ten reports retrieved in AERS are too small a number to allow for any further assessment concerning the post-marketing safety profile of acamprosate.

Reason for Request/Review: Division 170 has been reviewing the NDA for acamprosate for treatment of alcohol abstinence. Acamprosate is approved outside of the United States. In preparation for a pre-approval safety conference on 6/14/02, the Division has asked ODS for a summary of all post-marketing events submitted in AERS.

Search Date: 5/6/02	**Search Type(s):** AERS

Search Criteria: All events. Drug names: acamprosate (generic name), Aotal®, and Campral® (trade names outside of United States).

Search Results: Ten unique cases were found.

Reviewer's Signature / Date:	**Team Leader's Signature / Date:**
Martin L. Pollock, Pharm. D.	Lanh Green, R.Ph., M.P.H.
Division Director Signature / Date:	
Julie Beitz, M.D.	

[1]Serax (oxazepam) product labelling (Use in Pregnancy); Physician's Desk Reference, Medical Economics Co, Montvale, N.J. 1997

[2]Behnke M, Eyler FD. The consequences of prenatal substance use for the developing fetus, newborn, and young child. *nt J Addict* 1993; Nov;28(13):1341-91.

TABLE 1
ADVERSE EVENTS (AE's) FOR ALL CASES

ISR #	AE1	AE2	AE3	AE4	Additional AE's
3036637-4	Neuropathy	Vocal cord paralysis			
3105996-6	Overdose	hyperventilation	Hypertension		
3182197-7	Overdose	Tremor	Agitation		
3274179-1	Pustular rash	Maculopapular	Rash		
3480969-2	psychosis	Confusion	Agitation		
3520896-5	Fetal malformation	Cleft palate	Enlarged median and right lateral buds	Cerbellar hypoplasia	Microopthalmos, fetal maturation impaired, intrauterine growth retardation, caudal extremity hypertrophy, dilatation of fourth ventricle.
3550406-8	Suicide attempt (unsuccessful)	Coma	Respiratory depression	Miosis	Overdose
3802346-4	Bronchospasm	Oliguria	Hepatomegaly	Discolored urine	Increased weight, dermatitis, exfoliative pruritis, rash, erythematous rash, upper and lower edema
3839875-3	Convulsion	Syncope	Dyskinesia	Sweating	Overdose[+]
3868445-6	Blood creatinine increased	Phosphokinase increased	hyponatremia		

[+]overdose of Muciclar (carbocisteine, mucolytic)

TABLE 2
CASES WITH PRIOR MEDICAL HISTORY THAT MAY HAVE CONTRIBUTED TO ONE OR MORE ADVERSE EVENTS

ISR #	Prior medical history	Adverse event experienced with acamprosate
3480969-2	Anxiety	Delusion, confusion, agitation, psychosis, paranoid disorder
3550406-8	Suicide attempt, non-accidental overdose	Suicide
3802346-4	Herpes zoster	Exfoliative dermatitis, erythematous rash
3839875-3	Convulsions from tapering of medications	Convulsions

TABLE 3
ADVERSE EVENT TERMS (N=9 CASES) LABELLED AND UNLABELLED IN PROPOSED ACAMPROSATE LABELLING.

Labelled Events (n=20)			Unlabelled Events (n=18)		
System Organ Class[+]	**Event**	**Number of Events**	**System Organ Class**	**Event**	**Number of Events**
Cardiac	Syncope	1	Cardiac	Hypertension	1
Dermatologic	Pruritis	2	Dermatologic	Sweating	1
	Rash	3	General	Upper edema	1
				Lower edema	1
	--pustular	1	Hepatobiliary	Hepatomegaly	1
	--macropapular	1	Investigations	Increased weight	1
	--erythematous	1	Metabolic	Phosphokinase increased	1
	Dermatitis, exfoliative	1	Neurological	Vocal cord paralysis	1
Injury, poisoning	Overdose	3		Dyskinesia	1
Metabolic	Hyponatremia	1		Miosis	1
	Blood creatinine increased	1		Agitation	1
Neurologic	Neuropathy	1	Psychiatric	Delusion	1
	Agitation	1		Paranoid disorder	1
	Coma	1	Renal and urinary	Discolored urine	1
	Tremor	1		Oliguria	1
	Confusion	1	Respiratory	Respiratory depression	1
	Convulsion	1		Bronchospasm	1
Psychiatric	Psychosis	1		Hyperventilation	1
	Suicide attempt	1			

[+]MedDRA classification

Basham-Cruz, Lisa

From: Lenkel, Laurie
Sent: Friday, June 07, 2002 1:43 PM
To: Basham-Cruz, Lisa
Subject: acamprosate labeling

Lisa,

DDMAC will review the proposed labeling for acamprosate when the sponsor resubmits labeling in response to the expected "approvable" letter it will receive. Please provide the revised labeling to us as soon as available to allow sufficient time for review.

Thank you,

Laurie Lenkel

MEMORANDUM

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

Date: May 29, 2002

To: Cynthia McCormick, M.D., Director
Division of Anesthetics, Critical Care and Addiction Drug Products
(HFD-170)

Through: Deborah B. Leiderman, M.D., Director
Controlled Substance Staff (HFD-009)

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

Consult on: Sponsor responses to CSS questions on
Proposed preclinical abuse liability protocols
Acamprosate (Lipha Pharmaceuticals, Inc.)
NDA 21-431
Submitted May 3, 2002

Background:

The Controlled Substance Staff provided an initial consultation to HFD-170 on April 12, 20C2. Several questions were raised and directed to the Sponsor regarding its March 11, 2002, proposed preclinical protocols.

The Sponsor responded to these questions in a May 3, 2002, submission. These responses are addressed below.

Clarifications:

Hot Plate Test

In the original NDA submission, the Sponsor states in Section 5.2.5.1 (Effects on Central Nervous System, pg. 65) that "Acamprosate produced significant analgesic activity at 400 mg/kg" and that "Acamprosate potentiated morphine analgesia, with an ED50 of 210 mg/kg." This study is listed in the Summary of Safety Pharmacology (Table 5.2.3:3) as reference 71. If this study has been completed, it is unclear why the Sponsor submitted a new protocol in March 2002 to assess acamprosate potentiation of morphine analgesia in the hot-plate test.

In the CSS consultation of February 25, 2002, we requested that the Sponsor submit all primary data for the study showing that acamprosate can potentiate morphine analgesia. We request again that the Sponsor send these data for review.

Serotonin System Tests

In the original NDA submission, the Sponsor states in Section 5.1.1 (Nonclinical Pharmacology, pg. 11) that "Acamprosate interacted with the serotonergic system in a complex fashion. At high doses it appeared to be inhibitory when the serotonergic system was stimulated, but was agonistic when the activity in the serotonin system was low." While there does not appear to be a reference to this study in the Summary of Safety Pharmacology (Table 5.2.3:3), if this study has been completed, it is unclear why the Sponsor submitted new protocols in March 2002 to assess the ability of acamprosate to either induce or block head-twitches induced by administration of 5-HTP.

In the CSS consultation of February 25, 2002, we requested that the Sponsor submit all primary data for the study showing that acamprosate acts as a partial agonist in serotonin systems. We request again that the Sponsor send these data for review.

Other behavioral tests

The Sponsor has not yet submitted primary data, as requested in the CSS consultation of February 25, 2002, for self-administration studies or drug discrimination studies using acamprosate in animals trained to discriminate pentobarbital that were mentioned in the original NDA submission. We request again that the Sponsor send these data for review.

Conclusions:

The Sponsor should submit primary data from behavioral studies showing acamprosate potentiation of morphine analgesia and the ability of acamprosate to act as a partial agonist in serotonin systems, as mentioned in the NDA submission. If these studies have not been conducted, CSS is willing to prioritize discrimination and self-administration studies in monkeys over the need for new studies addressing the effect of acamprosate on analgesia or serotonin systems.

The Sponsor should submit primary data from behavioral studies investigating acamprosate self-administration and the ability of acamprosate to generalize to pentobarbital in drug discrimination studies.

The following responses to request for information are **adequate**:

-- *Experimental procedures for cell biology assays*

-- *Rationale for pretreatment times for acamprosate in the behavioral tests*

-- *Rationale for the route of administration to be used in benzodiazepine discrimination test.*

-- *Rationale for the substitution of lorazepam or chlordiazepoxide for flunitrazepam as the benzodiazepine comparator in the discrimination test.*

Lorazepam and chlordiazepoxide are both acceptable as the benzodiazepine comparator in the discrimination test. The Sponsor should choose one of these drugs as the comparator and submit proposed doses to be used.

The following responses to request for information are **inadequate**:

-- *Pretreatment times to be used in the benzodiazepine discrimination test*

Discrimination testing should be conducted when peak plasma levels of each drug will be obtained following the chosen route of administration. Information should be provided that show when peak plasma levels of acamprosate are obtained following i.m. administration, and discrimination testing should be scheduled to correlate to this peak plasma levels.

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/s/

Katherine Bonson
6/12/02 04:50:00 PM
PHARMACOLOGIST

Corinne Moody
6/12/02 05:00:27 PM
CSO
The original (hard copy) was previously signed by Dr. Leiderman. I am signing DFS copy for Dr. Leiderman.

FOOD AND DRUG ADMINISTRATION
OFFICE OF DRUG EVALUATION II

TO: Anita Goodman & Bruce Goddard
Phone Number: 978-542-1904 (x11, 12, or 14)
Fax Number: 978-542-1950

FROM: Lisa E. Basham-Cruz, Regulatory Project Manager

DIVISION OF ANESTHETIC, CRITICAL CARE AND ADDICTION DRUG PRODUCTS

CDER/DAACADP (HFD-170), 5600 Fishers Lane
Rockville, Maryland 20857

PHONE: (301) 827-7410 FAX: (301) 443-7068

Total number of pages, including cover sheet:___Date: 5/13/02

COMMENTS:

Anita & Bruce,

Attached are preliminary draft comments on the drug substance from the chemistry review. Drs Koble and Lewis would like to have a telecon later this week to discuss (Thurs or Fri).
Best Regards, Lisa

Redacted 2

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

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/s/

Lisa Basham-Cruz
6/5/02 02:13:21 PM
CSO

FOOD AND DRUG ADMINISTRATION
OFFICE OF DRUG EVALUATION II

TO: Anita Goodman
Phone Number: 978-542-1904 (x11, 12, or 14)
Fax Number: 978-542-1950

FROM: Lisa E. Basham-Cruz, Regulatory Project Manager

DIVISION OF ANESTHETIC, CRITICAL CARE AND ADDICTION DRUG PRODUCTS

CDER/DAACADP (HFD-170), 5600 Fishers Lane
Rockville, Maryland 20857

PHONE: (301) 827-7410 FAX: (301) 443-7068

Total number of pages, including cover sheet: 2 Date: 5/21/02

COMMENTS:

Anita,

Attached are additional draft chemistry comments and requests from the chemists that they may want to discuss today. Thanks!

Best Regards,
Lisa

Redacted 1

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

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/s/

Lisa Basham-Cruz
6/7/02 12:38:21 PM
CSO

FOOD AND DRUG ADMINISTRATION
OFFICE OF DRUG EVALUATION II

TO: Anita Goodman
Phone Number: 978-542-1904 (x11, 12, or 14)
Fax Number: 978-542-1950

FROM: Lisa E. Basham-Cruz, Regulatory Project Manager

DIVISION OF ANESTHETIC, CRITICAL CARE AND ADDICTION DRUG PRODUCTS

CDER/DAACADP (HFD-170), 5600 Fishers Lane
Rockville, Maryland 20857

PHONE: (301) 827-7410 FAX: (301) 443-7068

Total number of pages, including cover sheet: 2 Date: 5/23/02

COMMENTS:

Anita,

Attached are additional chemistry/biopharm requests.

Best Regards,
Lisa

Request for additional information regarding acamprosate dissolution methodology

The Applicant proposes the following specifications for acamprosate dissolution methodology:

Equipment type: [ ]

Medium: Acid stage: [ ]
Buffer stage: pH 6.8 [ ] medium maintained at 37°C ± 0.5°C

Speed of rotation: [ ]

Sampling time: [ ]

Analytical method: Assay of calcium-acamprosate by HPLC after direct detection using UV absorption [ ]

Dissolution specifications (% of calcium acamprosate dissolved):
- [ ]
- pH 6.8 buffer 120 min [ ] %.

Please submit the following requested information:

1. Justification of using Method B over Method A

2. Dissolution data from 333 mg enteric-coated "current" formulation tablet lot(s) used in pharmacokinetic studies using the proposed method, Method B (e.g., Lot # 1862 from BE study, etc.)

3. Justification of using [ ] speed; Are there any data from other speeds,

4. Justification for using pH 6.8; Are there any data at other pH values,

5. Justification of proposing [ ] % release [ ] when [ ] is actually measured.

6. Justification of proposing 120 minutes as a single time point for the buffer solution; Are there any data at time-points earlier than 120 minutes, e.g., 30, 60, etc.?

7. The complete dissolution profile data (pH 6.8 buffer) for all of the stability test stations for Batches 1500, 1501, and 1502. The stability reports only include single-point dissolution values (120 minutes) for pH 6.8 medium dissolution. The percent dissolution at 60 and 90 minutes for the stability studies (0, 3, 6, 9, and 12 months) are required.

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/s/

Lisa Basham-Cruz
5/30/02 05:45:37 PM
CSO

FOOD AND DRUG ADMINISTRATION
OFFICE OF DRUG EVALUATION II

TO: Anita Goodman
Phone Number: 978-542-1904 (x11, 12, or 14)
Fax Number: 978-542-1950

FROM: Lisa E. Basham-Cruz, Regulatory Project Manager

DIVISION OF ANESTHETIC, CRITICAL CARE AND ADDICTION DRUG PRODUCTS

CDER/DAACADP (HFD-170), 5600 Fishers Lane
Rockville, Maryland 20857

PHONE: (301) 827-7410 FAX: (301) 443-7068

Total number of pages, including cover sheet: 3 Date: 5/30/02

COMMENTS:

Anita,

Attached are comments and requests for information from the Controlled Substance Staff.

Best Regards,
Lisa

Controlled Substance Staff DRAFT comments and request for information.

1. The following request pertains to the PCP Discrimination protocol submitted April 16, 2002.

   Provide an explanation for what percent responding on the PCP lever constitutes full generalization during the acamprosate challenge tests, as well as how percent responding will be calculated. Additionally, provide details of how response rate will be calculated and assessed for significance.

2. The following comments and requests pertain to your response to our April 19, 2002, discipline review letter concerning the abuse liability protocols you submitted on March 11, 2002.

   a. **Clarifications:**

      (1) *Hot Plate Test:*

         (i) In the original NDA submission, you state in Section 5.2.5.1 (Effects on Central Nervous System, pg. 65) that "Acamprosate produced significant analgesic activity at 400 mg/kg" and that "Acamprosate potentiated morphine analgesia, with an ED50 of 210 mg/kg." This study is listed in the Summary of Safety Pharmacology (Table 5.2.3:3) as reference 71. If this study has been completed, please clarify why you submitted a new protocol in March 2002 to assess acamprosate potentiation of morphine analgesia in the hot-plate test.

         (ii) In our February 25, 2002, teleconference, we requested that you submit all primary data for the study showing that acamprosate can potentiate morphine analgesia. Please send these data for review. If these data are not available, please explain.

      (2) *Serotonin System Tests:*

         (i) In the original NDA submission, you state in Section 5.1.1 (Nonclinical Pharmacology, pg. 11) that "Acamprosate interacted with the serotonergic system in a complex fashion. At high doses it appeared to be inhibitory when the serotonergic system was stimulated, but was agonistic when the activity in the serotonin system was low." While there does not appear to be a reference to this study in the Summary of Safety Pharmacology (Table 5.2.3:3), if this study has been completed, please clarify why you submitted new protocols in March 2002 to assess the ability of acamprosate to either induce or block head-twitches induced by administration of 5-HTP.

         (ii) In our February 25, 2002, teleconference, we requested that you submit all primary data for the study showing that acamprosate acts as a partial agonist in serotonin systems. Please send these data for review. If these data are not available, please explain.

(3) *Other behavioral tests:*

You have not yet submitted, as requested in our February 25, 2002, teleconference, primary data for self-administration studies or drug discrimination studies using acamprosate in animals trained to discriminate pentobarbital that were mentioned in the original NDA submission. Please send these data for review. If these data are not available, it will be important to generate such data.

b. **Summary:**

(1) If available, you should submit primary data from behavioral studies showing acamprosate potentiation of morphine analgesia and the ability of acamprosate to act as a partial agonist in serotonin systems, as mentioned in the NDA submission. If new studies are required to generate all or part of the data discussed above, CSS is willing to waive the requirement for new studies addressing the effect of acamprosate on analgesia or serotonin systems in order to facilitate completion of discrimination and self-administration studies in monkeys.

(2) Submit primary data from behavioral studies investigating acamprosate self-administration and the ability of acamprosate to generalize to pentobarbital in drug discrimination studies.

(3) The following responses to our April 19, 2002, request for information are **adequate**:

(i) Experimental procedures for cell biology assays

(ii) Rationale for pretreatment times for acamprosate in the behavioral tests

(iii) Rationale for the route of administration to be used in benzodiazepine discrimination test.

(iv) Rationale for the substitution of lorazepam or chlordiazepoxide for flunitrazepam as the benzodiazepine comparator in the discrimination test. Lorazepam and chlordiazepoxide are both acceptable as the benzodiazepine comparator in the discrimination test. Choose one of these drugs as the comparator and submit proposed doses to be used.

(4) The following response to our April 19, 2002, request for information is **inadequate**:

Pretreatment times to be used in the benzodiazepine discrimination test. Discrimination testing should be conducted when peak plasma levels of each drug will be obtained following the chosen route of administration. Provided information that shows when peak plasma levels of acamprosate are obtained following i.m. administration, and schedule discrimination testing to correlate with peak plasma levels.

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/s/

Lisa Basham-Cruz
6/5/02 02:25:18 PM
CSO

Office of Clinical Pharmacology and Biopharmaceutics
New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	21-431	**Brand Name**	Not determined yet
OCPB Division (I, II, III)	II	**Generic Name**	Acamprosate
Medical Division	DACCADP	**Drug Class**	
OCPB Reviewer	Sandip Roy	**Indication(s)**	✓
OCPB Team Leader	Suresh Doddapaneni	**Dosage Form**	Enteric coated tablets
		Dosing Regimen	666 mg tid
Date of Submission	12/27/01	**Route of Administration**	oral
Estimated Due Date of OCPB Review	5/15/02	**Sponsor**	Lipha Pharmaceuticals
PDUFA Due Date	6/27/02	**Priority Classification**	1P
Division Due Date	5/17/02		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments if any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:	X	2		
Isozyme characterization:	X			
Blood/plasma ratio:				
Plasma protein binding:	X			
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X	2		2 IV studies
multiple dose:	X	2		
Patients-				
single dose:	X	1		
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:	X	4		Other formulations
Drug-drug interaction studies -				
In-vivo effects on primary drug:	X	4		
In-vivo effects of primary drug:	X	3		
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:	X	1		
pediatrics:				
geriatrics:				
renal impairment:	X	1		

hepatic impairment:	X	2		
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:	X	1		
II. Biopharmaceutics				
Absolute bioavailability:	X			
Relative bioavailability -				
solution as reference:	X	1		
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:	X	2		
replicate design; single / multi dose:				
Food-drug interaction studies:	X	1		
Dissolution:	X	1		
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan	X			Requested a deferral (age 12 and above)
Literature References				
Total Number of Studies		**26**		

Filability and QBR comments		
	"X" if yes	**Comments**
Application filable ?	X	
Comments sent to firm ?	No	
QBR questions (key issues to be considered)	**Is there a dose-response relationship?** **Are the TBM and Clinical formulations adequately linked?** **Are the ADME characteristics of drug adequately characterized?** **Is the food effect on the formulation adequately described?** **Is there a potential for drug-drug interactions?** **Is the pharmacokinetics adequately described in renal impairment subjects?** **Is the dissolution methodology and proposed specifications adequate for this product?**	
Other comments or information not included above		
Primary reviewer Signature and Date		
Secondary reviewer Signature and Date	**Suresh Doddapaneni, 2/13/02**	

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/s/

Suresh Doddapaneni
2/13/02 10:53:25 AM
BIOPHARMACEUTICS

MEMORANDUM

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

DATE: May 9, 2002

TO: NDA File

FROM: Lisa E. Basham-Cruz

SUBJECT: **request for information**
21,431, acamprosate

On March 14, 2002, Dr. Lewis, reviewing chemist, and I called Lipha Pharmaceuticals, Inc. to request the following information:

1. Provide a reference to the correct 21 CFR regulation regarding the [ ]
2. Regarding the [ ] foil, provide the qualitative and quantitative composition of the adhesive [ ] Provide the identity and quantitative composition of the labeling inks.
3. Regarding the [ ] plastic containers, provide the manufacturer/supplier for the bottles and caps. Identify the liner & innerseal. Provide a reference indicating compliance with the pertinent 21 CFR regulations regarding food-contact (bottle, cap, and liner). This may be done via reference (Letter of Authorization) to a Type III packaging DMF, or by a certification letter from the supplier/manufacturer of the packaging materials.
4. Provide updated stability data for the drug product.

Lipha submitted the requested stability data on April 19, 2002, which was received by the Agency on April 22, 2002. On May 9, 2002, I called the Sponsor to inquire on the status of the remaining requests. We agreed that I would hand deliver the Sponsor a list of the remaining items at the Psychopharmacologic Drugs Advisory Committee Meeting on May 10, 2002. The list will be delivered to the Sponsor in the form of this memo.

- Lisa Basham-Cruz, M.S.

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/s/

Lisa Basham-Cruz
5/9/02 04:41:22 PM
CSO

4/19/02

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-431

INFORMATION REQUEST LETTER

Lipha Pharmaceuticals Inc.
1114 Avenue of the Americas; 41st floor.
New York, New York 10036-7703

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

Dear Dr. Goodman:

Please refer to your December 27, 2002, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for acamprosate.

We also refer to your submission dated March 11, 2002.

The Controlled Substance Staff have reviewed your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. Provide the experimental procedures to be used for cell biology assays.

2. Provide the rationale for the doses of acamprosate to be used in the hot plate test and an explanation for why acamprosate is to be given orally when morphine is given intraperitoneally.

3. Provide the rationale for the doses of acamprosate and pretreatment times to be used in the head-twitch test, and an explanation for why acamprosate and nialamide are to be given orally when 5-HTP is given subcutaneously.

4. Rationale for the doses of acamprosate and pretreatment times to be used in the head-twitch antagonism test, and an explanation for why acamprosate and cyproheptadine are to be given p.o. when 5-HTP is given subcutaneously.

5. Provide the doses of all drugs and pretreatment times to be used in the benzodiazepine discrimination test.

6. The rationale for the doses of acamprosate and the route of administration to be used in benzodiazepine discrimination test is inadequate. Assumptions cannot be made about the behavioral effects induced by a particular dose of a drug based on behavioral effects induced by that dose given via a different route of administration in the absence of plasma levels of the drug.

7. Provide ther rationale for the selection of flunitrazepam as the benzodiazepine comparator in the discrimination test. Relative to other benzodiazepines, flunitrazepam has a very fast onset and is very potent. A rational should also be provided for the doses of flunitrazepam to be used in the benzodiazepine discrimination test.

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
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
4/19/02 03:13:36 PM

MEMORANDUM

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

DATE: May 14, 2002

TO: NDA file

THROUGH : Celia Winchell

FROM: Lisa Basham-Cruz

SUBJECT: **preparation for PDAC meeting May 10, 2002**
NDA 21-431, acamprosate

ATTENDEES:

Lipha	Title
Anita M. Goodman, MD	Exec. VP & COO, Lipha Pharmaceuticals, Inc.
Bruce Goddard, RAP	Sr. Dir., Compliance and Reg. Affairs, Lipha
Sylvie Chabac, MD	New Business Development; (former acamp. PM); MERCK/Lipha s.a.
Barbara Mason, PhD	Prof., Dept. of Psych. & Behav. Sci., Dir, Div. Of Substance Abuse; Univ. Miami School of Med.
[redacted]	[redacted]
[redacted]	[redacted]
Ralph Harkins, PhD	Exec, Dir, Biostatistics & Clinical Data Management; Forest Labs, Inc.
Robert Ashworth, PhD	Senior Director, Regulatory Affairs, Forest Labs, Inc.
FDA	**Title**
Cynthia G. McCormick MD	Division Director
Celia Winchell, M.D.	Medical Team Leader, Addiction Drug Products
Sue Jane Wang, PhD	Senior Mathematical Statistician
Tom Permutt, PhD	Mathematical Statistician, Team Leader
Sandy Titus, PhD	Advisory Committee Staff
Lisa Basham-Cruz, MS	Regulatory Project Manager

On May 2, 2002, Division representatives met with Lipha Pharmaceuticals to discuss the presentations for the Psychopharmacologic Drugs Advisory Committee (PDAC) meeting scheduled for May 10, 2002. The purpose of the PDAC meeting is to obtain guidance from the committee members on how to evaluate the disparate efficacy data submitted for pending NDA 21-431, for acamprosate. The indication sought for this drug is [redacted]

Dr. McCormick began the meeting by providing an overview of the progress of the NDA review. The clinical review is nearly completed in terms of efficacy and statistics. The safety review is still ongoing. With regard to the preclinical review, the Executive Carcinogenicity Assessment Committee (CAC) did not accept the results of the mouse study due to suboptimal dosing and nematode infestation. This study will have to be replicated. We can work through the timing and the implications on NDA approval. The CAC minutes will be faxed to the Sponsor.

The discussion moved on to the PDAC presentations. Dr. McCormick said that she would state, with the Sponsor's permission, that the safety issues are not yet settled. It is important for the committee to understand that not all parts of the review are complete. The Agency's presentation will focus on efficacy and the disparate results of the European and US trials. The Sponsor was concerned that, by not presenting safety data, the committee may get the impression that there are safety issues. Dr. McCormick said that she will clearly state that there is no particular problem with the safety review, but that it is not completed yet, and therefore cannot be commented on. It was agreed that the Sponsor may present observations of safety without interpretation or conclusions, i.e., no risk:benefit discussion. Dr. Winchell added that the PDAC meeting is intended to help determine what goes into the benefit part of the equation, so a risk:benefit presentation is not appropriate at this time. Dr. McCormick said that if the committee determines that this product is needed, and if there are no other issues to hold up approval, the mouse carcinogenicity study may be accepted as a post marketing commitment. A discussion ensued about the differences between the European and US studies that may have confounded the results, including differences in: motivation, abstinence, polysubstance abuse, data collection and analysis, failure of randomization, and demand characteristics.

It was agreed that Lipha would not present on the European supportive studies, safety, or risk:benefit, but would discuss the methodologies of data collection and compare and contrast the European and US studies. They will describe the TLFB (timeline follow back) method of data collection. They will include their theories about why the US study failed. The FDA presentation will describe the issues with both the European and US studies that are causing the dilemma for the Agency.

-Lisa E. Basham-Cruz, MS
-Celia J. Winchell, MD/concurrence

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/s/

Lisa Basham-Cruz
5/14/02 03:29:17 PM
CSO

Celia Winchell
5/14/02 03:35:57 PM
MEDICAL OFFICER

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and/or confidential

commercial information

(b5)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:
Division of Drug Marketing and Communication (DDMAC)
ttn: Laura Governale and Laurie Lenkel

FROM:
Cynthia G. McCormick, M.D.
Division of Anesthetic, Critical Care, and Addiction Drug Products (HFD-170)

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
4/19/02		21-431	NDA	December 27, 2001

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
acamprosate	High (PDUFA date June 27, 2002)	NME	June 14, 2002

NAME OF FIRM: Lipha Pharmaceuticals

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ■ OTHER *(SPECIFY BELOW)*:

Package Insert

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

Please review the attached package insert for acamprosate from a DDMAC perspective.

Contact Lisa E. Basham-Cruz at 301-827-7420 with any questions.

Please CC: Lisa Basham-Cruz (bashaml) and Aleta Crane (cranea) on response. Thanks!

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one) ☐ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANESTHETIC, CRITICAL CARE, AND ADDICTION DRUG PRODUCTS
HFD-170, Room 9B-45, 5600 Fishers Lane, Rockville MD 20857
Tel:(301) 827-7410

MEMORANDUM

DATE: April 15, 2002

FROM: Cynthia G. McCormick, MD, Director
Division of Anesthetic, Critical Care and Addiction Drug Products
Office of Drug Evaluation II, CDER, FDA

TO: Chair, Members and Invited Guests
Psychopharmacologic Drugs Advisory Committee

RE: Overview of the May 10, 2002 Meeting of the Psychopharmacologic Drugs Advisory Committee to discuss the efficacy of Acamprosate

Chronic alcoholism continues to be a widespread and debilitating disorder which places a tremendous burden on society in terms of healthcare costs, lost wages, and personal suffering. The need for effective pharmacologic agents for this disorder cannot be overstated. The FDA has received a New Drug Application (NDA) for acamprosate, a product that has been available in Europe for the treatment of chronic alcoholism for nearly 15 years. The FDA is seeking the advice of the Psychopharmacologic Drugs Advisory Committee and experts in clinical research in alcoholism on your assessment of the evidence provided in support of the efficacy of this product.

The efficacy database on which this application rests includes a number of European clinical trials performed over the last approximately 15 years, three of which are considered "pivotal" studies, and a single U.S. multicenter trial completed recently. The results of these studies, on their face, paint a conflicting picture. The review team has attempted to explore the apparent contradictions by evaluating the differences between the studies through a variety of analyses. The discussion of these factors and how they contribute to our understanding of the drug's efficacy will be the primary focus of this meeting.

The three pivotal European trials, Pelc II, Paille, and PRAMA, were of similar design, methodology and outcomes. The trials have been considered successful, and the review team concurs with this assessment. The U.S. study, on the other hand, was not successful in demonstrating superiority over placebo on the primary outcome and most secondary measures, and indeed on some measures, the drug appeared to perform less well.

Some differences between the European and U.S. studies can be clearly delineated. The European population was primarily one of pure alcoholics; the U.S. population was largely polysubstance abusers. The European patients had either recently undergone detoxification or were abstinent prior to randomization; the U.S. patients were generally not abstinent prior to randomization. The ascertainment of drinking data in the European studies was essentially retrospective and not diary-based; it was very methodical and rigorous in the U.S. study, using daily drinking diaries and there were tight follow-up provisions in place. The review team has attempted to apply the same conservative approach to analysis of the data in the U.S. and European studies but have obtained disparate results. Finally, the studies differed in terms of the formulation of acamprosate that was used and the regimen of administration, although the total daily dose (TDD) was essentially the same.

Other aspects of the application are straightforward. Preliminary evaluation of the clinical safety data has revealed no serious signals of toxicity, and there has been an absence of serious adverse event reports from the post marketing setting in Europe. There are elements of the drug's safety database which have not been fully evaluated at the time of this memorandum, such as the carcinogenicity profile. This is currently under evaluation and may require further exploration.

It is not uncommon for an NDA database to have both successful results and results which are not considered "positive". In general, the Agency's approach to such a situation is to consider the totality of the evidence, giving consideration and weight to such factors as the quality of the data, strength of the effect size, statistical significance, and assessment of whether the effects, even in the negative trials, are supportive, trend in the same direction, and are not contradictory. If a trial has truly failed, that is, demonstrated an effect that contradicts the remainder of the evidence, an attempt is made to understand the reason for the contradiction, and to determine, on balance, which results are more credible. Occasionally further clinical work is needed.

In this NDA, the differences between the studies are clear. The questions that remain, however, are whether these differences can adequately account for the disparate results, and whether the failure of acamprosate in the U.S. trial was a function of a difference in the responsiveness of the U.S. alcoholic population or a different manifestation of the disease. Stated differently, can the results of the European trials be generalized to the U.S. alcoholic population?

The FDA is inviting the committee to discuss a series of questions probing the issues surrounding the efficacy results, and to make recommendations that will enable the FDA to make a determination of approvability of this product for [redacted]

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

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

MEMORANDUM

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

Date: April 12, 2002

To: Cynthia McCormick, M.D., Director
Division of Anesthetics, Critical Care and Addiction Drug Products
(HFD-170)

Through: Deborah B. Leiderman, M.D., Director
Controlled Substance Staff (HFD-009)
(signed by Acting Director, Michael Klein, Ph.D. for Dr. Leiderman)

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

Consult on: Proposed preclinical studies for:
Acamprosate (Lipha Pharmaceuticals, Inc.)
NDA 21-431
Submitted March 11, 2002

Background:

Based on recommendations for further investigations made in the February 2002 Controlled Substance Staff consult, the Sponsor submitted 4 protocols for additional preclinical studies that they wish to conduct.

Conclusions:

* Most of the protocols appear to describe experimental conditions that are appropriate for the assays being conducted.

* Doses for acamprosate in these 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.

* Additional information should be provided for the following:

-- Experimental procedures for cell biology assays

-- Rationale for the doses of acamprosate to be used in the hot plate test and an explanation for why acamprosate is to be given p.o. when morphine is given i.p.

-- Rationale for the doses of acamprosate and pretreatment times to be used in the head-twitch test, and an explanation for why acamprosate and nialamide are to be given p.o. when 5-HTP is given s.c.

-- Rationale for the doses of acamprosate and pretreatment times to be used in the head-twitch antagonism test, and an explanation for why acamprosate and cyproheptadine are to be given p.o. when 5-HTP is given s.c.

-- Doses of all drugs and pretreatment times to be used in the benzodiazepine discrimination test

-- The rationale for the doses of acamprosate and the route of administration to be used in benzodiazepine discrimination test is inadequate. Assumptions cannot be made about the behavioral effects induced by a particular dose of a drug based on behavioral effects induced by that dose given via a different route of administration in the absence of plasma levels of the drug.

-- Rationale for the selection of flunitrazepam as the benzodiazepine comparator in the discrimination test. Relative to other benzodiazepines, flunitrazepam has a very fast onset and is very potent. A rational should also be provided for the doses of flunitrazepam to be used in the benzodiazepine discrimination test.

Review of submitted protocols

* In vitro pharmacology -- study of acamprosate and chlorure de calcium

Receptor binding assays will be conducted to evaluate the affinity of acamprosate for all major central nervous system neurotransmitter systems. The conditions listed in the tables appear to be appropriate for each assay.

Cell biology assays will also be conducted for NE, DA and 5-HT transporter sites, using rat brain synaptosomes. However, insufficient information is given describing the exact procedures from the cell biology assays.

* Interaction between acamprosate and morphine in the hot plate test in the mouse

Mice will be tested in the hot plate test (at 54 degrees Celsius) to see if acamprosate increases latency to first foot-lick, either alone or in combination with morphine. There will be seven groups: vehicle; acamprosate 200 mg/kg, p.o.; acamprosate 200 mg/kg, p.o. + morphine 4 mg/kg, i.p.; acamprosate 400 mg/kg, p.o.; acamprosate 400 mg/kg, p.o. + morphine 4 mg/kg, i.p.; morphine 4 mg/kg, i.p.; morphine 8 mg/kg, i.p. Drugs will be administered 30 min prior to each session.

It is unclear how doses of acamprosate were chosen, and why acamprosate is to be given p.o. when morphine is given i.p.

* Evaluation of acamprosate in the 5-HTP head-twitches potentiation in the mouse

The number of head-twitches in mice will be counted following administration of vehicle, 5-HTP (25 mg/kg, s.c., 10 min pretreatment time), acamprosate (200 and 400 mg/kg, p.o., 60 min pretreatment time) or nialamide (16 mg/kg, p.o., 60 min pretreatment time). All sessions are presumably 10 min but this is not stated.

It is unclear how doses of acamprosate and pretreatment times were chosen, and why acamprosate and nialamide are to be given p.o. when 5-HTP is given s.c.

* Evaluation of acamprosate in the 5-HTP head-twitches antagonism in the mouse

The number of head-twitches in mice will be counted following administration of 5-HTP (400 mg/kg, i.p., 30 min pretreatment time). Acamprosate (200 and 400 mg/kg, p.o., 60 min pretreatment time) or cyproheptadine (32 mg/kg, p.o., 60 min pretreatment time) will be administered prior to 5-HTP administration to see if these drugs can block the head-twitch response. All sessions are presumably 10 min but this is not stated.

It is unclear how doses of acamprosate and pretreatment times were chosen, and why acamprosate and cyproheptadine are to be given p.o. when 5-HTP is given s.c.

* Benzodiazepine-like discriminative stimulus effects of acamprosate

Four adult squirrel monkeys will be trained to respond under a fixed ratio 10 (FR10) schedule of stimulus-shock termination. Once responding is stable, monkeys will be trained to discriminate 0.3 mg/kg midazolam from saline, such that 10 responses on one of two levers will terminate a mild tail shock under midazolam conditions while 10 responses on the other lever will terminate the shock under saline conditions. It is not stated what route of administration will be used, nor the pre-treatment timing.

Following stable discriminative responding, training sessions will be expanded. There appears to be saline components followed by a final drug or saline component. The protocol states that "training sessions will be expanded to comprise 1-4 components, each consisting of a 10-min timeout period followed by 10 presentations of the FR10 schedule." Saline or midazolam are to be given at the onset of the 10-min timeout periods, with midazolam injected only during the final component if drug is to be given. Not all sessions will be drug sessions, though, so that on some days, only saline will be given to preclude association of the final component with drug administration. Following these extended training sessions, drug sessions with acamprosate or flunitrazepam will begin, with drug trials occurring no more than twice a week. Training sessions will occur on non-drug days.

The doses of acamprosate to be used are 3-100 mg/kg, i.m. Although the protocol states that these doses are based on behaviorally active doses of 3-10 mg/kg, i.v., there are no data provided indicating similarities in plasma levels from these doses between i.v. and i.m. routes of administration. There is no information given on what sort of behavior is produced at 3-10 mg/kg, i.v. or why it might suggest appropriate doses for benzodiazepine-like behavior. The protocol notes that doses above 100 mg/kg, p.o., produce "mild untoward effects" in monkeys, but no data are provided showing what dose of acamprosate given i.m. is equivalent to 100 mg/kg, p.o. Additionally, mild untoward effects are not necessarily detrimental in abuse liability testing, and may indicate doses that are equivalent to those that humans or lesser animals may find reinforcing.

The positive control in this study will be flunitrazepam, at doses of 0.01-0.30 mg/kg, i.m. No rationale for these doses of flunitrazepam is given. Full substitution from flunitrazepam or acamprosate will be considered to have occurred when drug lever responding is 90% or greater.

Cumulative dosing procedures will be used at first to determine the effects of acamprosate and flunitrazepam. When a dose is found that substitutes for midazolam, that dose will be given in a single injection, with a pretreatment time of 10 or 30 min to compare onset of behavioral effects. This presumably occurs on another session day, but this is not stated. A day after this confirmatory session, the effects of acamprosate will be "examined" to see if there are any prolonged effects from acamprosate. It is not described how the dose will be examined, although this presumably means animals will be tested to see if they chose the midazolam lever.

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/s/

Katherine Bonson
6/12/02 04:56:46 PM
PHARMACOLOGIST

Corinne Moody
6/12/02 05:12:46 PM
CSO
Original (hard copy) was previously signed off by Dr. Deborah Leiderman. I am signing the DFS copy for Dr. Leiderman

3/21/02

N 21-431 Acamprosate Calcium

45 DAY MEETING CHECKLIST
(Answer Yes or No to the questions below)

FILEABILITY:
On initial overview of the NDA application:

PROJECT MANAGEMENT:

(1) Do any of the following apply to this application (i.e., if YES, the application MUST BE REFUSED TO FILE under 314.100 (e) and there is no filing over protest):

(a) Is the drug product already covered by an approved application? **No.**

(b) Does the submission purport to be an abbreviated application under 314.55; however the drug product is not one for which FDA has made a finding that an abbreviated application is acceptable under 314.55(b)? **No.**

(c) Is the drug product subject to licensing by the FDA under the Public Service Act and Subchapter F of Chapter I of Title 21 of the CFR? **No.**

(2) Do any of the following apply to this application (i.e., if NO, the application MAY BE REFUSED TO FILE under 314.100 (d) and there is the potential for filing over protest):

Does the application contain a completed application form as required under 314.50 or 314.55 **Yes.**

(a) On its face, does the application contain the sections of an application required by regulation and Center guidelines? **Yes.**

(b) Has the applicant submitted a complete environmental assessment which addresses each of the items specified in the applicable format under 25.31 or has the applicant submitted evidence to establish that the product is subject to categorical exclusion under 25.24 of the CFR? **Yes.**

(c) On its face, is the NDA formatted in compliance with Center guidelines including integrated efficacy and safety summaries? **Yes.**

(d) Is the NDA indexed and paginated? **Yes.**

(e) On its face, is the NDA legible? **Yes.**

(f) Has the applicant submitted all required copies of the submission and various sections of the submission? **Yes.**

(g) Has the sponsor submitted all special studies/data requested by the Division during pre-submission discussions with the sponsor? **N/A**

(h) Does the application contain a statement that all nonclinical laboratory studies was conducted in compliance with the requirements set forth in Part 58 or a statement why a study was not conducted in compliance with those requirements? **Yes.**

(i) If required, has the applicant submitted carcinogenicity studies? **Yes.**

(j) On its face, does the application contain at least two adequate and well-controlled clinical trials? **Yes.**

(k) Does the application contain a statement that all clinical trials were conducted in accord with the IRB/Declaration of Helsinki provisions of the CFR? **Yes.**

(l) Have all articles/study reports been submitted either in English or translated into English? **Yes.**

(m) Has the applicant submitted draft labeling in compliance with 210.56 and 210.57 of the CFR? **Yes.**

(n) Has the applicant submitted the required FRAUD POLICY notice? **N/A**

(p) Has the applicant submitted copies of all package inserts (or their equivalent) from all countries in which this product has been previously approved for marketing? Have all non-English package inserts been translated? **Yes.**

(q) Has the applicant stated that the integrated summary of safety includes all safety data for this product of which they are aware from all sources, domestic and foreign?

What is the cut-off date for the preparation of the ISS? **July 31, 2001**

(3) From a project management perspective, is this NDA fileable? If "no", please State on below why it is not. **Yes.**

/S/

Lisa E. Basham-Cruz, Project Manager

/S/

Parinda Jani, Supervisory Project Manager

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/s/

Lisa Basham-Cruz
3/21/02 02:59:38 PM
CSO

Parinda Jani
3/21/02 03:29:55 PM
CSO

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: February 25, 2002

To: Anita M. Goodman	**From:** Lisa E. Basham-Cruz
Company: Lipha Pharmaceuticals Inc.	Division of Division of Anesthetic, Critical Care, and Addiction Drug Products
Fax number: 212-398-5026	**Fax number:** 301-443-7068
Phone number: 212-398-4602	**Phone number:** 301-827-7420

Subject: data required for abuse liability assessment of acamprosate

Total no. of pages including cover: 1

Comments:

Document to be mailed: ☐ YES ☑ NO

Anita, Here are the requests discussed in the telecon today:

1. GABA-A, GABA-B, and NMDA binding assays with acamprosate.
2. Behavioral studies showing that acamprosate can potentiate opioid-induced analgesia.
3. Studies showing that acamprosate acts as a partial agonist in seratonin systems.
4. Binding assays investigating the affinity of acamprosate for central nervous system receptors and reuptake site other than GABA or NMDA sites.
5. Drug discrimination studies testing whether acamprosate generalizes to a benzodiazepine.
6. Drug discrimination studies testing whether acamprosate generalizes to an NMDA receptor-channel antagonist like ketamine.

Best Regards, Lisa

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/s/

Lisa Basham-Cruz
6/4/02 06:09:34 PM
CSO

MEMORANDUM

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

Date: **February 25, 2002**

To: **Cynthia McCormick, M.D., Director**
Division of Anesthetics, Critical Care and Addiction Drug Products
(HFD-170)

Through: **Deborah B. Leiderman, M.D., Director**
Controlled Substance Staff (HFD-009)

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

Consult on: **Filing of NDA 21-431**
Acamprosate (Lipha Pharmaceuticals, Inc.)

The abuse liability assessment for acamprosate (NDA 21-431), including recommendations for the label, can be prepared in full upon receipt of the necessary materials listed below.

Conclusions:

* The abuse liability material from the NDA needs to be in one clearly-identified package.

* Primary data, not summaries, need to be submitted for all studies to be reviewed as part of the abuse liability assessment.

* Primary data especially need to be submitted for the following studies:

  -- GABA-A, GABA-B and NMDA binding assays with acamprosate

  -- Behavioral studies showing that acamprosate can potentiate opioid-induced analgesia

  -- Studies showing that acamprosate acts as a partial agonist in serotonin systems

  -- Self-administration studies with acamprosate in animals

-- Drug-discrimination studies using acamprosate in animals trained to discriminate pentobarbital

* Primary data from the following areas relevant to abuse liability should be submitted:

-- Binding assays investigating the affinity of acamprosate for central nervous system receptors and reuptake site other than GABA or NMDA sites.

-- Drug discrimination studies testing whether acamprosate generalizes to a benzodiazepine

-- Drug discrimination studies testing whether acamprosate generalizes to an NMDA receptor-channel antagonist like ketamine

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/s/

Katherine Bonson
6/12/02 05:06:15 PM
PHARMACOLOGIST

Corinne Moody
6/12/02 05:16:31 PM
CSO
Original (hard copy) was signed off by Dr. Deborah Leiderman. I am signing the DFS copy for her.

2/15/02

45 DAY MEETING CHECKLIST

FILEABILITY:

On initial overview of the NDA application: **YES** **NO**

PHARMACOLOGY:

(1) On its face, is the pharmacology section of the NDA organized in a manner to allow substantive review to begin? Yes

(2) Is the pharmacology section of the NDA indexed and paginated in a manner to allow substantive review to begin? Yes

(3) On its face, is the pharmacology section of the NDA legible so that substantive review can being? Yes

(4) Are all required (*) and requested IND studies completed and submitted in this NDA (carcinogenicity, mutagenicity, teratogenicity*, effects on fertility*, juvenile studies, acute adult studies*, chronic adult studies*, maximum tolerated dosage determination, dermal irritancy, ocular irritancy, photocarcinogenicity, animal pharmacokinetics studies, etc)? No 9/12day tox in dog, 1mo tox in dog requested to characterize to profile in dogs (Tim)

(5) If the formulation to be marketed is different from the formulation used in the toxicology studies, has the sponsor made an appropriate effort to either repeat the studies using the marketed product or to explain why such repetition should be required? NA

(6) Are the proposed labeling sections relative to pharmacology appropriate (including human dose multiples expressed in either mg/m^2 or comparative serum/plasma levels) and in accordance with 201.57? Yes

(7) Has the sponsor submitted all special studies/data requested by the Division during Pre-submission discussions with the sponsor? Yes

(8) On its face, does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the sponsor submitted rationale to justify the alternative route? Yes

(9) Has the sponsor submitted a statement(s) that all the pivotal Pharm/Tox studies have been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations? Yes

(10) Has the sponsor submitted a statement(s) that the Pharm/Tox studies have been performed using acceptable, state-of-the-art protocols which also reflect agency animal welfare concerns? Yes

(11) From a pharmacology perspective, is this NDA fileable? If "no", please state below why it is not. Yes

Reviewing Pharmacology Officer Date

Supervisory Pharmacology Officer Date

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/s/

Kathy Haberny
2/15/02 09:30:32 AM
PHARMACOLOGIST

Timothy McGovern
2/19/02 04:23:26 PM
PHARMACOLOGIST
I concur.

2/12/02

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-431

Lipha Pharmaceuticals, Inc.
1114 Avenue of the Americas, 41st Floor
New York, NY 10036-7703

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

Dear Dr. Goodman:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product:	Acamprosate tablets
Review Priority Classification:	Priority (P)
Date of Application:	December 21, 2001
Date of Receipt:	December 27, 2001
Our Reference Number:	NDA 21-431

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on February 25, 2002 in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be June 27, 2002.

Be advised that, as of April 1, 1999, 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 (63 *FR* 66632). If you have not already fulfilled the requirements of 21 CFR 314.55 (or 601.27), please submit your plans for pediatric drug development within 120 days from the date of this letter unless you believe a waiver is appropriate. Within approximately 120 days of receipt of your pediatric drug development plan, we will review your plan and notify you of its adequacy.

If you believe that this drug qualifies for a waiver of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of 21 CFR 314.55 within 60 days from the date of this letter. We will make a determination whether to grant or deny a request for a waiver of pediatric studies during the review of the application. In no case, however, will the determination be made later than the date action is taken on the

application. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" (PPSR) in addition to your plans for pediatric drug development described above. We recommend that you submit a Proposed Pediatric Study Request within 120 days from the date of this letter. If you are unable to meet this time frame but are interested in pediatric exclusivity, please notify the division in writing. FDA generally will not accept studies submitted to an NDA before issuance of a Written Request as responsive to a Written Request. Sponsors should obtain a Written Request before submitting pediatric studies to an NDA. If you do not submit a PPSR or indicate that you are interested in pediatric exclusivity, we will review your pediatric drug development plan and notify you of its adequacy. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity. FDA does not necessarily ask a sponsor to complete the same scope of studies to qualify for pediatric exclusivity as it does to fulfill the requirements of the pediatric rule.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA should be addressed as follows:

U.S. Postal/Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anesthetic, Critical Care, and Addiction Drug Products, HFD-170
Attention: Division Document Room
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, call me at (301) 827-7432.

Sincerely,

{See appended electronic signature page}

Kimberly Compton
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/

Kimberly Compton
2/12/02 05:31:51 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO (Division/Office):	FROM:
HFD-009 (Controlled Substances Staff), Corinne Moody	HFD-170 (Division of Anesthetic, Critical Care, and Addiction Drug Products), Dr. Cynthia McCormick, Kim Compton (for Lisa Basham); Project Manager

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
2/1/02		21-431	New NDA	12/21/01

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Acamprosate Calcium	Priority Review		Attendance at Filing Mtg. and continuing as needed throughout review process.

NAME OF FIRM: Lipha Pharmaceuticals, Inc.

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ■ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISION RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

Please review this NDA from the controlled substances perspective. This new chemical entity modulates glutamatergic and GABAergic neurotransmission and modifies neuronal excitability. It is indicated for [redacted]. The filing meeting is Friday 2-8-02 (Conf Rm 9B-45 at 1pm). This NDA will be reviewed under PRIORITY REVIEW and so will have a 6-month goal date of 6/25/02.

Please be prepared to provide on going input from the controlled substances perspective as needed throughout the review process.

If you have any questions, please contact Kim Compton or Lisa Basham, Regulatory Project Managers, at 301-827-7432. Please cc: all written responses to Kim Compton, Lisa Basham and Aleta Crane. Thank you for your assistance.

The text of the bulk of the information contained in this application is available in the Electronic Document Room (EDR) under this NDA # (21-431.)

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one)
Kim Compton:2-1-02/Initialed by Parinda Jani: 2-6-02	■ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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

/s/

Kimberly Compton
2/7/02 10:37:03 AM

Redacted 10

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

USER FEE VALIDATION SHEET

NDA # 21431 Supp. Type & # N 000 UFID # 4252
(e.g., N000, SLR001, SE1001, etc.)

1. (YES) NO **User Fee Cover Sheet Validated?** **MIS_Elements Screen Change(s):**

2. (YES) NO **APPLICATION CONTAINS CLINICAL DATA?**
(Circle **YES** if NDA contains study or literature reports of what are explicitly or implicitly represented by the application to be adequate and well-controlled trials. Clinical data do not include data used to modify the labeling to add a restriction that would improve the safe use of the drug (e.g., to add an adverse reaction, contraindication or warning to the labeling).

REF **IF NO CLINICAL DATA IN SUBMISSION, INDICATE IF CLINICAL DATA ARE CROSS REFERENCED IN ANOTHER SUBMISSION.**

3. YES (NO) **SMALL BUSINESS EXEMPTION**

4. YES (NO) **WAIVER GRANTED**

5. YES (NO) **NDA BEING SPLIT FOR ADMINISTRATIVE CONVENIENCE (other then bundling).**
If **YES**, list all NDA #s, review division(s) and those for which an application fee applies.

NDA #	Division		
N_____	HFD-_____	Fee	No Fee
N_____	HFD-_____	Fee	No Fee

6. (YES) NO **BUNDLING POLICY APPLIED CORRECTLY? No Data Entry Required**
(Circle **YES** if application is properly designated as one application or is properly submitted as a supplement instead of an original application. Circle **NO** if application should be split into more than one application or be submitted as an original instead of a supplement. If **NO**, list resulting NDA #s and review division(s).

NDA #	Division	NDA #	Division
N_____	HFD-_____	N_____	HFD-_____

7. (P) (S) **PRIORITY or STANDARD APPLICATION?**

/S/ 1/3/02
PM Signature / Date

/S/ 9/15/04
CPMS Concurrence Signature / Date

2/14/00

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

NDA 21-431 /SE____ - ____

Drug Acamprosate Calcium Applicant Lipha Pharmaceuticals, Inc.

RPM Lisa Basham-Cruz Phone (301) 827-7420

■505(b)(1)
☐505(b)(2) Reference listed drug ____

☐Fast Track ☐Rolling Review Review priority: ☐ S ■P

Pivotal IND(s) 51, 809

Application classifications:
Chem Class 1
Other (e.g., orphan, OTC) ____

PDUFA Goal Dates:
Primary : June 27, 2002
Secondary ____

Arrange package in the following order:

Indicate N/A (not applicable), X (completed), or add a comment.

GENERAL INFORMATION:

- User Fee Information: ■ User Fee Paid
  ☐ User Fee Waiver (attach waiver notification letter)
  ☐ User Fee Exemption

- Action Letter..... ☐AP ☐ AE ☐NA
  To be determined

- Labeling & Labels
  FDA revised labeling and reviews..... Labeling review deferred to next cycle
  Original proposed labeling (package insert, patient package insert) X
  Other labeling in class (most recent 3) or class labeling..... N/A
  Has DDMAC reviewed the labeling? ..... ☐ Yes (include review) ■ No deferred to next cycle
  Immediate container and carton labels X
  Nomenclature review ..... outstanding

- Application Integrity Policy (AIP) ☐ Applicant is on the AIP. This application ☐ is ■ is not on the AIP.
  Exception for review (Center Director's memo)..... ____
  OC Clearance for approval..... ____

Continued ⇨

- Status of advertising (if AP action) ☐ Reviewed (for Subpart H – attach review) — ☐ Materials requested in AP letter

N/A

- Post-marketing Commitments — N/A
  - Agency request for Phase 4 Commitments.....
  - Copy of Applicant's commitments .....
- Was Press Office notified of action (for approval action only)?..... — ☐ Yes ☐ No
  - Copy of Press Release or Talk Paper.....
- Patent
  - Information [505(b)(1)] ..... — X
  - Patent Certification [505(b)(2)]..... — N/A
  - Copy of notification to patent holder [21 CFR 314.50 (i)(4)]..... — N/A
- Exclusivity Summary ..... — N/A
- Debarment Statement ..... — X
- Financial Disclosure
  - No disclosable information ..... — X
  - Disclosable information – indicate where review is located .....
- Correspondence/Memoranda/Faxes ..... — X
- Minutes of Meetings ..... — X
  - Date of EOP2 Meeting October 27, 1998
  - Date of pre NDA Meeting January 27, 2000
  - Date of pre-AP Safety Conference N/A
- Advisory Committee Meeting ..... — X
  - Date of Meeting ..... — May 10, 2002
  - Questions considered by the committee ..... — X
  - Minutes or 48-hour alert or pertinent section of transcript ..... — flash minutes
- Federal Register Notices, DESI documents ..... — N/A

CLINICAL INFORMATION: — **Indicate N/A (not applicable), X (completed), or add a comment.**

- Summary memoranda (e.g., Office Director's memo, Division Director's memo, Group Leader's memo) .....
- Clinical review(s) and memoranda ..... — X

Continued ⇨

- Safety Update review(s) ..... Update not submitted

- Pediatric Information
  ☐ Waiver/partial waiver (Indicate location of rationale for waiver) ■ Deferred
  Pediatric Page..... N/A
  ☐ Pediatric Exclusivity requested? ☐ Denied ☐ Granted ☐ Not Applicable

- Statistical review(s) and memoranda X

- Biopharmaceutical review(s) and memoranda..... X

- Abuse Liability review(s) X
  Recommendation for scheduling ..... N/A

- Microbiology (efficacy) review(s) and memoranda ..... N/A

- DSI Audits X
  ■Clinical studies ☐ bioequivalence studies ..... _____

CMC INFORMATION: **Indicate N/A (not applicable), X (completed), or add a comment.**

- CMC review(s) and memoranda X

- Statistics review(s) and memoranda regarding dissolution and/or stability ..... N/A

- DMF review(s) X

- Environmental Assessment review/FONSI/Categorical exemption ..... X (Cat Excl)

- Micro (validation of sterilization) review(s) and memoranda ..... N/A (nonsterile product)

- Facilities Inspection (include EES report)
  Date completed pending ..... ☐ Acceptable ☐ Not Acceptable

- Methods Validation ..... ☐ Completed ■ Not Completed

PRECLINICAL PHARM/TOX INFORMATION: **Indicate N/A (not applicable), X (completed), or add a comment.**

- Pharm/Tox review(s) and memoranda X

- Memo from DSI regarding GLP inspection (if any) ..... N/A

Continued ⇨

- Statistical review(s) of carcinogenicity studies ..... N/A
- CAC/ECAC report X

LIPHA
PHARMACEUTICALS

Lipha

VIA Federal Express,

December 17, 2001

Food and Drug Administration (360909)
Mellon Client Service Center RM 670
Room 9B45
500 Ross Street
Pittsburgh, PA 15262-0001

Reference: Acamprosate NDA #21-431
User Fee Payment

Gentlemen:
In accordance with instructions from the Food and Drug andministration, enclosed herewith is our check [illegible] in the amount of $309,647 representing the user fee for a New Drug Application with clinical data (Acamprosate, NDA #21-431).

If you have any questions concerning this payment or should you require further information, please do not hesitate to contact me at (212)-398-4602, Extension 16.

Sincerely,

LIPHA PHARMACEUTICALS, INC.

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

Enc. As above

cc: Cynthia McCormick, M.D.
Division of Anesthetic, Critical Care, and Addiction Drug Products

Redacted 1

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

(b4)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0297
Expiration Date: February 29, 2004.

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: http://www.fda.gov/cder/pduta/default.htm

1. APPLICANT'S NAME AND ADDRESS

Lipha Pharmaceuticals, Inc.
1114 Avenue of the Americas
41st Floor
New York, NY 10036-7703

2. TELEPHONE NUMBER *(Include Area Code)*

(212) 398-4602

3. PRODUCT NAME

Acamprosate Calcium

4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER

21-431

5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?

☑ YES ☐ NO

IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW:

☐ THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.

☐ THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:

_____
(APPLICATION NO. CONTAINING THE DATA).

6. USER FEE I.D. NUMBER

4252

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

☐ A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92
(Self Explanatory)

☐ A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE
(See item 7, reverse side before checking box.)

☐ THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act
(See item 7, reverse side before checking box.)

☐ THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act
(See item 7, reverse side before checking box.)

☐ THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY
(Self Explanatory)

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION?

☐ YES ☑ NO

(See item 8, reverse side if answered YES)

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
Anita M. Goodman	Chief Operating Officer & Vice President	December 17, 2001

SPONSOR MEETING ATTENDEES

Meeting Date: January 27, 2000

Location: Parklawn Building, Potomac Room

IND/ Name: 51,809

Sponsor : Lipha Pharmaceuticals, Inc.

Type of Meeting: Guidance meeting

Meeting Chair: Dr. Celia Winchell, MD, Team Leader
Division of Anesthetics, Critical Care and
Addiction Drug Products, HFD-170

Lipha Pharmaceuticals, Inc.	Title
Anita M. Goodman, MD	Executive VP and COO
Bruce Goddard, R.A.C.	Senior Director, Compliance and Regulatory Affairs
Graig McMillan	Assistant Project Manager
Merck-Lipha, s.a.	
Sylvie Chabac, M.D.	International Product Manager
Thierry Hulot, Ph. D.	Head, Pharmacokinetic & Metabolism Dept.
Gabrielle Disselhoff, Ph. D.	Director of Regualtory Affairs
Consultants to Lipha	
Barbara J. Mason Ph.D.	Associate Professor, Dept. Psychiatry and Behavioral Sciences, University of Miami
[redacted]	
FDA HFD-170	
John Jenkins. MD	Office of Drug Evaluation II, Director
Cynthia G. McCormick MD	Division Director
Celia Winchell, MD	Medical Team Leader
Douglas Kramer, MD	Medical Reviewer, Addiction Drugs
Lucy Jean, PhD	Team Leader, Pharmacology
Belinda Hayes, PhD	Reviewer, Pharmacology
Thomas Permutt, PhD	Team Leader, Biostatistics
Sue Jane Wang, PhD	Reviewer, Biostatistics
Ramana Uppoor, PhD	Team Leader, Clinical Pharmacology and Biopharmaceutics
Judit Milstein	Regulatory Project Manager

The sponsor's background package and questions were discussed. The sponsor's presentation was cancelled at the Agency's request.

Question 1: *"Will results from the U.S. study ACAMP/US/96.1 (as described in the Draft report) and the German PRAMA study (submitted as Serial # 13 on May 29, 1998), combined with a full safety data base from all European studies, support the following labeling indication?*

[ ]

The Agency understands the reasons for the changes made in the analysis plan for the US trial, but based on the data presented, the US trial could not be viewed as positive and capable of serving as one of two trials used in support of marketing approval. Two additional positive trials will be needed, and it has been the Agency's understanding that Lipha has two European trials available as full reports (PRAMA and Paille) which could be capable of supporting approval. The conclusions regarding these trials would, of course, depend on the outcome of the review. In this context, Lipha indicated that the Paille trial was not conducted under their auspices and might be difficult to assemble in the degree of detail needed by the Agency.

There is some concern that American and European alcoholics are sufficiently different that a U.S. trial would be necessary to confirm that acamprosate would work in the American population. The data do suggest differences in the rate of comorbid polysubstance abuse, and in the treatment context in which the drug would be used. Unfortunately, differences in design between the European and US trials make it difficult to compare the outcomes and to use these studies as illustrations of the differences between the two populations. Had the US trial succeeded, concerns about differences between the two populations would have been assuaged. On the other hand, because of the differences between the two trials, uniqueness of American alcoholics cannot be concluded from the failure of the US trial.

If the European trials, upon review, support the efficacy of acamprosate, it would be possible to write labeling describing the patient selection and treatment used in the successful trials. It would be reassuring to see a subset analysis of the U.S. trial using *pre-randomization* variables that select a similar population. It appears from the material submitted that the indication would be [ ] The submitted summaries (notably the U.S. and U.K. trials) suggest that the drug is not effective in initiating abstinence in those currently drinking .It may be appropriate to seek NIAAA's input regarding the applicability of these selection and treatment methods in the US population.

The Agency also stressed that the *safety* data arising from the U.S. trial are essential. Even if it were possible to identify a subset of U.S. alcoholics who are likely to succeed, the probability of broader use beyond that population—particularly in polysubstance abusers—is very high. It would be necessary to have same safety data on this group of patients in order to approve the drug. The US trial should provide this information.

Further discussions on the specifics of what is to be submitted in the NDA are needed . The Agency is interested in full reports, with data, of all the trials for which data are available, but a meta-analysis is not necessary. It is common for psychiatric drugs to be approved in the face of some trials which have not fully succeeded in demonstrating efficacy, as long as there are strong positive findings from other adequate and well-controlled trials. Current practice is to include descriptions of true negative trials (as opposed to those which were incapable of showing a difference—i.e. active control failed to separate from placebo as well) in labeling as well as positive trials. This approach would be valuable in emphasizing the circumstances under which the drug is effective and making clear those in which it is unlikely to be effective. This will help ensure proper use of the drug.

Options for an NDA based on European efficacy data alone were discussed. Pharmacokinetic concerns were raised because the US trial did not provide direct evidence of efficacy for the bid dosing regimen using the 500 mg tablet. Because a positive trial for the 500 mg, two tablets bid, regimen was anticipated, the pharmacokinetic trial as designed (comparing bid dosing to the tid dosing regimen) was envisioned as adequate to provide a linkage between the two formulations to allow the European studies to provide the required supportive evidence of efficacy, not to establish bioequivalence. Without a positive trial using the new regimen, it is difficult to support approval of the bid dosing regimen using the 500 mg tablet. Even an optimally designed protocol would almost certainly reveal differences in peak and trough levels between the two regimens. The Agency does not generally allow substitution of one product for another based solely on equivalence of AUC's or steady-state levels.

Lipha could elect to submit an application for the 333 mg tablet marketed in Europe, with labeling for a 333 mg, 2 tablets tid. regimen, as tested in the European trials. In this case, the Agency would need only the multi-dose PK and comparative dissolution data (for the 333 mg and 500 mg tablets, since they are compositionally proportional) in three media in order to interpret the data from the US trial. An analysis to reconcile the findings of the US and European trials would be needed, as well as some evidence that there is a US population for whom this drug would be beneficial, to demonstrate that the product has a place in the US market.

Question #2:

Question # 3: *"Are there any outstanding pre-clinical issues that need to be addressed before filing the NDA?"*

The neurotoxicity of acamprosate needs to be addressed. There is evidence that acamprosate is a partial agonist at the NMDA receptor and therefore, may possess a neurotoxic effect.

The Agency asked Lipha to submit, for review, all the information they have available on the neurotoxic potential of acamprosate. If further studies were warranted, Dr. Hayes provided the following guidelines as to what information would be needed.

1. Repeated dose studies in two species (rodent and non-rodent),

2. Characterization of acamprosate's neutrotoxicity potential should consider

    a. Type of lesions observed.
    b. Mechanism for the drug-induced neurotoxicity.

c. Progression of the neurological changes.
d. Dose-response relationship; no effect dose and exposures.
e. Reversibility of lesions.
f. Sequelae of the neurological changes.
g. If possible, a method for monitoring the development of the neurological changes in-life.

3. It is recommended that Lipha consult with a panel of experts in the area of neuropathology on the appropriate histopathology techniques (e.g., staining), and to have a skilled neuropathologist examine the slides.

It is advised that Lipha submit all the protocols for review prior to the initiation of the studies

/S/

Judit Milstein
Regulatory Project Manager

CC: Original IND # 51,809
HFD-170/Div File
HFD-170/C. McCormick 2-25-2000
HFD-170/C. Winchell 2-14-2000
HFD-170/D. Kramer 2-16-2000
HFD-170/L. Jean 2-18-2000
HFD-170/B. Hayes 2-15-2000
HFD-170/T. Permutt 2-14-2000
HFD-170/S. Wang 2-18-2000
HFD-170/ R. Uppoor 2-16-2000, 2-18-2000
HFD-170/C. Schumaker 2-24-2000
HFD-170/j. Milstein

Drafted on: jm 2-14-2000
Reviewed on:
Finalized on:

Filename: N:\cso\milsein\51809 acamprosate\ sponsor meeting minutes 1-27-2000.doc

2/2000

Pre-NDA mins

IND 51,809

Lipha Pharmaceuticals, Inc.
1114 Avenue of the Americas, 41st floor
New York, New York 10036-7703

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

Dear Dr. Goodman:

Please refer to the meeting between representatives of your firm and FDA, on January 27, 2000.

The purpose of the meeting was to update the status of the acamprosate development program and to discuss the preliminary results of the Treatment Phase from the U.S. Phase 3 multi-center trial protocol # ACAMP/US/96.1 and its implication for Lipha's filing of an NDA for Acamprosate.

A copy of our minutes of that meeting is enclosed. These minutes are the official minutes of the meeting. You are responsible for notifying us of any significant differences in understanding you have regarding the meeting outcomes.

If you have any questions, call me at (301) 827-7410.

Sincerely,

/S/

Judit Milstein
Regulatory Project Manager
Division of Anesthetic, Critical Care, and
Addiction Drug Products
Center for Drug Evaluation and Research

Enclosure: Minutes of the telecon

cc:
Archival IND
HFD-170/Div. Files
HFD-170/J.Milstein
HFD-170/C.Schumaker

Drafted by: jrm 2-22-2000
Reviewed by:
Initialed by:
final:
filename: n:\\cso\milstein\. acamprosate \minutes sent 2-27-2000.doc

GENERAL CORRESPONDENCE (MINUTES SENT)

314.50 (5)(vii)
p. 103

EOP2 mins

MEMORANDUM OF MEETING MINUTES

Meeting Date: **October 27, 1998**
Time: 10:00 a.m.
Location: Parklawn Bldg. 3rd Floor Conference Room B

Application: IND 51,809 Acamprosate

Type of Meeting: FDA-Industry (Lipha Pharmaceuticals, Inc.)
Guidance meeting, End of Phase II

Meeting Chair: Cynthia McCormick, M.D.

Meeting Recorder: Tony Chite

FDA Attendees	Titles	Office/Division
Cynthia G. McCormick, M.D.	Division Director	HFD-170
Celia Winchell, M.D.	Team Leader/ Drug Abuse	HFD-170
E. Douglas Kramer, M.D.	Medical Reviewer/Drug Abuse	HFD-170
Albinus D'Sa, Ph.D.	Team Leader/Chemistry	HFD-170
Michael Klein, Ph.D.	Team Leader/CSET	HFD-170
BeLinda Hayes, Ph.D.	Pharmacology Reviewer/CSET	HFD-170
Anwar Goheer, Ph.D.	Acting Team Leader/Pharmacology	HFD-170
Kathleen Haberny, Ph.D.	Pharmacology Reviewer	HFD-170
Suresh Doddapaneni, Ph.D.	Pharmacokineticist Reviewer	HFD-870
Tom Permutt, Ph.D.	Team Leader/Biostatistician	HFD-170
Z. Jonathan Ma, Ph.D.	Biostatistician Reviewer	HFD-170
Corinne P. Moody	Chief, Project Management Staff	HFD-170
Tony Chite, P.D.	Project Manager	HFD-170

External Attendees:	Titles:
Sylvie Chabac, M.D.	International Strategic Product Manager
Sonia Davis, DR. P.H.	Biostatistician, Statistical Operations
Bruce Goddard	Senior Director, Compliance & Regulatory Affairs
Anita M. Goodman, M.D.	Exec. Vice Pres. & Chief Operating Office
Barbara J. Mason, Ph.D.	Associate Professor, Director, Alcohol Disorders Research Unit
Craig McMillan	Assistant Project Manager
[redacted]	[redacted]
[redacted]	Consultant

Meeting Minutes:
These minutes summarize an FDA-Industry Meeting between the Division of Anesthetic, Critical Care, and Addiction Drug Products and Lipha Pharmaceuticals; conducted so that Lipha can acquaint the agency with the status of their acamprosate development program and to obtain the Agency's guidance on some outstanding questions.

Presentation:

Acamprosate 500mg tablet, IND 51,809
Trade names of drug product: Campral; Aotal
Indication: [redacted]

Sponsor's presentation indicated that the abstinence rate per visit with acamprosate was higher than the placebo group for 360 days. (22% vs.12%)
The survival analysis for acamprosate, measuring time to first relapse and absolute abstinence was higher for acamprosate vs. placebo.
The incidence of adverse events does not appear to be dose related.

Objectives:

Lipha plans to do the following prior to filing an NDA

- Seek to confirm European experience in U.S. alcohol-dependent patients
- [redacted]
- Perform human abuse liability study to confirm lack of abuse potential seen in nonhuman primate study.

Lipha's Clinical Development Plan:

- Perform confirmatory U.S. study with 500mg dosage strength (ACAMP/US/96.1)
- Submit two European Phase III studies with 333mg dosage strength (PRAMA & Paille)
- Perform abuse liability study (ACAMP/US/98.1)
- Perform acamprosate/naltrexone drug interaction study (ACAMP/US/97.1)
- Support various investigator-initiated clinical pharmacology/clinical studies (eg. COMBINE studies)

SUMMARY OF ISSUES:

The statistical analysis plan was presented and discussed.

- Because there is only one parameter, the corrected cumulative abstinence duration, which does not treat dropouts in the most conservative way, it was suggested that the analysis may be more persuasive without that parameter.

- The agency proposed that the sponsor consider analyzing the data both with and without the CCAD. The plan as presented, however, was acceptable as the primary analysis.

- There was a question from the Agency regarding the timing of the unplanned sample size recalculation (increment) to increase the statistical power of the study. The decision was made in March of 1998, which was in the middle of the clinical trial period (5/97-5/98).

Clinical:

- The agency suggested that the sponsor should distinguish between withdrawal due to adverse events and other terminations.

- The naloxone interaction study was discussed. Lipha explained that study is an exploratory study. There are no current plans to make claims about combination therapy.

Pharmacology:

- The sponsor was asked to generate the AUC data at steady state by the dietary route for all doses for the carcinogenicity studies in mice and rats. This information is needed for the label and to evaluate the validity of the carcinogenicity studies.

- Lipha indicated that the studies pre-date clear requirements on toxicokinetic studies, so there may be only a limited amount of kinetics data available.

Abuse liability:

- Lipha is prepared to do a human abuse liability study. Normally, the results of animal studies determine the need for human studies. The agency has seen one paper on pre-clinical evaluation, drug discrimination and self-administration studies, of the drug. The Agency mentioned that there were several flaws in the design of these studies. The Agency requested raw data for review, which Lipha agreed to provide.

- If Lipha chooses to proceed with the abuse liability study although it is not required, the Agency will review the data. However, the Agency indicated that the proposed study, as currently designed, may not lead to conclusions that are useful. Because of the poor oral bioavailability, the concern would be abuse by the parenteral route. The Agency informed Lipha that the review team has suggestions on improving the study design, should Lipha choose to pursue the study. Lipha expressed a desire and a commitment to want to perform the human abuse liability study.