CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-431

Approval Letter(s)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-431

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

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

Dear Dr. Goodman:

Please refer to your new drug application (NDA) dated December 1, 2001, received December 27, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Campral (acamprosate calcium) Delayed-Release Tablets.

We acknowledge receipt of your submissions dated January 18 and 30, February 1, 6, 11, 22, and 26, March 6, 11(2), 13, 19, and 21(2), April 11, 12, 16(2), 17, 19, and 24, May 1, 3, 21, and 22(2), June 24 and 28(2), September 20, and November 14, 2002, January 29, February 12, March 25, May 22, July 23, September 5 and 11, October 23, and December 19, 2003, and January 26 and 28, February 3, April 29(2), May 3, 11, 14, 19, 25, and 28, June 18 (2) and 30, and July 8, 14, 20, 27(2), and 28(2), 2004.

The February 3, 2004, submission constituted a complete response to our June 27, 2002, action letter.

This new drug application provides for the use of Campral (acamprosate calcium) Delayed-Release Tablets for the maintenance of abstinence from alcohol in patients with alcohol dependence who are abstinent at treatment initiation.

We have completed our review of this application, as amended, and it is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert, immediate container and carton labels). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit an electronic version of the FPL according to the guidances for industry titled *Providing Regulatory Submissions in Electronic Format – NDA* and *Providing Regulatory Submissions in Electronic Format – Content of Labeling*. Alternatively, except for the content of labeling, which must be submitted electronically in PDF format, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-

weight paper or similar material. For administrative purposes, designate this submission "**FPL for approved NDA 21-431.**" Approval of this submission by FDA is not required before the labeling is used.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We are waiving the pediatric study requirement for ages 0 through 11 years and deferring pediatric studies for ages 12 through 16 years for this application.

Your deferred pediatric studies required under section 2 of the Pediatric Research Equity Act (PREA) are considered required postmarketing study commitments. The statuses of these postmarketing studies shall be reported annually according to 21 CFR 314.81. These commitments are listed below.

1. To conduct a pediatric study under PREA for the maintenance of abstinence from alcohol in patients ages 12 through 16 with alcohol dependence who are abstinent at treatment initiation.

Protocol Submission:	by August 5, 2005
Study Start:	by February 6, 2006
Final Report Submission:	by May 4, 2009

Submit final study reports to this NDA. For administrative purposes, all submissions related to this pediatric postmarketing study commitment should be clearly designated "**Required Pediatric Study Commitments.**"

We remind you of your postmarketing study commitments in your submissions dated July 27 and 28, 2004. These commitments are listed below.

2. To conduct a pharmacokinetic comparative study using at least six subject with severe renal impairment and at least six normal subjects.

   For this study, an appropriate dosing regimen for patients with severe renal impairment may be identified by using modeling and simulation analyses; the appropriateness of identified dosing regimen in severe renal impairment patients should be confirmed in this study to see if the exposure is comparable to that seen in the normal subjects receiving a recommended dose.

Protocol Submission:	by March 3, 2005
Study Start:	by August 5, 2005
Final Report Submission:	by August 8, 2007

3. To perform a study to determine, in the most appropriate animal model, whether the concomitant use of acamprosate and alcohol during pregnancy is more harmful to the fetus than either drug alone.

Protocol Submission:	by March 3, 2005
Study Start:	by August 5, 2005

Final Report Submission: by March 31, 2007

4. To perform a study that assesses the carcinogenic potential of acamprosate calcium in the mouse, via either a 2-year bioassay or an appropriate transgenic mouse model. Obtaining concurrence from CDER's Carcinogenicity Assessment Committee on the protocol prior to study initiation is strongly advised.

Protocol Submission:	by January 28, 2006
Study Start:	by May 29, 2006
Final Report Submission:	by July 28, 2009

Submit clinical protocols to your IND for this product. Submit nonclinical protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments should be prominently labeled "**Postmarketing Study Protocol**," "**Postmarketing Study Final Report**", or "**Postmarketing Study Correspondence**."

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to the Division of Anesthetic, Critical Care, and Addiction Drug Products, and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Please submit one market package of the drug product when it is available.

We have not completed validation of the regulatory methods. However, we expect your continued cooperation to resolve any problems that may be identified.

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at www.fda.gov/medwatch/report/mmp.htm.

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

Sincerely,

{See appended electronic signature page}

/S/
Robert J. Meyer, M.D.
Director
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

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

/s/

Robert Meyer
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Approvable Letter (S)

DEPARTMENT OF HEALTH & HUMAN SERVICES

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Food and Drug Administration
Rockville MD 20857

NDA 21-431

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

Attention: Anita Goodman, MD
COO and Vice President

Dear Dr. Goodman:

Please refer to your new drug application (NDA) dated December 21, 2001, received December 27, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Campral (acamprosate calcium) Tablets.

We acknowledge receipt of your submissions dated January 18 and 30, February 1, 6, 11, 22, and 26, March 6, 11 (2), 13, 19, and 21 (2), April 11, 12, 16 (2), 17, 19, and 24, and May 1, 3, and 21, 2002.

We also refer to your submissions dated May 22 (2) and June 24, 2002. These submissions have not been reviewed in the current review cycle. You may incorporate these submissions by specific reference as part of your response to the deficiencies cited in this letter.

We have completed the review of this application, as amended, and find that the information presented is inadequate. Therefore, the application is not approvable under section 505(b) of the Act and 21 CFR 314.125(b). The deficiencies are summarized as follows:

1. The data submitted in this application are inadequate to establish the efficacy of acamprosate for the treatment of chronic alcohol dependence. Evidence of problems with data reliability in the European studies precludes relying on these data as the sole evidence to support the proposed indication. Perform at least one additional adequate and well-controlled study using current standards of careful methodology for ascertainment of alcohol drinking data, prospective outcome measures, and statistical analysis plans. The study currently being conducted in the United States may serve to fulfill this requirement.

2. The data submitted in this application are inadequate to establish the safety of acamprosate. Methods used to collect adverse event data in all but five of the clinical studies limited the information collected to a prespecified finite list of adverse events, which could potentially bias the adverse event profile of this drug, failing to capture spontaneous events that were unexpected or not included in the list. Perform at least one additional adequate and well-controlled study to supplement the primary NDA database

using current standards of careful methodology for reporting and collecting adverse event data.

3. Errors and inconsistencies in the coding of AEs preclude an accurate and meaningful analysis of the safety database. Re-examine the COSTART coding of all AEs and reconcile discrepancies. Two different sets of abbreviations for body system were used. This complicates the generation of adverse event tables organized by body system. Re-code the adverse events dataset using only one set of abbreviations.

4. There was a failure to adequately account for, and inconsistency in the reporting of deaths in this NDA. Re-examine your entire database and identify and report all cases of deaths in all acamprosate clinical trials. Provide case report forms and narrative summaries for each case. Additional fatalities described in pharmacovigilence studies may be reported separately.

5. There is inconsistency in the reporting of serious adverse events (SAEs) in this NDA. Re-examine your entire database and identify and report all cases of SAEs in all acamprosate clinical trials. Provide case report forms and narrative summaries for each case. Include, but do not limit your search terms to: *fatality, fatal, death, died, arrest, coma, life-threatening, suicidal, depression, psychosis, arrhythmia, gast/gastro, bleed, abdominal pain, diarrhea, vomiting, syncope, fall, paralysis, stroke, convulsion, seizure, renal/kidney failure/dysfunction, hepatic/liver failure/dysfunction, hepatitis, anaphylaxis, agranuolcytosis, aplastic anemia, neutropenia, rash, pruritis, exfoliation, Stevens-Johnson, toxic epidermal necrolysis, rhabdomyolysis, tumor, birth defect, congenital anomaly.*

6. Examine the reasons for patient discontinuation in order to evaluate the appropriateness of the coding. The reasons for premature discontinuation have been categorized in such a way that some discontinuations due to adverse events or due to lack of efficacy may have been obscured in the category "other." Re-code all discontinuations to reflect the reason for withdrawal. Provide case report forms for all discontinuations due to adverse events.

7. Examine the safety database for all deaths, serious adverse events, and treatment-emergent adverse events occurring up to 30 days after last exposure to study treatment. Code and report these adverse events appropriately. The characterization of such events is important because of acamprosate's relatively long half-life, and because its central nervous system (CNS) activity may be assumed to be mediated through actions at receptors that may persist after plasma levels are no longer detectable.

8. In the text of the Integrated Summary of Safety (ISS), there was repeated shifting of cohorts of subjects included in various analyses. For every grouping, provide a separate presentation of the denominators so that rates may be calculated. Present rates overall, by treatment group, and by gender, age, and race across treatment groups. The continually

changing denominator requires that for every table the specific studies included in the grouping and the resultant N's for each group must be presented with each analysis.

9. The current NDA safety analysis cannot be confirmed by FDA reviewers because there is no clear variable in the adverse event data set indicating which AEs, SAEs, deaths, or dropouts due to AEs were included in the ISS and which were not. Provide a full detailed assessment of all AEs, SAEs, deaths, and dropouts due to AEs in the ISS.

10. Submit all future electronic data in a format that will facilitate review. Assign unique patient identifiers for each patient in the NDA. Include this number in all datasets such that merging of datasets can be done with some degree of accuracy. Include treatment assignment in every table of the dataset to avoid the need to merge to determine treatment assignment. Provide data definition tables with the column names in the same order as the dataset, with a comprehensive explanation of each data element, including explanation of the derivation for derived elements.

11. Verbatim terms related to suicide were not coded correctly and consistently. Re-code all such events so that all suicide attempts are identified and all completed suicides are included both as suicide attempt and death. Perform a separate analysis of any suicide, suicidal ideation, or intentional overdose that may have occurred during treatment, and upon withdrawal of the drug.

12. Provide a thesaurus that lists each preferred term and all verbatim terms subsumed under that term. Prior to submission, this thesaurus should be reviewed by an experienced and medically knowledgeable individual and gross errors should be corrected prior to submission. Correct and refine inconsistencies in coding.

13. Discrepancies exist between various electronic files within the safety data files. Resolve the discrepancies across datasets prior to resubmitting the safety datasets.

14. Since acamprosate is renally cleared, it can accumulate significantly in patients with moderate or severe renal impairment when a dosage regimen of 666 mg three times daily is used. Provide pharmacokinetic data on an appropriately adjusted dosage regimen for these patients that would result in plasma levels comparable to those seen in patients with normal renal function.

15. Provide comparative pharmacokinetic data in elderly subjects relative to young adults, since renal function is diminished in this subgroup, resulting in the potential for significant accumulation of acamprosate. If warranted, based on the results of these data, propose an appropriately adjusted dosage regimen

16. Provide pharmacokinetic data on the effect of disulfiram on the pharmacokinetics of acamprosate.

17. The preclinical evaluation of acamprosate did not include ion-channel studies (i.e., IKR studies, HERG studies) currently recommended for first-in-class new drugs and new chemical entities. Although review of the limited ECG data available did not indicate an effect on cardiac conduction, this review was based on machine-read ECGs. The Agency's standard recommendation is for blinded manual readings by cardiologists to assess the QT interval. Provide blinded manual readings performed by cardiologists for the specific dose-escalating pharmacokinetic studies that were performed in phase 1 to affirm the initial impression that this drug does not effect the QT interval. These studies include: Dewland I (n=18), Dewland II (n=6), Theodor II (n=62), and Jaillon (n=12).

18. Perform a one-month oral toxicity study, including full histopathology, in dogs using adequate doses to either characterize the toxicity profile or achieve the maximum feasible dose.

19. Repeat the gene mutation assay in Chinese hamster V79 cells and the chromosome aberration assay using adequate dosing and procedures according to current standards.

20. Repeat the carcinogenicity study in mice. Either a standard two-year assay or an appropriate alternative model may be performed. The Agency encourages the submission of a study protocol with supporting data for concurrence of dose selection by our Executive Carcinogenicity Assessment Committee prior to initiation of the carcinogenicity study.

21. Insufficient data have been provided to assess the abuse liability of acamprosate. Provide a discrete, comprehensive abuse liability package for review. This package should contain data from the following:

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

    b. Cell biology assays for dopamine, norepinephrine, and serotonin transporter sites.

    c. A drug discrimination behavioral test to determine if monkeys identify acamprosate as similar to a benzodiazapine.

       Prior to conducting the study, submit the protocol to your IND for acamprosate for review. In the protocol, identify whether lorazepam or chlordiazepoxide will be used as comparator drugs, the dose of the benzodiazepine to be used, and when the peak plasma levels of acamprosate and the chosen benzodiazepine occur following intramuscular administration, to guide selection of appropriate discrimination testing times.

d. A drug discrimination behavioral test to determine if rats identify acamprosate as similar to PCP.

Prior to conducting the study, submit the protocol for review. In the protocol, identify what percent response on the PCP lever constitutes full generalization during the acamprosate challenge tests, how percent response will be calculated, and how response rate will be calculated and assessed for significance.

e. A behavioral study in animals that investigates acamprosate self-administration and the ability of acamprosate to generalize to phenobarbital in drug discrimination studies.

f. Behavioral studies showing acamprosate potentiation of morphine analgesia and the ability of acamprosate to act as a partial agonist in serotonin systems. Doses of acamprosate to be used in behavioral studies should represent plasma levels of drug that are within the range of plasma levels of drug that will be seen clinically, as well as plasma levels that are 2-3 times greater than therapeutic levels, if this can be done safely.

22. With respect to the acamprosate enteric-coated tablet dissolution specification, provide the following:

a. Justification for using Method B over Method A.

b. 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.).

c. Justification for using [ ] speed. If available, provide data from other speeds, [ ]

d. Justification for using pH 6.8. If available, provide data at other pH values, e.g, [ ]

e. Justification for proposing [ ] when [ ] actually measured, or supportive data for the proposed acceptance criterion [ ]

f. Justification for proposing 120 minutes as a single time point for the buffer solution. If available, provide data for time-points earlier than 120 minutes, e.g., 30, 60 minutes, etc.

23. DMF [ ] which is referred to for the drug substance, acamprosate calcium, is not adequate to support NDA 21-431. The issues outlined in the deficiency letter sent to the DMF holder require an adequate response.

24. Provide a clarification of the differences between the information contained in DMF [ ] (homotaurine) and DMF [ ] (acamprosate calcium). Consolidate all pertinent information into one document.

25. The following documentation regarding the proposed commercial packages for the drug product is required:

    a. Letters of authorization (LOAs) allowing reference to the pertinent DMFs for all packaging components [ ].

    b. Certification that the raw materials of fabrication for the container closure systems (bottles, caps, liners, innerseals, and blister pack materials) comply with the requirements of the current 21 CFR regulations regarding food contact safety.

    c. Certification that the raw materials of fabrication for the bulk storage bags comply with the requirements of the current 21 CFR regulations regarding food contact safety.

26. Significant payments of other sorts must be disclosed during the time an investigator is carrying out a covered clinical trial and for one year following completion of the study. Submit a financial certification or disclosure statement for the U.S. trial per the requirements of 21 CFR 54.2(f).

The draft package insert and carton and container labels should be modified to reflect the above comments and submitted. Further labeling comments are being reserved at this time pending resolution of the aforementioned deficiencies.

All applications for new drug active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens must contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (21 CFR 314.55). Based on the information submitted, we conclude the following: [ ], we are waiving the pediatric requirement for this action for this application for patients under 12 years of age. We are deferring submission of pediatric studies for patients 12-[ ] years of age until 2 years following the ultimate approval of this product.

Under 21 CFR 314.102(d), you may request an informal meeting or telephone conference with the Division of Anesthetics, Critical Care and Addiction Drug Products to discuss what steps need to be taken before the application may be approved.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action, FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

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

Sincerely,

/S/

{See appended electronic signature page}

Robert J. Meyer, M.D.
Director
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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

/s/

Robert Meyer
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