



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}

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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