Minutes: May 10, 2002
Psychopharmacological Drugs Advisory Committee
Holiday Inn, Bethesda MD

Issue: NDA 21-431: Acamprosate 333 mg tablets (Lipha Pharmaceuticals, Inc.)

Prior to the meeting, the members and consultants had reviewed background material from the FDA and from Lipha. The meeting was called to order by Dan Oren, M.D., and Sandra Titus, Ph.D., read the conflict of interest statement into the record. Cynthia McCormick, M.D., highlighted the issues that the committee was asked to address. There were approximately 100 persons in attendance.

Attendance:
PDAC Members Present: Dan Oren, M.D., Chair, Richard P. Malone, M.D., Irene Ortiz, M.D., Matthew Rudorfer, M.D., Edwin Cook, M.D., Ph.D.,Andrew Winokur, M.D.,Irene Ortiz, M.D.

PDAC Consultant: Robert Hamer, Ph.D., Andrew Leon, Ph.D., Paul Keck, M.D.

PDAC Members Absent: Tana Grady-Weliky, M.D., Abby Fyer, M.D.

SGEs specific to Alcoholism : Richard Fuller, M.D.

Guests specific to Alcoholism: John Hughes, M.D., Alan F. Schatzberg, M.D., Linda Porrino, Ph.D., Charles O'Brien, M.D.

Candidate for Industry: Dilip Mehta, M.D.

FDA Participants: Sandra Kweder, M.D., Cynthia McCormick, M.D., Celia Winchell, M.D., Sue Jane Wang, Ph.D.

Lipha's Presentations:

Introduction
Anita M. Goodman, M.D., Executive Vice-President and COO, Lipha

European Development Program and Current Registration Status
Sylvie Chabac, M.D., International Project Manager, MERCK/Lipha s.a.

Acamprosate: Mechanism of Action, Preclinical Effects, & Pharmacokinetic Overview
George F. Koob, Ph.D., Professor, Director Neuropharmacology, Scripps Research Institute

Efficacy Results from 3 Pivotal Clinical Trials
Karl F. Mann, M.D., Department of Addiction Medicine, University of Heidelberg, Germany

Analysis of the US Study Results
Barbara J. Mason, Ph.D., Director, Division of Substance Abuse, U of Miami School

Closing Remarks
Anita M. Goodman, M.D

FDA Presentations

Clinical Issues on Efficacy
Celia Winchell, M.D., Medical Team Leader, Anesthetic, Critical Care and Addiction Drug Products

Statistical Perspective of Acamprosate Experience
Sue Jane Wang, Ph.D., Statistics Leader in Alcoholism Treatment Clinical Trials, Office of Biostatistics

Charge to the Committee
Cynthia McCormick, M.D.

Open Public Hearing Participants:
Victor Hasselbok, Ph.D.,Vice President Research Society on Alcohol
Steven Mirin, M.D., Medical Director, American Psychiatric Association
Edward Eder, MD, Medical Director, Comprehensive Addiction Treatment Program, Fairfax, VA
Mark Publicker, M.D., Kaiser, Washington DC

The committee was asked to consider the evidence of efficacy of acamprosate in the treatment of alcoholism and to provide advice on the following questions:

1. **How can the discrepant results between the older, European studies and the more recently conducted American study be reconciled?**

There was some consensus that the trials might not be able to be reconciled. It should be recognized as a failed study and no more worth than that should be attributed to the failure than normal.

One or more individuals made the following types of comments on the possible reasons that the American trial failed:

Maybe different cross sections of the population were used
Maybe the availability of detoxification centers in Europe
Maybe due to the number not detoxified in the American trial
Maybe the co-incidence of substance abuse
Maybe difference in co-morbid diagnoses
Maybe when the European studies were done there was less illicit drugs use
Maybe biological differences in alcoholism
Maybe due to the fact that there are biological differences in alcohol abuse
Perhaps we are mixing apples and oranges by trying to compare European trials to US trial because we do not understand phases of alcoholism

The point that seemed to have the most consensus was the fact that the European trials had 100% detox before trial began, which was not true in the American trial.

The American Trial's use of call back diary increased the therapeutic goal to not drink, and so this affected placebo group as well as treatment group and reduced possible differences between placebo and treatment groups.

2. Given the conflicting results, is there sufficient evidence of the efficacy of acamprosate in the treatment of alcoholism to warrant approval?

Yes= 9 **No =2**

The two no votes felt that the lack of prospectively defining outcomes and analysis plans was a major obstacle to approval and that it was not unreasonable to hold this drug to current clinical research standards.

Some of the yes votes qualified their vote. One felt that there was efficacy if the data could be verified. Another added that there were two positive trials under very narrow conditions.

The three guests, who could not vote, indicated that they felt there was enough evidence in the trials and that the field needed more treatment options because no one treatment would work with all people.

(The transcript will record the vote as 8 yes and two no. This is an error and the minutes reflect the actual count – which can be verified by counting the individual votes.)

3. Do the data support any conclusions regarding subgroups of patients more likely to benefit from acamprosate?

The committee had consensus that acamprosate should not be started for treatment until the patient was abstinent and had been detoxified.

There was some belief that being committed to treatment to be abstinent was related to a positive outcome; but some members also felt that people who are alcoholic had lots of ambivalence and often changed their goals; hence, this variable was less compelling and probably not of value for labeling.

A verbatim transcript of this meeting will be available on the FDA's Dockets Management Branch Website approximately 30 days after the meeting. The address is HTTP://www.fda.gov/ohrms/dockets/ac/acmenu.htm.

I certify that I attended the May 10, 2002 meeting of the Psychopharmacologic Drugs Advisory Committee and that these minutes accurately reflect what transpired.

/s/

Sandra Titus, Ph.D. Date
Executive Secretary, PDAC

/s/

Dan Oren, M.D. Date
Acting Chair, PDAC

Prepared on May 10, 2002/Sandra Titus, Ph.D.