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**M E M O R A N D U M**

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DATE: May 1, 2002

FROM: Cynthia G. McCormick, MD, Director  
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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 Acamprostate

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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 acamprostate, 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 the maintenance of abstinence in chronic alcoholism.