



AUG 23 1996

NDA 18-140/S-003

Wyeth-Ayerst Laboratories  
Attention: Mr. Roy Baranello, Jr.  
Director Regulatory Affairs  
P.O. Box 8299  
Philadelphia, Pennsylvania 19101-8299

Dear Mr. Baranello:

Please refer to your supplemental New Drug Application dated August 28, 1991, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ativan (Lorazepam) 2 mg/ml and 4 mg/ml Injection.

Reference is also made to Agency not approvable letters dated July 21, 1986, and December 6, 1989.

We acknowledge receipt of your amendments subsequent to the December 6, 1989 not approvable letter dated May 3, 1990, August 8, 1994, December 1, 1994, January 13, 1995, January 30, 1995, April 20, 1995, and April 21, 1995, August 25, 1995, June 5, 1996, and July 1, 1996.

The supplemental application provides for the use of Ativan Injection for the initial anticonvulsant treatment of status epilepticus.

Our review of the application has led us to conclude, based on the results of two adequate and well controlled clinical investigations, Study 411, a comparative trial of diazepam and lorazepam, and study 415/416, a dose-comparison trial of lorazepam, taken in conjunction with all other relevant evidence, that Ativan injection will be "effective in use" under the conditions of use proposed in draft labeling provided by the Agency (see ATTACHMENT).

Although Study 411 documents that Ativan is an effective agent by showing, under the conditions employed, that lorazepam treated patients had a greater response rate than those randomized to the control condition (diazepam), the study cannot reliably speak to the comparative performance of Ativan and Valium under conditions of actual use. Accordingly, any representation of the results of this study as evidence of Ativan's superiority to Valium will be viewed as a basis to refer the matter to our Office of Compliance for appropriate regulatory action.

Our review of this supplemental application has failed to identify any risk that would cause the application to be disapproved. Accordingly, we deem the application to be APPROVABLE. Before the application may be approved, however, it will be necessary for you to submit the following information and respond to the following issues:

**CLINICAL****1. Labeling****General**

The attachment to this letter provides a draft of the labeling that the Agency proposes be adopted for Ativan Injection upon its approval for use in the management of status epilepticus.

Although sections of this draft are taken verbatim from the labeling proposal that you provided in your resubmission of August 8, 1994, other sections have been extensively modified, and still others added *de novo*. These changes are intended to bring Ativan Injection labeling into greater conformity with the requirements of 21 CFR 201.57 and, more importantly, to provide guidance that we believe is essential to the prudent management of patients presenting with status epilepticus.

We have not provided text for every section of labeling that we require you to revise, however. Instead, throughout the draft, we have embedded requests (these are identified by their presentation within brackets, [ ], and the phrase, "NOTE TO SPONSOR:") that explain our purpose in asking you to modify the section involved. In some instances, these revisions require you to conduct reviews and provide the data or information necessary to support the statement or assertion that will be incorporated in the text requested.

**-Pediatric Use**

An important example of the kind of revisions just discussed are those that should be made to support the presentation in labeling of directions for the use of Ativan Injection in pediatric age patients presenting with status epilepticus. We are especially interested in this aspect of Ativan Injection labeling because it seems likely that the product will be used in pediatric patients whether or not specific instructions are provided. Accordingly, we believe it is very much in the public interest that Ativan labeling provide such guidance, but, before that may be allowed, you will have to develop the evidence and arguments, as required by regulation (21 CFR 201.57[f][9]), to justify extending the results of the adequate and well controlled trials conducted in adults, (i.e., those we have relied upon to conclude that Ativan Injectable is an effective treatment for status epilepticus) to those in the pediatric age group.

The argument that you develop to support pediatric use must make the case that status epilepticus is, at least insofar as the attributes that control response to a benzodiazepine, essentially the same in adults as in children despite the fact that the

distribution of the causes of status varies with age. You must also provide a justification for any dosing regimen recommended in children; this must be developed separately for each of the substrata involved [e.g., neonate, infant, etc.]. The argument presented must make the case 1) that the kinds of status seen in the subgroup are comparable to those seen in adults, 2) are such that they are likely to respond to treatment with sedative benzodiazepines, and 3) that the dosing regimen proposed for the subgroup provide exposures to lorazepam roughly equivalent to those produced in adults treated under the recommended conditions of use.

Finally, it will be necessary to identify the risks, if any, that are unique to the use of Ativan in pediatric age patients. For example, your labeling proposal takes note of reports of paradoxical excitement seen among children treated with Ativan. It would be useful to develop this information in greater detail (i.e., see Note to sponsor in labeling under Precautions).

**Section enumerating untoward events reported in association with the use of Ativan in the management of status epilepticus prior to the product's official approval for the indication (1980 to 1996)**

In view of Ativan's longstanding off-label use in the management of status epilepticus, the literature may contain numerous reports of untoward events that may not have been reported to Wyeth Ayerst and/or to the FDA. Because reports of these events are spontaneous, and arise in open, uncontrolled use, neither their incidence nor causal association are reliably known. Accordingly, although we believe it important to enumerate these events in labeling, we wish to do so with adequate circumspection. One possible strategy is to enumerate them in a section that carries the title given above. The section might begin with a short paragraph explaining the origin of these reports and why their causal relationship to Ativan is therefore, at best, problematic.

**Warning regarding generic considerations in management of the patient presenting with status epilepticus, etc.**

Although we are mindful that drug product labeling is not intended to provide definitive instruction for the management of a condition, the complexity involved in the treatment of status seems sufficient to justify the provision of more detailed advice than we normally would. Toward this end, we ask that you, in consultation with appropriate experts, develop a brief overview of the strategy and rationale for using a sedative benzodiazepine in the management of status. This discussion should address the issue of the maximum number of doses and the point in time at which it becomes appropriate to discontinue benzodiazepine use and to switch to another mode of therapy. It is our intent to include this discussion, not only in this location, i.e., in Warnings, but in the Dosage and Administration section as well.

**2. Safety Update**

Our review of the safety of lorazepam injection in the treatment of status epilepticus was based on data accumulated in 488 patients in 7 studies. You will need to submit a final safety update including any new safety data.

**3. World Literature Update**

Prior to the approval of lorazepam injection in the treatment of status epilepticus we require an updated report on the world's archival literature pertaining to the safety of lorazepam in this population. This report should cover all relevant published papers, including clinical or preclinical data, that were not submitted with the original NDA or in subsequent amendments.

We need your warrant that you have reviewed this literature systematically, and in detail, and that you have discovered no finding that would adversely affect conclusions about the safety of Ativan injection in this population. The report should also detail how the literature search was conducted, by whom (their credentials) and whether it relied on abstracts or full texts (including translations) of articles. The report should emphasize clinical data, but new findings in preclinical reports of potential significance should also be described. Should any report or finding be judged important, a copy (translated as required) should be submitted for our review.

**4. Foreign Regulatory Update/Labeling**

We require a review of the status of all actions with regard to lorazepam injection in the treatment of status epilepticus, either taken or pending before foreign regulatory authorities. Approval actions can be noted, but we ask that you describe in detail any and all actions taken that have been negative, supplying a full explanation of the views of all parties and the resolution of the matter. If lorazepam injection in the treatment of status epilepticus in any countries, we ask that you provide us current labeling for paroxetine in those countries, along with English translations when needed.

Please submit three copies of the introductory promotional and/or advertising campaign that you propose to use for this new indication. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional material and the package insert, directly to:

Food and Drug Administration  
Division of Drug Marketing, Advertising and Communications,  
HFD-40, Room 17B-17

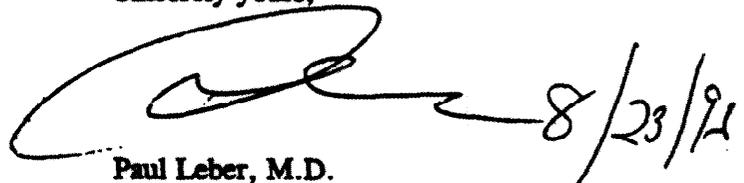
5600 Fishers Lane  
Rockville, Maryland 20857

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 the other options under 21 CFR 314.110. In the absence of such action on your part, the FDA may proceed to withdraw the application.

In accordance with the policy described in 21 CFR 314.102(d) and in the Center for Drug Evaluation and Research Staff Manual Guide CDB 4820.6, you may request an informal conference with the Division to discuss what further steps you need to secure approval. The meeting is to be requested at least 15 days in advance. Alternatively, you may choose to receive such a report via a telephone call. Should you wish this conference or a telephone report, or should any questions arise concerning this NDA, please contact Mr. Paul David, Project Manager, at (301) 594-5530.

This drug may not be legally marketed for the indication provided by this application until you have been notified in writing that the application is approved.

Sincerely yours,

A handwritten signature in black ink, followed by the date "8/23/91" written in a similar style.

Paul Leber, M.D.  
Director  
Division of Neuropharmacological  
Drug Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

ATTACHMENT