CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number: 18140/S003

Trade Name: ATIVAN

Generic Name: Lorazepam

Sponsor: WYETH-AYERST LABORATORIES

Approval Date: September 5, 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION: 18140/S003

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	Included	Pending Completion	Not Prepared	Not Required
Approval Letter	X			
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Chemistry Review(s)			X	
EA/FONSI	X			
Pharmacology Review(s)			X	
Statistical Review(s)	X			
Microbiology Review(s)				X
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Bioequivalence Review(s)				X
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Correspondence				

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: 18140/S003

APPROVAL LETTER

NDA 18-140/S-003

SEP 5 1997

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 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ativan (Lorazepam) Injection.

Reference is also made to Agency approvable letter dated August 23, 1996, and we acknowledge receipt of your amendments dated February 24, and September 4, 1997, providing for responses to our approvable letter.

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

We have completed our review of this supplemental application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the enclosed marked-up draft labeling (see ATTACHMENT). Accordingly, this supplemental application is approved effective on the date of this letter.

The labeling accompanying this letter should be used for marketing this drug product. This final labeling is based on an Agency telefacsimile sent to you dated August 27, 1997. We note your agreement to the Agency's proposed labeling, with minor modifications, in a telephone conversation dated September 4, 1997, between Mr. Kenneth Bonk of your firm and Mr. Paul David of this Agency. For convenience, all labeling changes made since your last approved labeling (Label Code: CL 3856-5) appear as shaded text (redlined) in the attached labeling.

Please submit three copies of the introductory promotional material that you propose to use for this product. 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
5600 Fishers Lane
Rockville, Maryland 20857

The final printed labeling (FPL) must be identical to the enclosed marked-up draft labeling. These revisions are terms of the supplemental NDA approval. Marketing the product before making the agreed upon revisions in the product's labeling may render the product misbranded and an unapproved new drug.

Please submit 20 copies of the printed labeling, ten of which are individually mounted on heavy-weight paper or similar material.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact Mr. Paul A. David, Project Manager, at (301) 594-5530.

Sincerely yours,

for PL 9/5/97

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

ATTACHMENT

cc:
ORIG NDA 18-140/S-003
HF-2/MedWatch
HFD-2/ORM
HFD-40/LStockbridge
HFD-92/DDM-DIAB
HFD-101/LCarter
HFD-120/DIV FILE
HFD-120/PLeber/RKatz/JFeeney 9/5/97
/GFitzgerald/AAtrakchi 9/5/97
/MGuzewska/WRzeszotarski
/JWare/MMille/David 9.4.97
HFD-860/RBaweja/SIbrahim 9/4/97
HFD-713/TSahlrootl
HFD-222/New Drug Chemistry Division Director
HFD-613
HFD-713/TSahlroot/DHoberman
HFD-735/DPE
HFI-20/Press Office
District Office
09/04/97pd
Doc # LTRATIVAN.AP1
SUPPLEMENTAL APPLICATION APPROVED (AP)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 18140/S003

APPROVABLE LETTER

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,

8/23/94

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

ATTACHMENT

cc:
ORIG NDA 18-140/S-003
HFD-2/MLumpkin
HFD-40/DDMAC
HFD-80
HFD-101/LCarter
HFD-120/DIV FILE
HFD-120/PLeber/RKatz/TLaughren
/JFeeney/PAndreason
/GFitzgerald/AAtrakchi
/SBlum/WRzeszotarski/PDavid
HFD-344/RYoung
HFD-860/RBaweja/SIbrahim
HFD-638
HFD-713/ENevius/TSahlroot
DISTRICT OFFICE
rd:12/06/95pd
rev:07/18/96pd;07/26/96jf;
ft:
Doc # LTRATIVN.WPC
SUPPLEMENTAL APPLICATION APPROVABLE (AE)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER : 18140/S003

MEDICAL REVIEW(S)

Review and Evaluation of Clinical Data
NDA 18-140, Amendment to Supplement SE1-003

Sponsor:	Wyeth-Ayerst
Drug:	Ativan (lorazepam) Injection
Proposed Indication:	Status Epilepticus
Material Submitted:	Proposed Labeling
Correspondence Date:	February 24, 1997
Date Received:	February 27, 1997

Attached to this cover document is a draft version of labeling prepared by me, taking into account the sponsor's proposed labeling and all the information available. There are 2 areas that need explanation:

1. Pediatric Labeling.

There are three components needed to provide adequate directions for use in pediatrics: efficacy information (or some rationale that the disease state is the same in pediatric and adult patients), safety information, and PK information. There have been no controlled trials in pediatric populations; the sponsor has provided a brief discussion about the similarities between SE in adult and pediatric patients (see their proposed labeling, Dosage and Administration Section). Aside from the efficacy question however, the pediatric safety experience consists almost entirely of literature reports encompassing 250 patients. Although the overall tone of these articles is a reassuring one (and benzodiazepines are generally viewed as safe for use), some problems have been described especially in younger age groups. These problems generally fall into the category of "paradoxical" excitation. The problems include seizures, myoclonus, tremors, agitation, and hallucination.

The PK in neonates is included in my proposed labeling and would argue for an 80% reduction in a mg/kg dosing regimen compared to adults (note that my proposed labeling describes a fixed dose for adults). Such a dose reduction was not used in the literature reports that I reviewed on the neonatal experience with Ativan. No PK information is available in infants below the age of 2 years. Information is provided for children and adolescents.

The lack of a systematically collected safety database, coupled with the known PK differences in neonates and the lack of PK information in infants, has resulted in my version of labeling **not** providing **specifically** for a pediatric indication with pediatric dosing guidelines. Initially, I was tempted, knowing the reduced clearance of lorazepam in neonates compared to adults, to provide a specific recommendation for a reduced mg/kg dosing regimen in neonates. This seemed especially appealing knowing that neonates have experienced some AEs such as myoclonus that adults have not experienced. On further consideration, however, I believe it remains purely speculation that any AEs in neonates have anything at all to do with PK differences. Further, an effective dose of Ativan for neonatal SE (assuming Ativan is effective in neonatal SE) has in no way been defined.

My version of labeling does provide the PK information and some of the described safety issues for pediatric populations.

2. Pregnancy Warnings.

My version of labeling is in keeping with the intent of the regulations for Category D drugs. SE is a serious and life-threatening disorder, for which there may not be other effective treatments for a given patient.

John Feeney, M.D.
Medical Reviewer
August 15, 1997

cc:
HFD-120
HFD-120/Leber/Katz/Feeney/David

Review and Evaluation of Clinical Data
NDA 18-140, Amendment to Supplement SE1-003

Reviewer:	John Feeney, M.D.
Date:	July 8, 1996
Sponsor:	Wyeth-Ayerst
Drug:	Ativan (lorazepam) Injection
Proposed Indication:	Status Epilepticus
Material Submitted:	Response to FDA Request
Correspondence Date:	July 1, 1996

Introduction: A June 5 submission from the sponsor raised questions which this submission addresses.

Current Submission:

1. In Study 411, the sponsor states that no patient was re-classified based on relapse within 30 minutes (the second part of the 10/30 rule). In the middle of the 3rd page the sponsor states, "A patient was called a responder to the first dose if seizure activity stopped within 10 to 15 minutes after administration was completed and control of status epilepticus was achieved without the need for a second dose of study medication and/or further i.v. antistatus medication."

2. Sponsor's Table 1 was designed to show the inter-infusion intervals for responders to first dose. Because it showed that many diazepam patients did not receive the second infusion, the sponsor was asked to show the same information for non-responders. Table 2 shows this information and reveals that all non-responders in both treatment groups received both infusions.

3. The sponsor reports that no patients received maintenance medication before being labeled responders. This is not important if no patients were re-classified using the 10/30 rule.

Conclusions: The sponsor has addressed concerns about post hoc re-classification of patients in Study 411 using the post hoc 10/30 rule.

John Feeney, M.D.
Medical Reviewer

cc:
HFD-120
HFD-120/Leber/Katz/Feeney/David

Review and Evaluation of Clinical Data
NDA 18-140, Amendment to Supplement SE1-003

Reviewer:	John Feeney, M.D.
Date:	July 3, 1995
Sponsor:	Wyeth-Ayerst
Drug:	Ativan (lorazepam) Injection
Proposed Indication:	Status Epilepticus
Material Submitted:	Amendment to Supplement
Correspondence Date:	August 8, 1994 with additional correspondence dated April 20, 1995 (responding to a February 28, 1995 teleconference)

Introduction:

Ativan injection is currently approved for the indication of preanesthetic medication, producing sedation, relief of anxiety, and a decreased ability to recall events related to the day of surgery.

Wyeth-Ayerst submitted an efficacy supplement in 1981 for the initial treatment of status epilepticus. The Agency issued a non-approvable letter for this efficacy supplement in 1986 based on problems of interpretation of active-control trials which demonstrated no difference. The sponsor responded to some of the issues in the first non-approvable letter, but the continuing problem of active-control trials which showed no difference resulted in a second non-approvable letter in 1989. Wyeth-Ayerst met with the Agency throughout the years to discuss measures that would be required to obtain approval of their efficacy supplement.

In the current amendment to their efficacy supplement, the sponsor has provided the results of two new studies in status epilepticus, Study 411 and Study 415/416. Study 411 was an active-control study of Valium and Ativan, a study where Ativan appeared to perform better than Valium. Study 415/416 was a comparison of three different doses of Ativan, 1mg, 2mg, and 4 mg.

Study 411 (Canada)

Investigators

Center	1	Bruni	n=1
	2	Guberman	n=6
	3	Langevin	n=1
	4		
	5	McLachlan	n=9
	6	Pillay	n=13
	7	Purves	n=6
	8	St. Hilaire	n=3
	9	Andermann	n=11
	10	Reiher	n=8
	Total		n=58

A. Study Design

This was a double-blind, active-control, parallel study of the effectiveness of Ativan vs Valium in stopping status. Status included generalized tonic-clonic status, simple partial status, complex partial status, and absence status. On presentation, some seizure activity had to be witnessed.

Pts with generalized tonic-clonic status were to have 1) 3 or more seizures within 1 hour, or 2) 2 or more seizures in rapid succession with no recovery of consciousness in between, or 3) a single seizure lasting 15 minutes or more.

Pts with absence status were to have a confusional state with a characteristic EEG (or a history of characteristic EEG changes).

Pts with complex partial status were to have repetitive temporal lobe seizures or a confusional state with characteristic EEG changes (or a history of characteristic EEG changes).

Simple partial status was to consist of frequent clinical and EEG

somatomotor seizures (or a history of characteristic EEG changes).

If patients met the inclusion/exclusion criteria, they were initially given either Ativan 4 mg IV or Valium 10 mg IV. Ten minutes later, if needed, a second dose of either drug could be delivered. Ten minutes later (twenty minutes from time 0), other interventions could be initiated if deemed necessary. Meanwhile, fifteen minutes from time 0 (in responders to the first dose) or 25 minutes from time 0 (in responders to the second dose), maintenance therapy could be initiated if the clinician foresaw the need for such. Typically, maintenance therapy would include loading with phenytoin. The implication, here, is that "response to a dose" is cessation of seizures prior to the passage of ten minutes, but then sustained for an additional 5 minutes. Unfortunately, the study report states that a responder must have a sustained response for 30 minutes to be a true responder (p16). Thus, the protocol leaves some ambiguity regarding the definition of "response." For instance, if a pt stopped seizing 8 minutes after a dose, regained consciousness 14 minutes after the dose, but then had another seizure 20 minutes after the dose (and 5 minutes into phenytoin loading); is that pt a responder ?

Inclusion criteria allowed patients to be enrolled a second time if 7 days or more had elapsed since the previous course of treatment. Exclusion criteria prohibited entering patients with focal status for 48 hours or more, status due to reversible metabolic derangement such as hypoglycemia, life expectancy less than 2 days, suspected alcohol or sedative drug withdrawal, and history of drug-resistant status associated with a progressive neurological deficit.

Clinical observations were to include: a) clock-time of completion of study drug injection, b) the time interval from the completion of study drug injection to the end of the last convulsive episode following which the patient eventually regained consciousness, and c) level of consciousness and vital signs at 5 minute intervals.

The protocol specified that "the primary efficacy parameters are proportion of patients responding to the first and second injections." The secondary parameter was to be the response latency-time i.e. the interval from completion of study drug injection to the end of the last convulsive episode following which the patient regained consciousness.

The protocol-specified analysis was the chi-square test for the proportions of pts responding to first and second doses. Survival analyses were planned for response-latency time.

The sponsor's power calculations, based on an expected 80% response rate after one injection of Ativan and a 60% response rate after one injection of Valium, demonstrated that a sample size of 40 patients per group would provide 90% power. The duration of the study was to be 15 months, with a maximum of 24 hours participation by each patient.

B. Subject Disposition and Baseline Comparison

The study was conducted between 10/89 and 2/91, approximately 14 months or just short of the protocol-specified duration. Only 62 cases of status were randomized to treatment in that timeframe, 18 fewer than the protocol expectation. 4 pts were enrolled twice; thus, only 58 unique patients were exposed to study drugs. 2/62 cases of status were determined retrospectively to have been pseudo-seizures. 1/62 cases of status was determined to have been due to hypoglycemia. If these last 3 cases are eliminated from the analysis, 59 cases of status remain.

The sponsor makes a case that the primary analysis should not include patients previously randomized to treatment, but being seen again for a new episode of status (vol.6,p16). This contradicts the protocol which allowed re-entry for a given patient if 7 days separated the different episodes of status. The argument made by the sponsor is that the additional observations on the same patient are not independent of the first observations.

The net effect of these different cuts of the data is 4 distinct groups:

1. **ITT, all episodes** This group, n=62, includes all episodes of status, whether in new patients or not, whether in patients wrongly included or not.

2. **ITT, first episodes** This group, n=58, includes all patients, whether wrongly included or not, but only for that patient's first evaluable episode of status. A second episode of status in the same patient is excluded from the analysis group.

3. **Evaluable, all episodes** This group, n=59, includes all episodes of status, even if the patient was entered twice. It excludes the 3 patients with pseudo-seizures and hypoglycemia.

4. **Evaluable, first episodes** This group, n=55, excludes second episodes of status in the same patient and excludes the 3 patients with pseudo-seizures and hypoglycemia.

There were no deaths or discontinuations in the study.

Looking across all 62 patients in the "ITT, all episode" group, there were no significant differences with respect to age, sex, race, seizure type, concomitant medications, and weight.

No discussion of out-of-hospital medication for the episode of status was presented for Study 411. Based on Study 415/416, I expected that at least some patients received Valium or phenytoin prior to study entry. The sponsor was asked to address this issue. The reply (dated April 20, 1995) was that "one patient received 300 mg i.v. phenytoin 26 minutes before the trial medication."

C. Efficacy Evaluation

ITT, first episodes: Response to first dose, although not operationally defined in the protocol, is presumably represented by lack of need for a second dose after ten minutes. Page 16 of the study report states, "Patients were considered to have responded if seizure activity stopped within 10 minutes after completion of the dose and did not recur for 30 minutes." Using this definition, 80% (24/30) of Ativan patients responded to first dose while only 57% (16/28) of Valium patients responded to first dose (p=0.089, Fishers exact test; 0.057, stratified analysis).

When overall response was evaluated (response to first plus second doses), there was no significant difference between the Ativan and Valium groups. 28/30 (93%) Ativan pts responded while 24/28 (85%) Valium pts responded; p=0.415.

When latency to response was evaluated, missing data for many responding patients (7 pts) and censored data for non-responders (7 pts)

combined to confuse interpretation. Additionally, 3 pts had times to response that exceeded 10 minutes (20min, 20min, and 15min) even though they "responded to the first dose." This emphasizes the point that investigators had no rules guiding them whether or not a second dose of Ativan or Valium was needed; for the 3 pts mentioned, investigators chose not to give a second dose and seizures stopped by the specified time anyway. For all these reasons, I believe the variable "minutes until response" is uninterpretable.

ITT, all episodes: Response to first dose: 27/34 (79%) Ativan pts responded, while 16/28 (57%) Valium pts responded; p=0.096 (Fishers exact), 0.042 (stratified analysis).

Overall response: 31/34 (91%) Ativan pts responded, while 24/28 (85%) Valium pts responded; p=0.69.

Evaluable, first episodes: Response to first dose: 24/29 (82%) Ativan pts responded, while 14/26 (53%) Valium pts responded; p=0.039 (Fishers), 0.015 (stratified).

Overall response: 27/29 (93%) Ativan pts responded, while 22/26 (84%) Valium pts responded; p=0.40.

Evaluable, all episodes: Response to first dose: 27/33 (81%) Ativan pts responded, while 14/26 (53%) Valium pts responded; p=0.026 (Fishers), 0.011 (stratified).

Overall response: 30/33 (90%) Ativan pts responded, while 22/26 (84%) Valium pts responded; p=0.68.

Summary of "Response to First Dose":

	ITT	Evaluable
All episodes	16/28vs.27/34 (.042)	14/26vs.27/33 (.011)
First episodes	16/28vs.24/30 (.057)	14/26vs.24/29 (.015)

Prognostic Variables: The sponsor investigated response rates by sex, age (<40 vs >40), race (white vs non-white), and sz subtype (generalized

tonic-clonic vs other) for the ITT, first episode population and the Evaluable, first episode population. No significant interactions were noted.

False-positives ("responders") and false-negatives: 3 pts are called responders to second dose, even though the minutes until response seem excessively long. Recalling that supplemental treatment (usually phenytoin loading) could begin at 15 minutes and that other interventions could begin beyond that, 3 pts are listed with response times of 45 min, 37 min, and 65 min. The protocol is not clear on this point, but it seems to allude to 20 minutes (10 min after the second dose) as the maximum time window for a true responder.

Five subjects drew my attention with regard to an analysis of "response to first dose":

1. Three were listed as responders to first dose, but the times for response are listed as 15, 20, and 20 minutes respectively. By protocol, investigators were allowed to give a second dose at 10 minutes, raising the question whether these pts should be considered true responders.

2. Two pts were listed as non-responders to first dose and responders to second dose, even though the time to response is listed as 4 and 8 minutes respectively. These pts could be re-classified as responders to first dose.

If the five false-positives and false-negatives above are incorporated into the analyses, the following responder rates emerge:

	ITT	Evaluable
All episodes	16/28vs.26/34(.172)	15/26vs.26/33(.096)
First episodes	16/28vs.23/30 (.163)	15/26vs.23/29(.143)

Transient vs complete response: "A transient response was defined as the relapse of seizure activity before maintenance therapy became effective." In practice, however, it appears that transient was defined as a relapse between 31 and 90 minutes, a period of time when other medications such as phenytoin would be expected to predominate in controlling seizures. While the data to substantiate these categories cannot be found in the study report, p29 of the study report summarizes the data from the sponsor's perspective. For both the ITT, first episodes and the Evaluable, first episodes populations, the number of complete responses vs transient responses favored Ativan over Valium. 27/28 Ativan pts vs 20/24 Valium pts had complete responses in the first group. 26/27 Ativan pts vs 18/22 Valium pts had complete responses in the second group.

Seizure control and time until response by seizure type: Sponsor's table from p32 of the study report shows response for the different seizure types: GTC, simple partial, complex partial, and absence status. In particular, for GTC, 15/17 (88%) Ativan pts vs 7/13 (54%) Valium pts responded to the first dose (p=.049). This difference disappears for overall response and for the time to response analysis.

Investigators

US	
Investigator	N
Asconape	6
Barkley	2
Langendorf	20
Unwin	5
Pierre-Louis	7
McGoldrick	34

Canada	
Investigator	N
Andermann	18
Grand'Maison	3
Purves	8
Pillay	2
Jones	8
McLachlan	14
Young	3

A. Study Design

This was a double-blind, parallel, randomized, multicenter study of 3 different doses of Ativan in the treatment of status. Patients were randomly assigned to receive either 4, 2, or 1 mg Ativan IV at time zero. If required, an open-label 4 mg Ativan dose could be given at 10 minutes;

likewise, if required, an open-label 4 mg Ativan dose could be given at 20 minutes. Patients were considered responders to the first dose if no further clinical or electrical seizure activity was observed during the 30-minute period that followed completion of the first dose. Maintenance therapy with IV phenytoin could be initiated 10 minutes after the first injection of Ativan at the discretion of the investigator.

Status included GTC, simple partial status, complex partial status, and absence status. The definition of GTC was the same as in Study 411 except that 3 seizures within 2 hours (instead of within 1 hour) qualified for GTC status.

The definition of absence status was the same as in Study 411.

The definition of complex partial status was the same as in Study 411.

The definition of simple partial status was the same as in Study 411.

Exclusion criteria were standard and the same as in Study 411. In particular, if the investigator deemed that "adequate anticonvulsant drug therapy for the current status episode" had been given before arrival in the emergency room, the pt would be excluded. Inclusion criteria did allow patients to be enrolled a second time if 7 days or more had elapsed since the previous course of treatment.

The primary efficacy variable was the % of pts who responded within 10 minutes after the first dose and maintained the response for 30 minutes or greater. There were 4 secondary variables:

1. the % of pts responding after the first or second dose
2. the % of pts responding after the first, second, or third dose
3. the % of pts experiencing a relapse between 31 and 90 minutes
4. the time until response to the first dose

The protocol-specified analysis plan stated that the "two primary comparisons will be between the high and low dose groups and between the middle and low dose groups." The Mantel-Haenszel was the dictated analysis.

The sponsor's power calculation hypothesized response rates to be 75% for the high dose group and 25% for the low dose group. With 40 per group,

the study was powered at 98%.

B. Subject Disposition and Baseline Comparison

As in Study 411, four distinct study populations were defined:

1. ITT, first episode; n=119
2. ITT, all episodes; n=130
3. Evaluable, first episode; n=109
4. Evaluable, all episodes; n=118 (sponsor lists only 116 on p36 of study report

130 pts constituted the ITT, all episodes group. This included the 119 unique pts, 8 of whom were enrolled a second time, and 3 of whom were enrolled a third time.

Baseline demographic information for the full 130 pt, ITT, all episodes population are listed in the sponsor's table (p32 study report). No significant differences between groups are noted for age, sex, race, height, or primary diagnosis. 85-90% of pts had GTC (60-70%) or complex partial (12-29%) status. Weight was the only factor that differentiated the treatment groups at baseline.

There were two reasons why a patient would be considered non-evaluable. The first was that protocol violations existed. The second was that pts enrolled at sites where one or two of the treatment groups lacked a single pt were excluded from the pairwise comparisons that were affected.

3 pts were excluded because the open-label dose was administered sooner than was allowed by the protocol. 2 of these 3 were in the 4mg group. The issue then becomes whether non-response to first dose is defined as need to give the second dose or, alternatively, as continued seizures 10 minutes after the first dose. If the former rule is followed, these 3 patients should be considered evaluable.

5 pts were excluded because the diagnosis was a protocol violation (pseudoseizures in 4 pts and alcohol withdrawal syndrome in 1 pt; 3/4 pseudoseizure exclusions occurred in the same pt who was re-entered on 3 separate occasions). For 8 pts, a data pair did not exist for at least one of the comparisons at that center.

Note from the sponsor's baseline demographic table that 14 entered pts had received some pre-study treatment, either Valium or phenytoin; of these 14, only 4 pts are listed on p34 of the study report as non-evaluable because of prestudy Valium administration "within 10 minutes before study medication." The implication is that if pts received Valium more than 10 minutes prior to study entry, then they were considered evaluable. Likewise, the prestudy administration of phenytoin did not render any of these pts (total of 2) non-evaluable. In a subsequent April 20, 1995 submission, the sponsor acknowledged that one patient who had received Valium 8 minutes before study drug should have been excluded but, in error, was not.

Roughly 70% of pts in each treatment group were listed as being on concomitant anticonvulsants. Roughly 30% of pts in each treatment group were listed as being on concomitant antiepileptic drugs. It is not clearly stated what the overlap might be between "anticonvulsants" and "antiepileptics."

C. Efficacy Evaluation

As in Study 411, the sponsor considers the first-episode analyses to be the primary analyses.

As mentioned under "study design" above, the protocol dealt with the multiple-comparison issue by, first, requiring a significant difference between the 1 and 4 mg groups. If significance was reached, the middle (2mg) and low (1mg) dose groups would then be compared. In fact, the initial comparison between the high and low dose groups was not significant. "Therefore, based on the multiple-comparison control procedure that was specified in the protocol, no comparison could be declared statistically significant."(p25 of study report)

The sponsor has performed the following analyses:

1. All pairs of treatment groups were compared for response to first dose using:
    a. the stratified Mantel-Haenszel procedure with some sites combined
    b. the generalized estimating equations procedure

2. A combined 1- and 2-mg treatment group was compared to the 4-mg group for response to first dose using the stratified Mantel-Haenszel procedure with some sites combined

3. A trend test was done using the modified Bartholomew procedure

4. All pairs of treatment groups were compared for response to the first or second dose by using the stratified Mantel-Haenszel procedure with some sites combined

Response to first dose: As can be readily seen from the sponsor's table (p42 study report), the 1 mg and 2 mg dose groups could not be distinguished from each other for response to first dose. This was true for each of the four study populations, ITT/first, ITT/all, Evaluable/first, and Evaluable/all.

Likewise, the 1 mg and 4 mg dose groups could not be distinguished, although for the ITT/first and ITT/all populations, p values approached .05 (.085 and .086 respectively). The Evaluable populations yielded p values of .169 and .219; presumably the evaluable populations should be the more appropriate groups of study.

The 2 mg and 4 mg groups could be distinguished and the p values were more significant for the Evaluable groups than the ITT groups. For the Evaluable/first group the p value was .037.

The sponsor also analyzed the same data with generalized estimating equations. The overall pattern of p values was similar; p values were generally lower.

Since the 1 mg and 2 mg groups could not be distinguished, it would make sense to combine the two groups and compare the composite 1-or-2 mg group to the 4 mg group. The sponsor did this, revealing significant p values for all 4 populations; the most significant difference was found for the Evaluable/first population, p=.037.

The Bartholomew analysis will not be discussed here. The results can be found on p46 of the study report.

Response to first or second dose: Before moving beyond response to

first dose alone, one has to remember that investigators were allowed to begin other interventions for status at 10 minutes, the same time that the second dose of Ativan could be given. From the information provided, I cannot ascertain which pts received other interventions (presumably this would be phenytoin loading). "Response to first or second dose" (or third dose) is meaningless unless interpreted in light of concomitant anti-status treatments. Never-the-less, the following analyses are reviewed as presented by the sponsor.

Once again the 1 mg and 2 mg groups could not be distinguished. In contrast to the "response to first dose only" category above, the 4 mg group could be distinguished from the 1 mg group, but not the 2 mg group. As above, since the 1 mg and 2 mg groups could not be distinguished, it would make sense to combine the two groups and compare to the 4 mg group; the sponsor has not presented this analysis for the "response to first or second dose" outcome variable.

Response to first, second, or third dose: The results of this analysis are presented in sponsor's table 11. Basically, response rates were uniformly high (89,100, and97%) for all 3 dose groups and, at least for the Evaluable/first population, the 3 groups could not be distinguished from each other.

Duration of seizure control: Only 2 pts who were controlled by the first dose had subsequent seizure activity after 30 minutes.

Time to response: No statistically significant differences between the dose groups were observed. My own observation is that, even among responders, the time to response was so frequently missing from CRFs as to make any interpretation of these results meaningless.

Consistency of response across investigators: Sponsor's table 12 shows the exact p values for the treatment-by-site interaction; none were above 0.10 for the main analyses.

Response by Age, Sex, Race, Weight, and Diagnosis: Sponsor's tables 14-18 show the interaction p values and response rates by treatment group. None of the interaction p values were significant.

Lorazepam plasma concentration data: The protocol called for the

collection of plasma samples to check drug concentrations 4 minutes after the completion of the initial dose. However, in actuality, plasma levels were checked from 4 to 29 minutes after dosing. The sponsor presents an analysis based only on levels drawn between 4 and 12 minutes after the initial infusion; these results are shown below. The justification for this subgroup analysis, as presented by the sponsor, is that levels fall rapidly after IV infusion and exhibit large interpatient variability.

Dose Group	N	Mean Conc.	Median Conc.
1 mg	28	24	21
2 mg	21	32	34
4 mg	24	68	60

Based on these data, the 1 and 2 mg groups could not be distinguished, while the 4 mg group could be distinguished from each of the other two dose groups.

A comparison between responders and nonresponders within each dose group was made with respect to plasma concentrations. At the lowest dose, the mean lorazepam concentration was significantly higher in the responders than the nonresponders; at the two higher doses, this difference was not found and, in fact, for the 2 mg group, the nonresponder group had a higher mean plasma level.

Adequacy of blinding: No tests to assess the blinding were conducted.

Generalized Tonic-Clonic Seizures/Simple Partial Seizures

The protocol-defined endpoint for Study 411 and Study 415/416 seems unrealistic in some regards. "Response to first dose" is a categorical variable that requires some evidence of response prior to the time when a second dose could be given. For absence status and partial complex status, I do not believe a definite time cutoff exists for the end of status. Both of these clinical entities are defined in part by a confusional state; this confusional state is operationally difficult to separate from the post-ictal period.

I asked the sponsor to specify how time of response was determined for patients with absence status and partial complex status. In the April 20, 1995 submission, the sponsor responded that "the response time determination was made solely on clinical grounds."

For this reason, a subgroup analysis including only patients with generalized status and simple partial status has value. Using only the ITT populations from studies 411 and 415/416, the following results emerge for response to first dose:

	Study 411	415/16; 1mg vs 4 mg
All episodes	12/22vs22/27 (.029)	20/35vs26/32 (.039)
First episodes	12/22vs20/24 (.054)	20/33vs22/25 (.036)

Generalized Tonic-Clonic Seizures

In reality, generalized tonic-clonic status is the clinical entity that demands immediate attention. It is also a clinical entity where a defined cutoff exists between a convulsive and a non-convulsive state. For these reasons, analyses of "response to first dose" merit special attention in generalized tonic-clonic status.

Study 411

The following results represent responders to first dose for the Ativan vs Valium groups and the four different study populations:

	ITT	Evaluable
All episodes	16/18vs.8/14 (.096)	16/18vs.7/13(.043)
First episode	15/17vs.8/14(.097)	15/17vs.7/13(.049)

No allowances are made in the above table for false positives or false negatives.

Study 415/416

The following results represent responders to first dose for the 1 vs 2 vs 4 mg groups and the four different study populations. The p values represent the Fishers Exact Test comparing the 1 and 4 mg groups.

Episodes	ITT	Evaluable
All	18/31,16/25,23/29 (.10)	18/27,16/23,22/24 (.042)
First	18/29,15/24,19/22 (.066)	18/25,15/22,19/20 (.059)

No allowances are made in the above table for false positives or false negatives.

Now, as mentioned previously, the sponsor's designation of patients as "non-evaluable" in Study 415/416 encompasses more than etiology of status, the cutoff used in Study 411. If only etiology is used to define the evaluable pt population in Study 415/416, the following results emerge:

	Evaluable
All episodes	18/29,16/25,23/27 **(.072)**
First episodes	18/27,15/24,19/22 **(.182)**

This analysis excludes only the following pts:

41510-015	1mg	Pseudoseizures
41604-001	1mg	Alcohol withdrawal syndrome (partial sz)
41605-003	1mg	Pseudoseizures
41605-004	4mg	Pseudoseizures
41603-007	4mg	Pseudoseizures

The sponsor may want to repeat the above analyses excluding all patients who received any pre-study medications to treat status (regardless of time window). This issue is not raised at all in the current 411 study report and is treated piecemeal in the 415/416 study report depending on whether the pre-study medication was given "within 10 minutes of the study medication."

Study DMT

A. Study Design

This was an open-label, randomized, active-control study comparing Ativan and phenytoin in the treatment of status. This single-center, academic investigation was not specifically designed to support a marketing application; Wyeth did not sponsor or monitor the study.

The study was conducted between 1982 and 1987.

After status was confirmed, the pts were randomly assigned to receive an IV infusion of either Ativan 0.1 mg/kg or phenytoin 18 mg/kg. Pts were considered responders if no further seizure occurred between 15 and 75 minutes following the end of the first infusion. Pts who did not respond were crossed over to the other treatment. If status was not controlled by the alternate drug, pts were treated outside the trial.

While EEGs were to be monitored continually during the infusion and for at least 75 minutes thereafter, these data were not made available to Wyeth by the investigator.

B. Subject Disposition and Baseline Comparison

79 pts, ages 32-87 yrs, were enrolled. 6 pts were re-enrolled after a period of at least 2 months. At baseline, there were no significant differences between groups in demographic or prognostic variables.

Importantly, it is not clear in the demographics section what the sponsor means by "pretreatment medication." Does this mean chronic maintenance anticonvulsants or does this mean use of Valium for status just prior to study entry ? Pts having received pre-study Valium should probably be excluded from the analysis; i.e. an evaluable pt analysis might then become more appropriate than the ITT analyses presented by the sponsor. The description of "pretreatment medication" on p21 of the study report seems to indicate use of Valium just prior to study entry in up to a quarter of pts in both treatment groups. The numbers in the table on that page do not match up with numbers in the demographic table on p20 of the

study report.

C. Efficacy Evaluation

In the ITT, all episodes population there was a significantly greater response to Ativan 33/44 (75%) than to phenytoin 23/43 (53%); p=0.045. In the ITT, first episodes population there was a greater response to Ativan 27/38 (71%) than to phenytoin 23/41 (56%), but the difference was not statistically significant (p=0.243).

The median response time (nonresponders included) to Ativan was 39 minutes, while the median response time to phenytoin was > 75 minutes; statistically significant using the Wilcoxon test, but not the log rank test. Note that, for this analysis, pts who were not actively seizing at the time of the first infusion were excluded from the analysis. Thus, data are only included for 26 Ativan pts and 33 phenytoin pts.

D. Conclusions

For the ITT, all episodes population, a statistically significant difference in favor of Ativan over phenytoin was found. However, the large proportion of pts in both treatment groups who were treated with Valium prior to study entry obscures the interpretation of these results greatly. This is a situation where an evaluable pt population, excluding pts pretreated with anti-status medications prior to entry, would seem more appropriate for analysis purposes.

Likewise, while the median response time shows a statistically significant difference in favor of Ativan over phenytoin (at least with the Wilcoxon test), the analysis includes only pts actively seizing during drug administration. Once again, the problems of case definition and distinct outcome assessments in studies of status epilepticus become evident in deciding who should be included in "time to response" analyses and how to define the "end" of status.

Study 100

Investigators

Homan
Dallas, Texas N = 19 + 12 = 31

Leppik
St. Paul, MN N = 51 + 5 = 56

McCutchen
San Diego, CA N = 2

Ramsay
Miami, FL N = 9 + 3 = 12

* Note that the supplemental NDA dated August 28, 1981 had a cutoff date of May 8, 1981 for data from each site. Additional data from 12, 5, and 3 pts, respectively, has been included in the current amendment. Dr. McCutcheon enrolled only 2 pts so her site was combined with Dr. Ramsay's site for the analysis because Dr. Ramsay enrolled fewer pts than the other two investigators.

A, Study Design

The supplement previously reviewed included the results of the Leppik, Ramsay, and Homan/Walker studies, both individually and pooled. Dr. Temple's July 21, 1986 not approvable letter stated, "Our review of the original IND submissions did not yield any evidence of your intent to pool the study results. Therefore, we feel that a retrospective decision to pool the study results is inappropriate, and the studies have been considered as separate trials." The Ramsay and Homan/Walker studies were felt to be too small to allow a conclusion that the demonstration of no difference between treatment groups is evidence that Ativan is effective in this setting. "The study by Dr. Leppik may be considered to be an adequate and well controlled study, provided that additional data are submitted. Specifically, since this was a study which failed to demonstrate a difference between response rates seen with Ativan and diazepam, the

interpretation that the study demonstrates the efficacy of Ativan is dependent upon the assumption that diazepam is effective in this setting." The sponsor was told to provide evidence that diazepam is an effective agent in status. Meanwhile, Dr. Nevius from our Biometrics Department reviewed the power of the three studies, taken as a whole, to show a difference; he commented (May, 1986 memo) that "even if a rationale exists for combining the 3 studies in this submission, the total of 80 pts would yield only a power of .61 for differences such as 82% compared to 69% but .95 for larger differences such as 70% compared to 30%."

The current submission presents pooled data for the three previously presented studies with the addition of data from an additional site and the addition of data from the same sites that was collected prior to 1981, but not included in previous submissions because of the cutoff date for data.

In addition, efficacy analyses which paralleled those of studies 411 and 415/416 were carried out in the current submission; in the original supplement, the outcome criterion was cessation of seizure activity, judged clinically or by EEG, without consideration of time to response or duration of response. The newer criterion calls for cessation of seizure activity within 10 minutes after dosing and lasting for 30 minutes.

The study design was similar for all 4 sites: double-blind, parallel, randomized, active-control studies to compare the efficacy of Ativan IV versus Valium IV. Pts initially received either Ativan 4 mg or Valium 10 mg. If seizures continued or recurred after a 10-15 minute period, a second dose could be administered. If the second dose did not control the status within 10 minutes, other measures could be instituted. If status was controlled, phenytoin loading could begin after the passage of one hour.

Inclusion/exclusion criteria were essentially the same as in previously described studies.

No prospectively declared outcome assessment existed in the protocol; nor did a prospectively declared analysis plan exist.

B. Subject Disposition and Baseline Comparison

101 pts were enrolled in all studies combined. Records on 1 pt were all lost. Of the 100 pts remaining, 50 received Valium and 50 received Ativan. 2/100 were missing efficacy data. 3/100 were considered nonevaluable. 95 pts were considered evaluable for efficacy: of these, 49 received Ativan and 46 received Valium. 96 seizure episodes were considered evaluable for efficacy: of these, 50 were treated with Ativan and 46 were treated with Valium.

As in other studies, 4 patient populations were considered:

1. ITT, first episodes
2. ITT, all episodes
3. Evaluable, first episodes
4. Evaluable, all episodes

2 pts enrolled more than once; one enrolled twice and one enrolled three times.

Data from 3 pts were excluded from the efficacy evaluation (evaluable). Pt 11-023 (Valium) may not have had status. Pt 11-125 (Valium) had hysterical seizures. Pt 11-144 (145 and 146 on subsequent enrollments) was receiving lidocaine.

This number excluded appears to be a lower number than that in previous submissions and reviews. Six additional pts could have been excluded, but were included in the current submission. 3 pts were considered not to be in status; 2 pts received Valium before study entry; and 1 pt had an infiltrated IV line.

C. Efficacy Evaluation

In the current amendment, the sponsor presents 4 different analyses for each of the 4 identified pt populations:

1. response to 1st dose using the "stop criterion"
2. response to 1st dose using the "10-30 criterion"
3. response to 1st or 2nd dose using the "stop criterion"
4. response to 1st or 2nd dose using the "10-30 criterion"

The "stop criterion" is defined by the sponsor as cessation of seizure

activity after dosing without consideration to how long it took for the seizures to stop or how long the seizure control lasted." The sponsor also presents another set of outcome assessments: "response" vs "response, not requiring next dose of medication." A few pts judged to have responded to the first dose also received a second dose. Thus, one analysis included all pts originally assessed by the investigator to have responded to the first dose; the second analysis excluded those pts who received a second dose.

For the ITT, first episodes population, the following response rates were obtained using the 10-30 criterion:

Response	Ativan	Valium	Difference	p Value
To 1st Dose	34/49 (69%)	28/48 (58%)	11%	0.277
Overall	35/49 (71%)	31/48 (65%)	7%	0.507

Since this pooled study was the subject of previous FDA review, I reference Dr. Rouzer's clinical review dated December 12, 1983. On p6 of that review: "Seizure activity was terminated by a single injection of lorazepam in 29 (78%) of 37 episodes, as compared with 19 (58%) of 33 terminating after diazepam administration (not statistically significant). A second dose of lorazepam was given to eight persons; seizures ceased in four. For diazepam, a second dose was given to 8 of the 14 persons not responding initially; seizures ceased in six." The curious point raised by these numbers is that in the Valium group, 6 pts who did not respond to the initial dose were **not** given a second dose. This raises two questions: 1) why weren't these pts given a second dose ? and 2) if they weren't given a second dose, why weren't they considered responders to the first dose ? (**In fact,** the published article on this study states that 13/14 pts in the Valium group received a 2nd dose; ? source of discrepancy betw. published report and Dr. Rouzer's review)

If these 6 pts were in fact responders, then 25/33 (76%) Valium treated pts responded after a single dose, a proportion essentially identical to Ativan as opposed to a difference of 20% More importantly, though, are the questions about investigator bias raised by this deviation from the protocol.

Safety

Volume 13 of this submission includes the sponsor's Integrated Summary of Safety. Note that Ativan Injection is already approved as a preanesthetic at doses up to 4mg IV. Sponsor's Tables A.3 and B.3 in the Appendices outline the demographics and safety profile of an Ativan-treated cohort in the following double-blind, controlled studies: 411, 415/416, and 100. In this group of studies, 215 episodes of status were treated with Ativan and 80 episodes of status were treated with diazepam. The Ativan treated episodes could have included doses from 1mg given only once (from 415/416, low-dose group) to 4mg given 2 or 3 times at 10 minute intervals. 77% of this Ativan cohort had either generalized tonic-clonic status or simple partial status. Adverse events were most prominent for the 3 body systems: cardiovascular, nervous, and respiratory. The events of concern are somnolence, hypoventilation, and hypotension. In this comparative analysis, only hypotension was more prevalent in the Ativan group (2% vs 0%).

Safety data from a total of 7 studies is presented, accounting for 488 patients and 521 episodes of status (patients could reenroll for different episodes of status). 360 episodes of status were treated with Ativan alone; 108 episodes of status were treated with diazepam alone; 25 episodes were treated with phenytoin alone. 28 episodes were treated with the sequence of Ativan/phenytoin or phenytoin/Ativan. Again the safety concerns of interest were hypotension, hypoventilation, and somnolence.

The sponsor has presented some dose-response data, but it appears that patients were grouped by the total dose of Ativan received without reference to the highest single dose given as a bolus i.e. 1mg vs 2mg vs 4mg. Table 5.2 represents the sponsor's analysis.

There was only 1 premature withdrawal from the studies: a patient with a respiratory arrest 10 minutes after a 4mg dose of Ativan.

The incidence of death was 7.5% (27) of the 360 episodes of status treated with Ativan alone. 3% (3) of the 108 episodes treated with diazepam alone resulted in death. 25% (7) of the 28 episodes treated with phenytoin alone resulted in death. None of these deaths were judged by the investigator to be drug-related. Appendix C includes narratives for

patients with serious AEs or death; review of these narratives did not add to the known profile for Ativan.

Section 7.1 outlines the sponsor's analysis of safety by age, sex, and race. The sponsor concludes that sex and race do not affect safety, but that age over 65 may be associated with more CNS events and more respiratory depression. The number of patients enrolled over age 65 was small.

Section 7.2 outlines data in children. Dr. Rouzer has previously reviewed one open, uncontrolled efficacy study in a pediatric population. Here, publications from non-Wyeth studies are also reviewed. "However, paradoxical excitation characterized by tremors, agitation, euphoria, and logorrhea and brief episodes of visual hallucinations were observed in 10% to 30% of the children under 8 years of age. Both children and adults with atypical petit mal SE developed brief tonic-clonic seizures shortly after Ativan Injection was given."

Drug overdose information is reviewed by the sponsor. The sponsor states, "Treatment of overdosage is mainly supportive until the drug is eliminated from the body." The sponsor may wish to incorportate some information about the use of flumazenil in this section, even if it is contraindicated in the setting of status.

Section 8.0 addresses some of the properties of propylene glycol. The data to support the statements made here has not been reviewed to my knowledge; to attribute all of the adverse events seen with Ativan to propylene glycol is probably incorrect.

Conclusions:

A. Study Design

The problems inherent in studies of status epilepticus are well known and have been discussed in previous reviews of this Supplement. I would like to stress several problematic areas:

1. Inclusion/Exclusion Criteria: Vague operational definitions exist in these protocols for simple partial, complex partial, and absence status. In particular, no criteria for length of confusional state or number of focal seizures/unit time exists.

Additionally, the exclusion of patients who have received "adequate therapy" for the given episode of status is open to interpretation. One could argue that if the patient was still in status on entry, any earlier therapy was not "adequate." The sponsor used this leeway in creating an evaluable patient population in Study 415/416, excluding only patients who received valium or phenytoin "within 10 minutes of study entry."

2. Outcome Variable "Response to First Dose": One definition of response implied that the episode of status ended at the conclusion of a given seizure after which the patient regained consciousness. There are several problems with this definition. First, for the confusional states of partial complex status and absence status, I do not believe a sharp demarcation exists between cessation of seizures and beginning of the post-ictal period. Given that investigators had to make a decision whether or not to give a second dose of medication at 10 minutes, I believe the outcome, "response to first dose," will be obscured by individual investigators' biases regarding the administration of the second dose in this situation.

Second, some patients who entered the study had underlying disease processes that would prevent return to full consciousness. These would include degenerative CNS disorders and brain tumors.

Third, in the study reports, the sponsor expands the definition of response to the so-called 10-30 rule, response by 10 minutes without relapse within 30 minutes. This rule is legitimate only if all patients are treated equally for the full 30 minutes with regard to initiation of maintenance therapy, etc. The data to support this equity is not presented, while the

protocol clearly left it to the discretion of the investigator whether or not to begin other treatment within that 30 minute window. In particular, if a patient responded to first dose, but relapsed at 25 minutes in the absence of maintenance medication, should that patient be treated differently than a patient who responded to first dose but did not relapse in the face of a phenytoin infusion.

3. Outcome Variables Other Than "Response to First Dose": Other variables include response to first and second doses, time to response, etc. I believe all of these other outcomes are flawed and that only "response to first dose" can be interpreted. After review of CRFs, it is clear that investigators frequently used their own discretion about treatment, once it was clear the patient had not responded to the first dose. For instance, if a patient had been in status for an hour or more and did not respond to the first dose, the investigator might have paralyzed the patient and begun high dose barbiturates. The time to response analysis would be flawed by missing data or, especially for absence status and partial complex status, problems in defining the "end" of status.

B. Sponsor's Analyses

As mentioned above, the sponsor has used some leeway in defining an evaluable patient population for Study 411 and Study 415/416. In Study 411, no mention is made of pre-study medication for the episode of status. In Study 415/416, only some of the patients who received pre-study medication were excluded from the evaluable patient analysis. In both studies, some patients are excluded because of pseudoseizures, alcohol withdrawal, or hypoglycemia. The appropriateness of excluding these patients and including others would require review of all CRFs and all lab data. Because of all these issues, I believe an ITT analysis is really the only valid analysis at this time.

Looking at ITT analyses of response to first dose for all seizure types, whether it be for first episodes only or all episodes, a level of significance of .04-.06 is achieved in Study 411, but not Study 415/416.

C. Analysis of Generalized Status and Simple Partial Status

The ITT analysis that excludes partial complex and absence seizures is

clearly positive for both studies, whether for all episodes or first episodes only.

The ITT analysis that includes only generalized tonic-clonic status is not positive but demonstrates a strong trend in favor of Ativan.

Recommendations:

The prospectively designated analysis from Study 415/416 fails to corroborate the evidence provided by Study 411. Thus, the usual level of evidence to support marketing approval is not provided for Ativan in status epilepticus.

However, I believe a fairly strong rationale exists to exclude patients with partial complex seizures and absence seizures from these analyses. The arguments to support this approach are outlined in the review. If these patients are excluded, the analysis of response to first dose is positive in both Study 411 and Study 415/416. The analysis of response to first dose including only generalized tonic-clonic seizures shows a trend in favor of Ativan, but the numbers are too small to show statistical significance.

Ideally, this information would be used to plan a prospective study of Ativan in patients with generalized tonic-clonic status or simple partial status, or, alternatively, in tonic-clonic status alone. However, given the problems in implementing studies in status and given the general acceptance of Ativan in the treatment of status, it seems appropriate to accept the evidence provided and approve Ativan for the treatment of generalized tonic-clonic status or simple partial status.

John Feeney, M.D.
Medical Reviewer

cc:
HFD-120
NDA 18-140
HFD-120/Leber/Katz/Feeney/Sahlroot/David

8/3/94

Review and Evaluation of Clinical Data
NDA 18-140, Amendment to Supplement SE1-003

Reviewer:	John Feeney, M.D.
Date:	June 14, 1996
Sponsor:	Wyeth-Ayerst
Drug:	Ativan (lorazepam) Injection
Proposed Indication:	Status Epilepticus
Material Submitted:	Response to FDA Request
Correspondence Date:	June 5, 1996

Introduction: A telecon between Wyeth-Ayerst and our division was held on April 8, 1996. In that telecon, several questions relevant to Studies 411 and 415/416 were posed to the sponsor. On April 17, the sponsor faxed a list of the pertinent questions, as they understood them, to our division. On April 30, Paul David from our division notified the sponsor that their list of questions was indeed correct.

Current Submission:

In the study reports, the sponsor defined a responder as a patient who responded within 10 minutes **and did not relapse for 30 minutes.** However, the 411 protocol defined responders only as patients who responded within 10-15 minutes. Therefore, we asked the sponsor to perform an analysis according to the protocol definition in Study 411. They have not done this.

We asked the sponsor where, on the Case Report Form, the information on relapse within 30 minutes was placed. The sponsor shows on the last page of their submission the CRF page where this information was located. Basically, investigators were to note "Subsequent Seizure Activity and Treatment." What the sponsor has not done is to provide the numbers of patients (in both studies) who were reclassified based on seizure relapse within 30 minutes.

Pertinent to the last point, maintenance therapy was optional for all patients. Given that relapse within 30 minutes, and therefore the sponsor's definition of responder, could be affected by use of maintenance therapy, the sponsor was asked to provide a list of maintenance therapy. The list shows an equal distribution between treatment groups in 411; no

high-dose patients received maintenance therapy in 415/416, favoring the 1 mg and 2 mg groups. **However**, the listing provided only lists maintenance therapy given **after seizures stopped.** My understanding is that maintenance therapy could begin even before seizures "stopped," i.e. at 15 minutes real time. If my understanding is correct, this issue needs to be re-addressed.

The sponsor provided a list of inter-infusion times for Study 411. The interesting point from the sponsor's Table 1 is that almost all of the Ativan responders received 2 infusions of the first dose, but only half the Valium responders received 2 infusions of the first dose. Knowing this, it now seems important to examine the same information for **non-responders.** If a greater proportion of non-responder-Valium patients than non-responder-Ativan patients received only one infusion of the first dose, that fact may explain the greater number of Valium non-responders.

Conclusions: The issues raised in the April 8, 1996 telecon have still not been fully addressed. A telecon with the sponsor will be held to discuss the above points.

John Feeney, M.D.
Medical Reviewer

cc:
HFD-120
HFD-120/Leber/Katz/Feeney/David

REVIEW AND EVALUATION OF CLINICAL DATA MAY 10 1988

NDA 18-140/S-003 (Amendment)

Sponsor:	Wyeth Laboratories Inc.
Drug:	Activan (lorazepam) Injection
Supplemental Indication:	Status Epilepticus
Date of Amendment:	February 19, 1987
Date of Review:	September 23, 1987

1.0 Background

The firm responds to the nonapproval letter of July 21, 1986 with additional information it believes sufficient to meet the regulatory requirement for "substantial evidence" of effectiveness of Activan in Status Epilepticus (SE).

1. Modification of the proposed labeling from "initial therapy" to "adjunct in the treatment of status epilepticus" consistent with that of Valium, the control employed in the studies.

2. An argument in support of the use of historical control in studies of status epilepticus.

3. The identification of the Walker study #82W as meeting the requirements for an adequate and well-controlled study, based upon the above reason. It identifies the two pivotal studies as the study by Dr. Leppik (#01011) and this study by Dr. Walker distinct from the Homan/Walker (#01021) cited in the nonapproval letter. That study (#01021) was reviewed previously and specifically commented upon in the nonapproval letter. It was considered too small to permit a conclusion that the demonstration of no difference between the active control is evidence of effectiveness. No further comment is needed at this time.

The Walker study #82W now identified by the firm as pivotal was not examined in the original NDA review. It employs a historical control which the firm defends based upon the precedence established by the Valium approval for this indication. The study will be evaluated below.

4. A (New) Open Study of Intravenous Lorazepam for the Treatment of Status Epilepticus in Children and Adolescents sponsored by Wyeth and completed in 1985 is reported.

5. The submission of several additional published studies of lorazepam in status epilepticus using historical control, namely Levy and Krall, Lacey et al., Deshmukh et al.

These responses are considered in turn.

2.0 Amended Labeling/Indication

In a letter of October 22, 1985, the firm submitted a change in the proposed labeling to emphasize Activan's effectiveness as an adjunct in the treatment of status epilepticus and severe recurrent seizures. The amended labeling reads:

> "Injectable Activan (lorazepam is a useful adjunct in the treatment of status epilepticus and severe recurrent convulsive seizures)."

This change was made in conformity with the approved labeling of injectable Valium, the control used in four of the active-controlled trials. Furthermore, as the firm is now requesting the same labeling as used for Valium, it believes that no additional data need be submitted regarding this particular study (Leppik). Specifically, the firm states its belief that the change in labeling negates the need to submit additional data proving that the control agent diazepam is an effective agent in the treatment of SE.

Comment:
Certainly labeling modification is a strategy we have employed on previous occasion to effect a new indication (e.g., Tegretol for primary therapy). However, we only use the technique once we have made a decision on the evidence.

3.0 Use of Historical Control in Studies of Status Epilepticus

The sponsor makes this argument by documenting that historical control was considered adequate in efficacy studies of Valium (diazepam) for the treament of convulsive seizure disorders in children. FDA Medical Officer's Review of NDA 16-087 (Valium) is excerpted:

...The study is regarded as having a historic control. The latter would be an indefinite series of patients who would not have been treated or a series receiving intravenous barbiturates, paraldehyde, or diphenylhydantoin. Considering the nature of the condition being treated, I believe such a control to be appropriate for the following reasons: The purpose of blinding in clinical studies is an attempt to eliminate bias on the part of the patient or both the patient and individual assessing clinical response. Major convulsive seizures with loss of consciousness cannot be suggested away. Blinding of the observer is not necessary in this case because the effect is objective and the kind of judgement that needs to be made is not likely to be greatly influenced by level of expectation...

Comment:
I cannot determine whether this was excerpted in toto. In any event, the argument concerns the issue of blinding rather than control. This cannot be considered an adequate argument in support of historical control. Moreover, several recent studies (Shorvon, Callaghan) have reported new information regarding the prognosis for seizures and epilepsy which is modifying some of the views and treatment of epilepsy, although none have specifically examined status epilepticus.

4.0 Identification of the Two Pivotal Studies

4.1 Dr. Leppik #01011

In the nonapproval letter, we identified the active-control study by Dr. Leppik (#01011) as a candidate for an adequate and well-controlled study, provided that additional evidence that diazepam is an effective agent in the treatment of SE in a patient population comparable to the one studied be provided. As the study failed to demonstrate a difference between Activan and diazepam, the interpretation of evidence of efficacy is dependent upon the assumption that diazepam is effective in this setting.

The firm's response to this request is that the change in labeling to identity with that of Valium negates that need to submit data proving that diazepam is an effective agent in the treatment of SE, since the study demonstrates that Activan is at least equal to Valium in safety and effectiveness.

Comment:
It is standard for us to require of a positive control study a measure of the study's sensitivity to detect a difference between the two treatments, either by an assessment of the active control's performance in other studies of similar design or by providing either confidence limits or a measure of the power of the study. Therefore the firm's response is inadequate.

4.2 Dr Walker (#82W) Protocol 345B-201: Determination of the Safety, Dose Range and Efficacy of Intravenous Lorazepam in the Treatment of SE.

This was an open study to determine the safety, dose range and effectiveness of intravenous lorazepam in the control of SE, defined as recurring generalized seizures (3 or more) occurring with a frequency of one or more every 10 minutes without recovery of normal consciousness. Twenty-five patients aged 5 to 81 were enrolled, two more than once for a total of 28 episodes. Excluded were patients with hypoglycemia, hypocalcemia, or presumed alcohol withdrawal seizures.

Patients were given 4mg lorazepam regardless of body weight intravenously over a 2 minute period. If the seizures were not terminated during a 15 minute observation period, an additional 4mg dose was administered. If seizures persisted for another 15 minutes, rescue medication either phenytoin or phenobarbital was administered. A second 5mg dose was required in 5 of the episodes.

The primary efficacy criterion was prompt cessation of seizures. Secondary measures included time of latency and duration of seizure control. An investigator global rated the results as satisfactory/unsatisfactory. EEG monitoring was to be attempted. Blood samples for determination of plasma concentrations of lorazepam were collected at 15, 30, 45, and 120 minutes after drug administration. Neurological and medical exam was performed prior to drug administration. Abnormal findings were recorded on admission, following admission, 24 and 48 hours later, and at discharge. Safety precautions included intubation and intravenous line. Vital signs and neurological signs were recorded prior to and 5 minutes following the termination of each injection. Lab tests including CBC, chemistries, and U/A were performed.

26 patients entered and received at least one dose of lorazepam. Patient #010 was excluded due to loss of medical record. Demographics included mean age 44 (range 5-81), sex 18 M, 7 F. Ten patients did not have a specified history of previous seizure disorder, 14 did, 1 patient's history was unknown. Twenty-two were being treated with a variety of anticonvulsants before the study. Patient #011 was enrolled three times, each time receiving 4mg. Approximately 43 hours after initial enrollment, she enrolled a second time, and approximately 19 hours later she enrolled a third time. Patient #021 reenrolled 60 hours after initial enrollment.

RESULTS OF TREATMENT BY TYPE OF SEIZURE

Type	# Episodes	# Controlled By 4 mg	# Controlled By 8 mg	# Not Controlled By 4 mg	# Not Controlled By 8 mg
Gen'd	12	10(83%)	0	0	2(17%)
Gen'd , Focal Onset	3	1(33%)	2(67%)	0	0
Focal	9	7(78%)	1(11%)	1(11%)	0
Spike-Wave Stupor	3	2(67%)	0	1(33%)	0
Unspecified	1	1(100%)	0	0	0
	28	21(75%)	3(11%)	2(7%)	2(7%)

Time of latency was reported for 17/24 successfully treated patients.

TIME OF LATENCY*(N=17)

Immediate	15 min	15-30 min	30-60 min	1-4 h	4 h
4(24%)	9(53%)	1(6%)	1(6%)	1(6%)	1(6%)

*Time from start of injection to end of seizure activity

Here I would argue that patients responding after 60 minutes cannot be considered successfully treated.

Duration of seizure control was reported for 16/24 "successes":

DURATION OF SEIZURE CONTROL* (N=16)

4 h	4-8 h	8-12 h	12-24 h	24 h
2(12%)	2(12%)	3(18%)	0	9(56%)

* Measured from time seizure ended to either seizure recurrence, additional anticonvulsants, or patient discharge.

Lorazepam was effective in terminating a variety of seizure types in 24 of the 28 episodes (86%). A single 4mg injection was sufficient to produce this result in 21 episodes and a second 4mg injection stopped an additional 3 episodes. 76% of the episodes that were treated successfully were terminated in less than 15 minutes. The duration of seizure control was at least 24 hours in 56% of the episodes. The physician rated treatment as satisfactory in 18 of the 21 episodes (86%).

Five adverse effects were reported in 3 of the 28 episodes and included hypotension, respiratory arrest, hallucinations, and ataxia. The firm identifies this study as adequate and well-controlled. The firm admits that it was open but can be considered historically controlled.

Comment:
The firm asserts that this study satisfies the criteria for an adequate and well-controlled by the use of historical control. They have provided information documenting that historical control was considered and accepted in the FDA evaluation of Valium for the treatment of convulsive seizure disorders in children (Medical Officer's Review of May 1, 1975), and the rationale as to why historical control is appropriate for studies involving the treatment of status epilepticus. The argument was based upon the viewing of SE seizures as "clearly objective," thus obviating the need for blinding to guard against bias.

4.0 Additional Published Studies Asserted to be Adequate and Well-Controlled.

4.1 Levy and Krall. Treatment of Status Epilepticus with Lorazepam. Arch Neurol 41, 1984 605-611.

This was a retrospective review of 21 episodes of SE in 18 patients who were treated over a 15 month period ending in October 1982. Twenty-three episodes of SE in 20 patients were treated with lorazepam during this period. Two episodes were excluded from the study due to unavailability of charts for review. SE was defined as a series of two or more seizures without full recovery of consciousness between seizures or continuous clinical and/or electrical seizures lasting at least 30 minutes with or without impairment of consciousness. Patients were stratified into either generalized or partial SE based upon clinical characteristics. Those patients with partial SE were further subdivided according to their degree of responsiveness, altered or intact. There were no cases of absence SE.

Lorazepam was administered intravenously in doses of 1 to 4mg. The maximum total dose was 9mg, mean total dose 4 mg per patient. A minimum of five minutes was present between injections. Phenytoin or phenobarbital or both were given to all patients as maintenance anticonvulsants in appropriate loading doses over one to eight hours following lorazepam.

Lorazepam abolished generalized tonic-clonic and generalized clonic seizures within 15 minutes in 7/7 patients, usually in less than 10 minutes. 2/11 episodes of partial SE with altered responsiveness were resolved completely within 10 minutes, and the remaining 9 episodes were resolved either partially, transiently, or not at all. Two patients had partial SE with intact responsiveness, and both responded within 10 minutes.

Side effects included respiratory depression in five instances (2 requiring intubation) and was associated with transient loss of brainstem reflexes, hypotension, and decorticate posturing in three cases. In an additional 4 patients, marked lethargy developed.

Comment:
Due to its retrospective nature and lack of control, this study cannot be considered adequate and well-controlled, although the firm considers this a "dose-controlled study." As this was a retropective chart review, lacking prospective entry criteria or assessments, this data is of no regulatory value and may be dismissed on face.

4.2 Protocol Number: 345B-312 Open Study of Intravenous Lorazepam for the Treatment of Status Epilepticus in Children and Adolescents. (Lacey et al. Lorazepam Therapy of Status Epilepticus in Children and Adolescents. J Ped 108:771-774).

In this Wyeth sponsored study, four investigators enrolled 31 children or adolescents experiencing status epilepticus to treatment with intravenous lorazepam.

Design

The purpose of the study was to evaluate the safety and efficacy of intravenous lorazepam when given to children and adolescents who were experiencing status epilepticus.

Children or adolescents aged 2 to 18 years who were experiencing the following types of status were eligible:

1. Generalized convulsive (tonic-clonic, grand mal) status epilepticus, consisting of three or more generalized seizures within one hour or two or more seizures in rapid succession without intervening recovery of consciousness.

2. Generalized absence (petit mal) status consisting of a confusional state associated with generalized 3-Hz spike and wave activity on EEG.

3. Partial elementary (focal motor) status.

4. Partial complex (psychomotor) status epilepticus consisting of confusional states with EEG abnormalities.

A medical history was obtained and a physical examination performed before lorazepam was administered. Vital signs (respiratory rate and description of rhythm, pulse rate and rhythm, blood pressure, temperature) and neurologic signs (level of consciousness, pupillary light response, response to painful stimuli, DTR's, and plantar response) were recorded before the administration of lorazepam and 15 minutes after each injection.

CBC and urine specimens were obtained. Additional laboratory tests were done as required for treatment.

Exclusion Criteria

Patients were excluded from the study if they had a history of sensitivity to benzodiazepines or other constituents of the intravenous formulation, if they currently were or recently had been taking monoamine oxidase inhibitors, or if their status was due to an acute reversible metabolic disorder such as hypoglycemia. Also excluded were terminally ill patients with a life expectancy of less than two days, persons with hypotension requiring continuous pressor treatment, or cardiac arrythmias requiring continuous management, or females of childbearing potential.

Dose

Before lorazepam was administered, standard precautions used in treating status epilepticus were taken: monitoring of vital signs, establishment of an i.v., and airway, endotracheal tube and laryngoscope were available.

Lorazepam injectable (Lot #0581-01) was supplied in individual patient packets containing 2 mg/ml lorazepam in a 10 ml multidose vial. Subjects were administered a 0.05 mg/kg injection of lorazepam at a rate of 1 ml/min. If seizures continued or recurred within 15 minutes after the injection, a second 0.05 mg/kg dose could be administered; after an additional 15 min, a third 0.05 mg/kg dose could be given if necessary.

If the third injection was not successful, other medications and procedures could be used at the discretion of the investigator. Otherwise, the observation period was 6 hours.

Efficacy Variables

Efficacy assessments included whether the seizure stopped, latency (time from end of injection to end of seizure activity), and the duration of seizure control. In those cases where patients received a loading dose of another anticonvulsant after the last lorazepam injection, duration of seizure control was recorded as time from termination of the seizure to time of administration of the other anticonvulsant. The clinician provided a global rating of satisfactory/unsatisfactory. For patients suffering focal motor, partial elementary, or partial complex status epilepticus, EEG monitoring was obtained before and during the drug infusion whenever possible.

Safety Evaluation

Adverse effects were recorded on the case report forms and rated according to severity (mild, moderate, severe) and causal attribution (related, probably, possibly, or not related to therapy).

The injection site was observed routinely after each injection. More frequent observations were made if needed.

Statistical Methods

Summary tabulations were made for demographic, dose, and efficacy data; no statistical analyses were performed.

This multicenter open trial was conducted at the following four sites:

	Number of Patients
Herbert E. Gilmore (331204) New England Medical Center, Inc. Boston, MA 02111	1
Samuel J. Horowitz, M.D. (331202) Chief, Division of Child Neurology Rainbow Babies & Children's Hospital Cleveland, OH	4
Daniel Lacey, M.D., Ph.D. (#31201) Department of Neurology Children's Hospital of Buffalo Buffalo, NY 14222	19
William D. Singer, M.D. (#31203) Associate Professor of Pediatrics (Neurology) New England Medical Center Boston, MA	7

RESULTS

Patient Demographics

Thirty-one (31) patients were enrolled and included in the efficacy evaluation. Two patients (#31203-001 and #31203-003) were enrolled in the study twice. Dose and efficacy data on these second episodes are not included in the following summary tables but are included in the patient listings.

Characteristic	Number of Patients (N=31)
Age	
2 - 4 y	2 (6%)
5 - 6 y	12 (39%)
7 -11 y	10 (32%)
12-18 y	7 (23%)
Weight(kg)	
Mean	28
Range	
Sex	
Male	20 (65%)
Female	11 (35%)
Seizure Type	
Partial Elementary	7 (23%)
Partial Complex	3 (10%)
Generalized Absence	8 (36%)
Generalized Convulsive	12 (39%)
Myoclonic	1 (3%)
History of Seizures	
Yes	28 (90%)
No	3 (10%)

Dose

Although the protocol provided for up to three 0.05 mg/kg i.v. doses of lorazepam at 15 min intervals, in fact, 9 subjects received doses of 0.04, 0.07, 0.10. or 0.11 mg/kg per injection. Twenty patients received one injection, seven received two, and four received three injections, as summarized in the following table:

	Number of Injections		
Dose	1	2	3
mg/kg	(n=20)	(n=7)	(n=4)
0.04	1	0	1
0.05	16	4	2
0.07	1	1	0
0.10	0	2	1
0.11	2	0	0

Mean cumulative dose was 2.0 mg.

Efficacy

Results of treatment by seizure type are given in the attached Table. Seizure activity stopped in 25(81%) of patients: 6/7 partial 2/3 partial complex, 6/8 . lonic status.

Safety
No drug-related adverse experiences were reported.
Respiratory arrest occurred in a 5-year old girl (#31202-003) who received one injection of lorazepam, diazepam 15 minutes later, and phenytoin 15 minutes after that. Respiratory arrest occurred 15 minutes later, necessitating intubation and ventilation. The investigator regarded the event not related to treatment with lorazepam.

Comment:
Lorazepam was certainly contributory to respiratory depression in this case.

There were no reports of reactions at the injection site. No drug-related effects on vital signs and neurologic assessments were reported by the investigator, rather they were considered consistent with the patient's disease at the time of drug administration. No drug-related trends were reported for 1.

Comment
This was an open study, although the firm asserts that it is "historically controlled", but have failed to provide any further supportive evidence of the response rates of status epilepticus to various drug therapies. Thus, this study cannot be considered adequate.

4.3 Deshmukh, Wittert, et al. Lorazepam in the Treatment of Refractory Neonatal Seizures. American Journal of Diseases of Children. Vol 140, Oct 1986 1042-1044.

This was a pilot study of the safety and efficacy of lorazepam in seven neonatal patients gestational age 30-43 weeks suffering from status epilepticus secondary to perinatal asphyxia and hypoxic-ischemic encephalopathy unresponsive to conventional therapy. The age of onset of seizures ranged from less than 1 to 72 hours. All patients had clinically documented seizures of the multifocal clonic and subtle types. Infants were enrolled in the study if seizures persisted after loading doses of phenobarbital and phenytoin. Therapeutic levels of pb (20 to 30 mg/L) were documented in all seven infants; therapeutic levels of phenytoin (10 to 20 mg/L) were documented in five. In the other two infants, phenytoin levels were subtherapeutic when lorazepam was administered.

Infants received lorazepam 0.05 mg/kg per dose given intravenously over two to five minutes. In 3/7 infants, EEG was monitored before, during, and after injection. In all infants, EEG monitoring was performed within 24 hours of lorazepam administration. Lorazepam was considered to be effective on their basis of immediate cessation of clinical seizure activity and suppression of seizure activity on EEG where performed.

Comment
This may be a valuable study due to the EEG monitoring, although due to this specialized neonatal population characterized by different pharmacokinetics and seizure types, the results do not directly pertain to an adult claim.

5.0 Conclusion

This amendment fails to correct the deficiencies of the original application by providing unambiguous evidence of effectiveness for the new claim. It did not provide evidence of the efficacy of diazepam in a comparable population to support the active-controlled Leppik study, and none of the other studies identified as controlled in fact meet our definition of adequate and well-controlled. The supplement remains non-approvable.

Janeth Rouzer-Kammeyer, M.D.

cc/NDA 18-140/S-003
HFD-120
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DOC 0351n

REVIEW AND EVALUATION OF CLINICAL DATA
SUPPLEMENT FOR NEW INDICATION

NDA 18-140/S-003

Drug: Ativan Injection (Lorazepam)

Pharmacology: Benzodiazepine

Indication: Status epileptieus

Sponsor: Wyeth Laboratories, Inc.

Date of Submission: August 28, 1981

Date of Review: December 12, 1983

Introduction

Ativan (Lorazepam) Injection, a benzodiazepine with half-life of elimination of approximately twelve hours, was initially approved in 1980 with the indication as preanaesthetic in adult patients for anti-anxiety and sedative effects. The present supplement provides for the addition of status epilepticus as an indication for this product.

Lorazepam has been shown to possess potent anticonvulsant activity in animal studies. Parenteral lorazepam was more potent than diazepam in elevating the threshold of electroshock seizures. Lorazepam is five times more potent than diazepam in controlling metrazol-induced seizures in mice. In both the maximal electroshock and metrazol tests, lorazepam was more potent than phenobarbital and phenytoin as judged by the median effective dose (E.D.50).

Some clinical trials have indicated that intravenous lorazepam may be useful in the treatment of status epilepticus. Its pharmacokinetic profile suggest that it may have certain advantages over diazepam, a benzodiazepine which is widely used as first treatment for status, but limited by its short duration of anticonvulsant activity due to rapid redistribution of the drug within body stores. Pharmacokinetic studies have shown that lorazepam injection maintains effective clinical activity for considerably longer periods than diazepam. Clinically effective blood concentrations persist for several hours after injection, even though the elimination half-life of free lorazepam is relatively short averaging twelve hours. There are no active metabolites. More than 75% of lorazepam is excreted in the urine as its inactive metabolite, lorazepam glucuronide.

General considerations re: establishment of efficacy of products for the treatment of status epilepticus.

There are inherent features of status epilepticus which impose certain conditions and limitations upon the design and conduct of clinical trials to demonstrate the efficacy of drugs for its treatment.

Firstly, it is a symptom complex, not a diagnosis, which may occur in the presence of diseases of widely differing etiologies, including primary epilepsy, withdrawal of alcohol or drugs, acute central nervous system insults, such as cerebral infarction, meningitis, encephalitis, head trauma, cerebral anoxia, cerebral neoplasms and from metabolic disturbances such as hypoglycemia, hypernatremia, etc. Thus there may be considerable delay in the establishment of a diagnosis for the underlying etiology. This feature dictates that a certain number of patients entered into a prospective study of status epilepticus may be later disqualified due to entry criteria regarding patient diagnosis.

Secondly, status epilepticus is presently classified according to three clinical presentations (with four EEG equivalents), namely (1) convulsive status epilepticus, in which the patient does not recover to a normal alert state between repeated tonic-clonic attacks, (2) nonconvulsive status epilepticus, including absence status and complex partial status, in which the clinical presentation is a prolonged "twilight" state, or (3) continuous partial seizures, "epilepsia partialis continuans," in which consciousness is preserved. Of these clinical presentations, tonic-clonic status epilepticus is a neurologic emergency which should be stopped as soon as possible. It should not be allowed to last longer than 6 minutes if severe permanent brain damage or death is to be prevented. Recent mortality rates after tonic-clonic status have been reported 10 to 12 percent. Persistent memory loss and aphasia have been reported following complex partial status and absence status. Persistent motor weakness may be a permanent residue of epilepsia partialis continuans.

Because of the morbidity associated with status, and the fear attendant to even a single tonic-clonic seizure, it has often become medical practice to stop seizures as quickly as possible, usually with intravenous diazepam. Thus, there may be certain patients entered into a treatment protocol whose observed seizures were self-limiting and did not represent true status. Thus an operational definition of tonic-clonic status must be established to include provision for a time period of historical observation of seizure activity to avoid error of both over or under diagnosis.

The establishment of efficacy criteria is inseparable from a comparison with the drugs used currently in the management of status epilepticus, and will certainly include latency to termination of convulsions and duration of effect. Presently, optimum management of convulsive status epilepticus is achieved with a combination of diazepam and phenytoin. Intravenous diazepam administered at a rate 2 mg/min to a maximum of 20 mg stops convulsions within three minutes in 33% of patients with status and within five minutes in 80%, ten to twenty minutes after cessation of intravenous diazepam, seizures may recur due to rapid distribution of the drug to body stores. To prevent recurrence of seizures, intravenous phenytoin is administered no faster than 50 mg/min to a total of 18 mg/kg. Phenytoin stops seizures in 30% of patients after approximately 400 mg has been administered, that is, about 10 minutes after the start of its infusion. Maximal anticonvulsant effects appear only after the full dose of phenytoin has been administered.

The ideal drug to treat status epilepticus is one that acts rapidly, has a prolonged duration of seizure control and produces minimal side effects. No presently available drug fulfills these criteria; present management employs a combination of two drugs, one for its rapid action, the other for its prolonged duration of effect. Each has its spectrum of side effects

A final issue to be addressed in a clinical trial of drugs used in the treatment of status epilepticus is the use of concomitant anticonvulsants. In nascent status, at issue is whether the subject was entered directly into the study protocol without prior treatment. In my opinion, this condition should be a requirement. There is also a population of "epileptics" who may break through and present with status and have detectable levels of other anticonvulsants upon entry into the study. In my opinion, these patients who have demonstrable levels of other anticonvulsants should not be excluded from the efficacy analysis.

Open Clinical Studies: (Protocol 345B-201)

Intravenous Lorazepam in Status Epilepticus.

Investigators:

82W Jonathan E. Walker, M.D.
84W Michael Andriola, M.D.
88W Gregory Hamington, M.D.
89W Patrick A. Griffith, M.D.

These were open studies enrolling 25(82W), 6(84W), 6(88W) and 9(89W) patients per center in which status was defined variably as:

"recurring generalized seizures (3 or more) occurring with a frequency of one or more every ten minutes without recovery of normal consciousness,

a series of 2 or more seizures of variable duration, generalized or focal, without full consciousness between seizures, and

two or more seizures of a generalized or focal nature without recovery between seizure of normal level of consciousness."

Included in the efficacy analyses were patients with generalized tonic-clonic, focal motor, mixed focal and major motor, and non-convulsive status. A standardized treatment protocol was employed in which lorazepam 4 mg was administered intravenously over a 2-minute period. Following a 15-minute observation period, a second 4 mg dose of lorazepam was administered to those patients still convulsing. Rescue with intravenous phenytoin and phenobarbital occurred for those patients still seizing after an additional 15 minute observation period. Patients were monitored with vital signs, neurological exam, and lorazepam levels. Efficacy evaluation included termination of seizure activity, latency of action, and duration of control. Safety evaluation included the reporting of adverse effects along with the investigator's assessment of the severity and relationship to treatment.

Results

Efficacy: Lorazepam was effective in terminating a variety of seizure types in 74% of subjects (pooled data). The average latency time was less than ten minutes.

Safety: Adverse effects occurred and included hypotension, respiratory arrest, hallucinations, and ataxia. The severity was rated mild to moderate. No specific treatment other than supportive measures or sequellae of these adverse effects were reported.

It was concluded that lorazepam is safe and effective in the treatment of status epilepticus.

General Comments

These studies were flawed by poor documentation, particularly the absence of recorded latency times, when several patients with prolonged latency times (four hours, 2 hours, 50 minutes) were considered responders by the investigators. Many of the patients were receiving a variety of anticonvulsants currently and at various times prior to the administration of the study drug. Three of the studies were too small to be analyzed independently. The spectrum of side effects does not appear to differ from those associated with diazepam. When used for this indication, when pooled, the body of data provides supportive evidence of the efficacy of lorazepam in the initial treatment of status epilepticus.

Controlled Clinical Studies: Multicenter Study

Title: Double-blind Evaluation of Intravenous Lorazepam Versus Intravenous Diazepam in the Treatment of Status Epilepticus.

Investigators:

011 - I.E. Leppik, M.D., University of Minnesota-St. Paul Ramsey Medical Center, St. Paul, Minnesota

021 - R.W. Homan, M.D. and J.E. Walker, M.D., Verterans Administration Medical Center, Dallas, Texas

031 - R.E. Ramsay, M.D., Veterans Administration Hospital, Miami, Florida

Subject Selection and Study Design:

Adult patients with convulsive, absence, partial elementary, or partial complex status epilepticus were eligible for the study. Convulsive status was defined as three or more generalized tonic-clonic seizures in one hour or two or more in rapid succession without intervening recovery of consciousness. Generalized absence was defined as a confusional state of 15 minutes or more associated with 3/sec spike and wave pattern on EEG. Partial elementary and

partial complex status were left to the investigators to define. Exclusion criteria were presence of a terminal illness, cardiac arrythmic, hypotension, any acute metabolic disorder causing status epilepticus (e.g., hypoglycemia), a history of sensitivity to benzodiazepines, or childbearing potential. Prior treatment with anticonvulsants did not preclude entry except in study 01021.

Patients appearing to meet the study criteria were treated with the study agent as soon as the regulations regarding informed consent formulated by the institutional review boards had been fulfilled. A total of 78 patients were investigated at three centers (University of Minnesota, St. Paul, 50; University of Texas, Dallas, 19; University of Miami, 9).

The study drug was provided as 2 ml intravenuous solution of either 5 mg/ml diazepam or 2 mg/ml lorazepam in closed-injection (Tubex) syringes to assure blinding. After an IV infusion and emergency airway measures were initiated, 2 ml of the study drug (10 mg of diazepam or 4 mg of lorazepam) was injected over a period of 2 minutes. A second 2 ml dose of the same drug was administered at the discretion of the treating physician if seizures continued or recurred after 10 minutes. If this injection was unsuccessful, phenytoin at 18 mg/kg was given at 50 mg/min. If seizures still persisted, other drugs for the treatment of status including phenobarbital, paraldehyde, and general anaesthesia could be used at the discretion of the treating physician. Because of the known duration of action of diazepam of 20 to 30 minutes, most patients were given a loading dose of phenytoin even if seizures had not recurred 30 minutes after administration of study drug.

Safety Monitoring and Assessment Criteria

Data on seizure type, diagnosis, previous use of antiepileptic drugs, and seizure frequency before and after infusion of study drug were recorded at the time of the infusion and verified during the admission. Vital signs, level of consciousness, pupillary light response, and basic neurological examinations was recorded at 5 minute intervals for 15 minutes. EEG monitoring was to be performed prior to and during infusion for focal motor, partial elementary or partial complex status. Blood for complete blood counts, chemistry assessments, and benzodiazepine levels were collected during and after treatment.

Regarding outcome assessment, the protocol makes the general statement that differences in treatment effects will be evaluated regarding safety, discontinuations (sic) and efficacy. Efficacy responses will be analyzed with respect to changes from baseline within treatment groups and differences between treatment groups.

Results

Patient Selection: Eleven of the 81 episodes studied did not meet all the entry criteria for status epilepticus retrospectively. Four episodes were excluded from the efficacy evaluation because they were not clearly status epilepticus. In one episode, the patient had an invalid seizure type

(hysterical). In another episode, the drug infiltrated the IV site. Lidocaine was used prior to study drug administration in three episodes. Diazepam was given before the study drug in two episodes.

Of the 70 episodes studied, 33 were treated with diazepam and 37 with lorazepam. There were no significant differences between treatment groups with respect to age, sex, or type of seizure. Regarding classification, generalized seizures either primarily (33%) or secondarily (23%) generated and partial elementary (22%) comprised the majority of seizure type. There was a history of seizures in 70% of subjects.

Efficacy:

Efficacy analysis included termination of seizure activity and latency of action. The phenytoin loading procedure prevented the determination of the duration of action of lorazepam.

Seizure activity was terminated by a single injection of lorazepam in 29 (78%) of 37 episodes, as compared with 19 (58%) of 33 terminating after diazepam administration (not statistically significant). A second dose of lorazepam was given to eight persons; seizures ceased in four. For diazepam, a second dose was given to 8 of the 14 persons not responding initially; seizures ceased in six. Overall, one or two doses (10 or 20 mg) of diazepam terminated seizure activity in 25 (76%) of 33 episodes, and lorazepam (4 or 8 mg) was effective in 33 (89%) of 37 cases (not statistically significant).

Latency of action ranged from immediate effectiveness to ten minutes (median two minutes) for diazepam in all patients whose seizures were controlled. For lorazepam, the range was immediate to 15 minutes (median, three minutes), not statistically significant.

Adverse Effects

Adequate data to assess safety was available for all 78 patients enrolled in the study, including two patients enrolled more than once. Of the 81 episodes analyzed, 41 had been treated with diazepam and 40 with lorazepam. Adverse effects occurred on ten occasions (12%); these included 5 (12%) of 41 treatments with diazepam and 5 (13%) of 40 with lorazepam. The profile of side effects was similar for both drugs and included respiratory depression, respiratory arrest, hypotension, and sedation. Four of the five experiencing side effects with lorazepam had concurrent medical illness (diabetes, alcoholism, active gastroentestional bleeding, renal failure) whereas none of the patients who experienced side effects after diazepam administration had concurrent problems. All episodes resolved spontaneously after symptomatic treatment.

Conclusion

It is concluded that lorazepam is at least as safe and effective as diazepam in the initial treatment of status epilepticus. No clinically or

statistically significant differences between these drugs were found with regard to safety or efficacy, as determined by termination of seizure activity and latency of action.

Comments

This was a well designed study whose protocol provided for a well-defined classification of types of status epilepticus accepted for study. Efficacy criteria, although not explicitly set forth in the protocol, were clearly defined in the data analysis and could be derived from the recorded observations.

Examination of individual case reports from the three participating centers revealed that the study was well conducted. There was consistent application of entry criteria in the inclusion of subjects in the efficacy analysis.

This study provides evidence that lorazepam acts as quickly as diazepam in the termination of status epilepticus of various types. It was shown to be as safe as diazepam, but not safer with respect to incidence of respiratory depression and hypotension. In fact, one could argue that respiratory depression may occur so long after the intravenous administration of lorazepam that vigilance might have elapsed, and adverse consequences might ensue It did not provide evidence of efficacy in that group of patients who do not respond to diazepam and phenytoin; however, the protocol was not so designed. Nor, due to phenytoin loading "rescue" at 30 minutes, could the study design provide evidence of the duration of action of lorazepam and whether it could replace both diazepam and phenytoin in the treatment of status.

Recommendation:

Ativan injection should be approved for the indication: "safe and effective in the initial treatment of status epilepticus."

Janeth Rouzer MD

Janeth Rouzer, M.D. (HFN-120)

cc:
Orig:
HFN-120
HFN-220

HFN-120/PLeber/RKatz/
HFN-120/JRouzer/Rev/7/5/84
rd/mb/12/19/83
ft/mb/7/5/84
DOC 8514B

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 18140/S003

ENVIRONMENTAL ASSESSMENT AND/OR FONSI

ENVIRONMENTAL ASSESSMENT

AND

FINDING OF NO SIGNIFICANT IMPACT

FOR

ATIVAN ® INJECTION
Lorazepam

2 mg/mL and 4 mg/mL

NDA 18-140:S-003

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

DIVISION HFD-120

DATE COMPLETED 31-AUG-95

FINDING OF NO SIGNIFICANT IMPACT

NDA 18-140/S-003

ATIVAN INJECTION

Lorazepam

2 mg/mL and 4 mg/mL

The National Environmental Policy Act of 1969 (NEPA) requires all federal agencies to assess the environmental impact of their actions. FDA is required under NEPA to consider the environmental impact of approving certain drug product applications as an integral part of its regulatory process.

The Food and Drug Administration, Center for Drug Evaluation and Research has carefully considered the potential environmental impact of this action and has concluded that this action will not have a significant effect on the quality of the humnan environment and that an environmental impact statement therefore will not be prepared.

In support of their supplemental new drug application for the use of ATIVAN Injection in the initial treatment of status epilepticus, Wyeth-Ayerst Laboratories has prepared an environmental assessment in accordance with 21 CFR 25.31a(a) which evaluates the potential environmental impacts of the manufacture, use and disposal of the product.

Lorazepam is a chemically synthesized drug which is administered as an injectable at 2 and 4 mg/mL, currently used for relief of preoperative anxiety and for decreased ability to recall events related to the day of surgery. Wyeth-Ayerst Laboratories seek approval of a Supplemental NDA for the marketing of ATIVAN (lorazepam) Injection for use in the treatment of status epilepticus. The product has been marketed since 1980 with no adverse environmental impact observed or reported. The drug substance is manufactured by: Technochemie GmbH, Dossenheim, Germany and the drug product by: Wyeth-Ayerst Laboratories, Marietta PA. The finished drug product will be used in hospitals and clinics.

Lorazepam may enter the environment as the result of manufacture and use. As the result of intravenous administration at locations throughout the United States, lorazepam and its metabolites will be excreted and will enter the wastewater stream, where they are susceptible to degradation in waste water treatment facilities. Significant environmental effects are not expected because the maximum expected environmental concentration will be very small after considering metabolism and degradation in the wastewater treatment facilities.

Disposal of the drug may result from out-of-specification lots, discarding of unused or expired product, and user disposal of empty or partly empty used product and packaging. Returned or out-of-specification drug substance will be shipped back to the supplier, and rejected or returned drug product will be disposed of according to established Wyeth-Ayerst procedures as previously described. The solid waste generated by rejected packaging will be disposed of at the licensed landfill facility. At hospitals and clinics, empty or partly empty packages will be disposed of according to hospital/clinic regulations. It is stated in the EA that this product will only be used in hospitals/clinics.

The Center for Drug Evaluation and Research has concluded that the product can be manufactured, used and disposed of without any adverse environmental effects. Precautions taken at the site of manufacture of the bulk product and its final formulation are expected to minimize occupationsal exposures and environmental release. Adverse effects are not anticipated upon endangered or threatened species or upon property listed in or eligible for listing in the National Register of Historic Places.

NDA 18-140:S003 FONSI for ATIVAN (Lorazepam) Injection

31-AUG-95
DATE

W. Janusz Rzeszotarski, Ph.D., HFD-120

9/22/95
DATE

DIVISION CONCURRENCE
Stanley W. Blum, Ph.D.
Supervisory Chemist
Division of Neuropharmacological Drug Product
HFD-120

12/1/95
DATE

~~APPROVED~~ Concurred
Environmental Scientist
Center for Drug Evaluation and Research

DATE

retired
CONCURED
Robert A. Jerussi, Ph.D.
Associate Director for Chemistry
Center for Drug Evaluation and Research

Attachments:
Environmental Assessment
MSDS (drug Substance)
FOI - Releasable EA

cc: Orig: NDA 18-140
HFD-120/Division File
HFD-120/WJRzeszotarski
HFD-120/PDavid
HFD-120/SBlum
HFD-004/ FONSI File [NDA 18-140]
HFD-004/Docket file
HFD-019/FOI

Filename: n018140.fon

FOI Releasable Environmental Assessment Information

for Ativan® (lorazepam) Injection

NDA 18-140

April 5, 1995

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EXECUTIVE SUMMARY

Wyeth-Ayerst Laboratories is requesting approval for Ativan® (lorazepam) Injection for use in the initial treatment of status epilepticus. The proposed action will provide a new indication of the drug product previously approved for the relief of preoperative anxiety and for a decreased ability to recall events related to the day of surgery.

This Environmental Assessment is part of the Supplemental New Drug Application for Ativan® (lorazepam) Injection. The document format is arranged as required in 21 CFR 25.31(a).

It has been shown that the manufacture and subsequent exposure of Ativan® Injection will not create adverse effects to the environment. The manufacture will not cause any facility to exceed permit limits for wastewater or air emissions. Also, it does not threaten any endangered or threatened species or cause a depletion of any natural resources that are in critically short supply.

Ativan® Injection has been formulated and marketed since 1980 and to date, no adverse environmental impacts have been observed or reported.

Ativan® Injection does not pose a threat to environmental organisms exposed to the substance. The maximum expected environmental concentration from use was calculated to be mg lorazepam/L.

The drug substance will be manufactured by:

Technochemie GmbH
Verfahrenstechnik
Postfach 40
D-6901 Dossenheim, Germany

The manufacture of Ativan® Injection will not affect the environment either directly or indirectly. Also, the marketing of this substance will provide therapeutic benefits for persons with status epilepticus.

1. DATE

Original: January 13, 1977
Revision 1: June 30, 1994
Revision 2: April 5, 1995

2. NAME OF APPLICANT

Wyeth-Ayerst Laboratories

3. ADDRESS

P.O. Box 8299
Philadelphia, Pennsylvania 19101-1245

4. DESCRIPTION OF THE PROPOSED ACTION

4.1 Requested Approval

Wyeth-Ayerst Laboratories is requesting approval of a new indication for Ativan® Injection. This product contains lorazepam at concentrations of 2 and 4 mg/mL. This Environmental Assessment is part of the Supplemental New Drug Application (S-003) and is intended to update the environmental assessment located in Volume 1, p. 130 of our original NDA No. 18-140, dated March 16, 1978. The document format is arranged as required in 21 CFR 25.31(a).

4.2 Need for Action

Applicant seeks approval of a Supplemental NDA for the marketing of Ativan® (lorazepam) Injection for use in the treatment of status epilepticus. Ativan® Injection is currently marketed for relief of preoperative anxiety and for a decreased ability to recall events related to the day of surgery.

4.3 Location of Production — Environmental Conditions at the Site

Manufacturer of Drug Substance.
Lorazepam is synthesized by:

Technochemie GmbH
Verfahrenstechnik
Postfach 40
D-6901 Dossenheim, Germany

No increase in production, and therefore no additional affect to the environment, is expected due to the action requested in this Supplemental NDA. A certification

that the manufacturer of the drug substance is in environmental compliance as required in the Federal Republic of Germany is included in Section 6.3.1 of this document.

Manufacturer of the Drug Product.
Wyeth-Ayerst will manufacture and package the final drug product. The dosage form is formulated, filled into containers, and packaged by:

Wyeth-Ayerst Laboratories
Wasp & Biddle Streets
Marietta, Pennsylvania 17547

The production facility is located on an 84-acre site, with 26 buildings totaling 300,000 square feet. The site is located on the outskirts of a rural city and is surrounded by topography of rolling hills.

All statements made in this report regarding environmental controls, waste management, worker protection, manufacturing processes, use of resources and energy, and training and emergency procedures refer to drug product formulation and packaging at the Wyeth-Ayerst facility.

The drug product is currently manufactured and will continue to be manufactured as Ativan® (lorazepam) Injection after the proposed action is approved.

4.4 Locations of Use and Disposal

As a prescribed treatment for status epilepticus, this drug will be administered intravenously and will be distributed at locations throughout the United States. The amount that is eliminated or excreted will enter the wastewater stream.

At the Wyeth-Ayerst production site, solid waste generated from mixing and formulating this product will consist of rejected filled containers. These wastes will be crushed and solids will be sent to landfill at fully permitted facilities in the area. One such facility is:

Modern Landfill
Operated by: Waste Management Incorporated

Modern Landfill operates according to RCRA Subtitle D regulations under PA DER permit #100113. This Module 1 permit application, to accept crushed glass waste, was approved on 3/29/91 and has no expiration date. Residual waste from the Wyeth-Ayerst facility is characterized yearly and found to be acceptable for disposal at Modern Landfill. The Modern Landfill facility also operates under NPDES permit #PA0046680. The NPDES permit has an expiration date of

11/20/91. The facility filed a new NPDES application, prior to the expiration of the existing permit. On 6/7/91, the PA DER authorized the facility to continue operating under the existing permit. Modern Landfill continues to await final permit approval and extension of the expiration date. The landfill facility also operates under PA Air Quality permit #67-330-004 (expiration 5/1/98).

Rejected raw material would be shipped back to the supplier. During the processing of Ativan® (lorazepam) Injection, a maximum of 568 L/year of waste material, as reported to the Drug Enforcement Agency (DEA), would be discarded from filled containers to the on-site wastewater treatment facility.

Goods returned due to expiration of drug product, drug recall or for any other reasons, will be disposed of in an appropriate manner according to established procedures by Wyeth-Ayerst.

5. IDENTIFICATION OF CHEMICAL SUBSTANCES THAT ARE SUBJECT TO THE PROPOSED ACTION

This supplemental NDA is for Ativan® (lorazepam) Injection. The relevant drug substance and active ingredient is lorazepam.

5.1 Nomenclature

5.1.1 Chemical Name

7-chloro-5-(o-chlorophenyl)-1,3-dihydro-3-hydroxy-2H-1,4-benzodiazepin-2-one

5.1.2 United States Adopted Name (USAN)

Lorazepam

5.1.3 Laboratory Code

5.2 CAS Registry Number

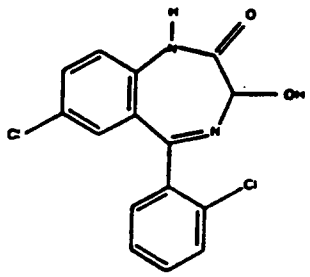
CAS RN: 846-49-1

5.3 Molecular Formula and Weight

$C_{15}H_{10}Cl_2N_2O_2$

Molecular Weight = 321.16

5.4 Structural Formula



5.5 Material Safety Data Sheet

The Material Safety Data Sheet for lorazepam is provided in Appendix A.

5.6 Physical Description

5.6.1 Appearance

Lorazepam is a white or nearly white crystalline powder.

5.6.2. Solubility

Solvent	Solubility (mg/mL)
Alcohol	14
Water	0.08
Propylene Glycol	16
Chloroform	3
Ethyl Acetate	30

5.7 Additives

The composition of the drug product is as follows:

* Equivalent to 2 mg or 4 mg per mL plus excess.

5.8 Drug Substance Impurities and Degradation Products

IMPURITIES	LABORATORY CODE
DEGRADATION PRODUCTS	**LABORATORY CODE**

6. INTRODUCTION OF SUBSTANCES INTO THE ENVIRONMENT

6.1 Substances Generated During Production of Drug Substance

Production of the drug substance, identified specifically in paragraph 5 will take place at the Technochemie GmbH facility identified in paragraph 4.3. .The synthesis of lorazepam complies with the German government environmental laws. Whenever possible, the material, byproducts, and/or emissions from manufacturing are reused/regenerated/recycled back into the process. Where reuse/recycling is not feasible, the materials in question are disposed of or emitted in accordance with appropriate laws and regulations. A Certificate of Environmental Compliance for the foreign manufacturer is included in Section 6.3.1.

6.2 Substances Generated During Production of Drug Product

The manufacturer of the drug product, identified specifically in paragraph 4.3, is located in Pennsylvania. The process for manufacturing is a batch operation in the following sequence: (1) formulation, (2) sterile filling of containers, (3) inspection of filled containers, and (4) packaging. Manufacturing controls and permit information for that facility are described below:

Wastewater

Wastewater from mixing and formulating this product is generated from wash waters, setup waste from the container-filling step, QA samples, and broken containers. The approval of this action is not expected to result in an exceedence of the permitted average daily flow of 170,000 gallons per day for this discharge point.

All wastewaters flow to the waters of the state of Pennsylvania (Evans Run Creek) in accordance with discharge permit PA 0013862 (expiration 3/31/1999). The wastewater treatment facility is a tertiary treatment plant using an extended aeration biological treatment with phosphorous removal. There are currently no specific restrictions on any of the chemicals used during manufacture of this product.

Based on anticipated manufacturing losses, the maximum chemical load of drug substance on the on-site treatment facility is anticipated to be 0.20 mg/L. The wastewaters enter a tertiary treatment plant that uses an extended aeration biological treatment with phosphorous removal. The organic constituents in the wastes are expected to be destroyed to levels >84% measured as Biochemical Oxygen Demand and >84% measured as Chemical Oxygen Demand. Thus, the expected environmental concentration is 0.03 mg/L. Calculation of drug substance flow to wastewater treatment plant and expected removal efficiency is located in Appendix B.

Air Emission

During all manufacturing of this product, particulates are removed from the work environment via HEPA filter and dust collection systems. Particulate emissions would not be expected to pose an environmental hazard. Personal safety equipment is worn by operators when handling the drug substance.

No components of this drug product are expected to volatilize. Approval of this action is not expected to adversely impact the environment.

Solid Waste

Solid waste generated from formulating and packaging this product will consist of rejected filled containers. These wastes will be crushed and solids will be sent to landfill as described in paragraph 4.4.

6.3 Compliance of Proposed Action with Applicable Emission Requirements

6.3.1 Drug Substance Manufacturer

The Technochemie GmbH facility is in compliance with all applicable environmental programs. A Certificate of Environmental Compliance and a certified English translation of the Certificate are included on the following pages.

REGIERUNGSPRÄSIDIUM KARLSRUHE

Regierungspräsidium Karlsruhe · Postfach 5343 · 76035 Karlsruhe

Firma
Technochemie GmbH
Verfahrenstechnik
Postfach 12 65

69216 Dossenheim

EINGANG
23. MRZ. 1995
Erledigt:

Korrespondenz-Adresse: Postfach 5343
76035 Karlsruhe

Liefer-Adresse: Schloßplatz 1-3
76131 Karlsruhe

Ihr Zeichen, Schreiben vom	Unser Aktenzeichen: (bitte bei Antwort angeben)	Bearbeiter/-in ☎(0721) 926-	Karlsruhe
Fi/Ko 06.03.1995	72b1-8823.12/4.1	6557 Frau Dr. Bertsch	13.03.1995/Kö

"Umweltbewertung" zur Vorlage bei der amerikanischen Food and Drug Administration (FDA)

Sehr geehrte Damen und Herren,

die Herstellung des pharmazeutischen Produktes Lorazepam wurde mit der immissionsschutzrechtlichen Genehmigung des Regierungspräsidiums Karlsruhe vom 07.01.1986 genehmigt.

Nach den dem Regierungspräsidium Karlsruhe vorliegenden Erkenntnissen wird die Anlage zur Herstellung von organischen Feinchemikalien, pharmazeutischen Wirkstoffen und Laminarharzen, in dem dieser pharmazeutische Wirkstoff hergestellt wird, derzeit entsprechend den behördlichen Genehmigungen des Regierungspräsidiums Karlsruhe betrieben.

Immissionsschutzrechtliche Genehmigungen werden auf Antrag (detallierte Dokumentation) nach gründlicher Prüfung erteilt, wenn die in den einschlägigen Vorschriften genannten Genehmigungsvoraussetzungen erfüllt sind. So bestimmt § 6 des Bundes-Immissionsschutzgesetzes (BImSchG) daß die Genehmigung zu erteilten ist, wenn

1. sichergestellt ist, daß die sich aus § 5 und einer aufgrund des § 7 erlassenen Rechtsverordnung ergebenden Pflichten erfüllt werden und

2. andere öffentlich/rechtliche Vorschriften und Belange des Arbeitsschutzes der Errichtung und dem Betrieb der Anlage nicht entgegenstehen.

Mit freundlichen Grüßen

Dr. Bertsch

INTERTECH
TRANSLATIONS LTD
MEDICAL & PHARMACEUTICAL SPECIALISTS
671 S. GULPH ROAD • P.O. BOX 60762 • KING OF PRUSSIA, PA 19406
TEL: (610) 265-7776 • FAX/MODEM (610) 337-4994

KARLSRUHE REGIONAL ADMINISTRATION

To: Technochemie GmbH
Procedure
Postfach 12 65
69216 Dossenheim

Karlsruhe, March 13, 1995

Re: your letter of March 6, 1995
Our ref.: 72b1-8823.12/4.1

Environmental Evaluation for Submission to the U.S. Food and Drug Administration (FDA)

Ladies and gentlemen:

The manufacture of the pharmaceutical product lorazepam was approved with the the immission protection approval issued by the Karsruhe regional administration on January 7, 1986.

Based on the knowledge available to the Karlruhe regional administration, the facility for manufacturing fine organic chemicals, pharmaceutical substances and laminar resins in which this pharmaceutical substance is produced is currently operated in compliance with the official requirements for approval of the Karlsruhe regional administration.

When applied for (with detailed documentation), immission protection approval is granted after thorough investigation if the conditions for approval cited in the pertinent regulations are met. Thus section 6 of the Federal Immission Law (BImSchG) provides that approval can be granted if

1. it is determined that the obligations under section 5 and under any legal decree issued on the basis of section 7 are met, and

2. other public/legal regulations and concerns for the protection of workers in the building and operation of the facility are not violated.

Sincerely,
[signed]
Dr. Bertsch

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TEL: (610) 265-7776 • FAX/MODEM (610) 337-4994

TRANSLATOR'S DECLARATION

I, Stanley G. Hart, Ph.D., am authorized to make this Translator's Declaration for INTERTECH TRANSLATIONS LTD.

To the best of my knowledge and belief, the statements in the German language in the Karlsruhe Regional Administration Statement of Compliance and the statements in the English language in the translated Karlsruhe Regional Administration Statement of Compliance attached to this certificate have the same meaning.

(Stanley G. Hart)

NOTARY'S DECLARATION

On this fourth day of April, 1995, at King of Prussia, Montgomery County, Pennsylvania 19406, U.S.A., Stanley G. Hart identified himself to me as the person who signed the declaration above.

(Notary)

NOTARIAL SEAL
CONSTANCE LEE THIM, Notary Public
Upper Merion Twp., Montgomery Co.
My Commission Expires Feb. 6 1996

6.3.2 Drug Product Manufacturer

The pollution control devices in use and the waste disposal methods used at the facility serve to minimize release of environmental emissions resultant from the production of Ativan® (lorazepam) Injection. The Wyeth-Ayerst — Marietta plant complies with the following federal and state regulations:

Clean Air Act, as Amended

The Wyeth-Ayerst facility has an air permit to operate ETO/CFC scrubbers (Permit #36-313-071, expiration 4/30/1998) and a boiler operating permit (Permit #36-302-016A, expiration 1/31/1999). Addition of this process is not reasonably expected to affect the compliance status of this facility.

Federal Water Pollution Control Act of 1972, the Clean Water Act, and the Water Quality Act of 1987, as amended

The facility is in compliance with the state-issued sewage discharge permit and with the effluent guidelines for pharmaceutical mixing/compounding and formulation (40 CFR 439), as described above in paragraph 6.2. Approval of this action is not reasonably expected to affect the compliance status of this facility. Please refer to Appendix B.

Resource Conservation and Recovery Act (RCRA) of 1976 and Amendments of 1984

Solid Waste

The facility is in compliance with all federal and state regulations governing hazardous waste generators.

Nonhazardous solid waste generated from mixing and filling this product will be disposed of at fully permitted landfills.

No hazardous wastes are generated.

Workplace

Chemicals in the workplace are stored, handled, and managed in accordance with Good Manufacturing Practice (GMP) and OSHA standards. Ventilation, air filtration, personal protection equipment, and industrial hygiene monitoring are employed to ensure containment of chemicals and minimal exposure of workers and the workplace to chemicals. GMP regulations are followed for all equipment and operating procedures.

6.4 Introduction and Concentration of Lorazepam Introduced in the Environment from Product Use

Lorazepam enters the environment in the United States through the injection and subsequent elimination of the drug by human patients. A lorazepam ADME profile has been generated in rats, dogs and humans. In the rat, oxidative metabolites were noted whereas in the later two species, the major metabolic route was glucuronidation at the 3-hydroxy group. Lorazepam is rapidly eliminated in all species after iv dosing (intended route of therapeutic use) with mean $t_{½}$ values of 0.5, 0.5, and 15.0 hr, respectively. The drug is mainly excreted in the feces of rats and in urine of dogs and humans where as much as 50% of the dose can be accounted for as the lorazepam glucuronide. These metabolites, entering water treatment systems in small amounts, would be expected to be rapidly further degraded and pose no environmental concerns.

For purposes of this Environmental Assessment, the parent molecule is used to evaluate environmental release mechanisms and estimated environmental concentrations.

6.4.1 Maximum Expected Emitted Concentration (MEEC)[1]

Based on 1994 market estimates, the MEEC is expected to be:

mg/L.

A decline in production estimates is forecasted after 1994 (See Appendix C for five year market estimates) due to the expiration of the patent for Ativan® Injection. Thus, the MEEC value reflects a worse case scenario.

The MEEC value was calculated using the following equation:

$$MEEC = (A)/(B)(C)(D)$$

where:

A = mg lorazepam/year

B = 365 days/year

C = 568 L/person-day

D = 246 million persons (U.S. population)

7. FATE OF EMITTED SUBSTANCES IN THE ENVIRONMENT

7.1 Aqueous Waste from Production

The wastewaters from the formulation and packaging of the drug product at the Wyeth-Ayerst facility in Marietta, PA enter a tertiary treatment plant that uses an extended aeration biological treatment with phosphorous removal. The organic constituents in the wastes are expected to be destroyed to levels >84% measured as BOD and >84% measured as COD.

7.2 Intravenous Pharmacokinetics of Drug

The MEEC from product use is mg/L. Lorazepam is rapidly eliminated in humans with a $t_{½}$ value of 15 hours. The drug is mainly excreted in the urine where 50% of the dose can be accounted for as the lorazepam glucuronide. Thus, the expected Environmental Concentration (EEC) for lorazepam from product use is mg/L, an extremely small amount.

The metabolites of the drug product entering the water treatment system are expected to be rapidly further degraded and pose no environmental concerns.

7.3 Air Emissions

No components of this drug product are expected to volatize during the formulation and packaging of Ativan® Injection. Particulate emissions are removed by local HEPA filters.

7.4 Solid Waste

Solid waste generated from formulating and packaging Ativan® Injection consist of rejected filled containers. These wastes will be crushed and solids will be sent to landfill as described in paragraph 4.4.

8. ENVIRONMENTAL EFFECTS OF RELEASED SUBSTANCES

8.1 Potential Effect on the Environment

The market projections for Ativan® Injection are included in Appendix C.

Based on the low production quantity and the controlled disposition of wastes from production, no drug substances will be discharged into the environment at levels greater than 1/100 of the concentration that causes 50 percent mortality of a test organism species.

As defined in 21 CFR 25.15 (b) (6), a substance is considered toxic in the environment if the maximum concentration of the substance at any point in the environment, i.e., either at any point of entry or any point where higher concentrations are expected as a result of bioaccumulation or other types of concentration processes, exceeds the concentration of the substance that causes any adverse effect in a test organism species (minimum effect level) or exceeds 1/100 of the concentration that causes 50 percent mortality in a test organism species, whichever concentration is less.

8.2 Potential Toxicity Effects

Toxicity studies in rats and mice indicate that the LD_{50} values for lorazepam administered orally are 4500 and 1850 mg/kg, respectively. 1% of the LD_{50} value for lorazepam is conservatively calculated to be 18.50 mg/kg using the lowest reported oral LD_{50}. The MEEC for Ativan® Injection is mg/L.

The amount of drug substance estimated to be released into wastewater treatment systems as a result of production is extremely small, less than of the total annual production or 0.20 mg/L lorazepam. The organic constituents in the wastes are expected to be destroyed to levels >84% measured as BOD and >84% measured as COD. Thus, the expected environmental concentration is 0.03 mg/L.

Ativan® Injection has been marketed since 1980 with no adverse environmental impacts observed or reported.

9. USE OF RESOURCES AND ENERGY

The raw materials used to manufacture Ativan® (lorazepam) Injection are readily available. The production of the drug product and the energy use involved therein do not deplete any natural resources that are in critically short supply.

The energy consumed in the manufacture of the drug product is less than 0.5% of the total energy consumption of the facility. This process is not expected to have any significant impact on energy usage.

The manufacturing facility is in compliance with laws governing the protection of threatened and endangered species. There are no known endangered or threatened species and no historic places are found at or near the facility.

10. MITIGATION MEASURES

The manufacturing process for Ativan® Injection is relatively innocuous, involving only

In addition, the Marietta facility conducts Waste Minimization/Pollution Prevention meetings quarterly. During these meetings new wastestreams and production processes are reviewed and evaluated so that additional waste minimization/pollution prevention opportunities, not already built into the manufacturing process, can be evaluated and incorporated into the manufacturing Standard Operating Procedure (SOP),if applicable.

Wyeth-Ayerst has taken all necessary measures (described in paragraph 6) to achieve compliance with the regulations governing the manufacture of Ativan® Injection.

No other potential adverse environmental impact is associated with the manufacture of Ativan® Injection.

11. ALTERNATIVES TO THE PROPOSED ACTION

The primary alternative to the proposed action is that of no action, with the resulting deprivation to those experiencing status epilepticus, a potentially life threatening condition, of beneficial therapy. However, due to the lack of environmental impact of the proposed product, no alternatives are proposed.

12. PREPARER

Diane L. Smith, Ph.D.
Wyeth-Ayerst Laboratories

Ed Helmig
Wyeth-Ayerst Laboratories

Craig Seyfried
Wyeth-Ayerst Laboratories

The preparers' resumes are provided in Appendix D.

13. CERTIFICATION

The undersigned certifies that the information presented is true, accurate, and complete to the best of the knowledge of Wyeth-Ayerst Laboratories.

Date: 4/10/95

Signature: Lisa K. Smith for Craig F. Seyfried

Craig F. Seyfried
Associate Director — Environmental Control
Wyeth-Ayerst Laboratories

14. REFERENCES

(1) Pharmaceutical Manufacturers Association, 1991, *Interim Guidance to the Pharmaceutical Industry for Environmental Assessment Compliance Requirements for the FDA.* July 1991.

15. APPENDICES

Appendix A. Material Safety Data Sheet

Appendix B. Calculation of Wastewater Treatment Plant Loading/Removal

Appendix C. Five-Year Production Pro Forma

Appendix D. Preparers' Resumes

Appendix A — Material Safety Data Sheet

MATERIAL SAFETY DATA SHEET

OCCUPATIONAL HEALTH SERVICES, INC.
11 WEST 42ND STREET, 12TH FLOOR
NEW YORK, NEW YORK 10036
1-800-445-MSDS (1-800-445-6737) OR
1-212-789-3535

FOR EMERGENCY SOURCE INFORMATION
CONTACT: 1-615-366-2000 USA

SUBSTANCE IDENTIFICATION

CAS NUMBER: 846-49-1
RTECS NUMBER: DF0350000

SUBSTANCE: LORAZEPAM

TRADE NAMES/SYNONYMS:
2H-1,4-BENZODIAZEPIN-2-ONE, 7-CHLORO-5-(2-CHLOROPHENYL)-1,3-DIHYDRO-3-HYDROXY-;
7-CHLORO-5-(2-CHLOROPHENYL)-1,3-DIHYDRO-3-HYDROXY-2H-1,4-BENZODIAZEPIN-2-ONE;
2H-1,4-BENZODIAZEPIN-2-ONE, 7-CHLORO-5-(ORTHO-CHLOROPHENYL)-1,3-DIHYDRO-3-HYDROXY-;
7-CHLORO-5-(ORTHO-CHLOROPHENYL)-1,3-DIHYDRO-3-HYDROXY-2H-1,4-BENZODIAZEPIN-2-ONE;
ATIVAN; ORTHO-CHLOROOXAZEPAM; ORTHO-CHLOROXAZEPAM; TAVOR; TEMESTA; WY 4036; WYPAX; DEA 2885; C15H10CL2N2O2; OHS12985

CHEMICAL FAMILY:
Benzodiazepine

MOLECULAR FORMULA: C15-H10-CL2-N2-O2

MOLECULAR WEIGHT: 321.16

CERCLA RATINGS (SCALE 0-3): HEALTH-2 FIRE-1 REACTIVITY-0 PERSISTENCE-3
NFPA RATINGS (SCALE 0-4): HEALTH-U FIRE-1 REACTIVITY-0

COMPONENTS AND CONTAMINANTS

COMPONENT: LORAZEPAM
CAS# 846-49-1
PERCENT: 100.0

OTHER CONTAMINANTS: NONE

EXPOSURE LIMITS:
No occupational exposure limits established by OSHA, ACGIH, or NIOSH.

LORAZEPAM:
Subject to California porposition 65 cancer and/or reporductive toxicity warning and release requirements-(July 1,1990)

PHYSICAL DATA

DESCRIPTION: White to off-white crystalline powder.

MELTING POINT: 331-334 F (166-168 C) SPECIFIC GRAVITY: not available

SOLUBILITY IN WATER: 0.08%

SOLVENT SOLUBILITY: Soluble in ethyl acetate, propylene glycol, alcohol; slightly soluble in chloroform.

FIRE AND EXPLOSION DATA

FIRE AND EXPLOSION HAZARD:
Slight fire hazard when exposed to heat or flame.

FIREFIGHTING MEDIA:
Dry chemical, carbon dioxide, water spray or regular foam (1990 Emergency Response Guidebook, DOT P 5800.5).

For larger fires, use water spray, fog or regular foam (1990 Emergency Response Guidebook, DOT P 5800.5).

FIREFIGHTING:
Move container from fire area if you can do it without risk. Do not scatter spilled material with high-pressure water streams. Dike fire-control water for later disposal (1990 Emergency Response Guidebook, DOT P 5800.5, Guide Page 31).

Use agents suitable for type of surrounding fire. Avoid breathing hazardous vapors, keep upwind.

TOXICITY

LORAZEPAM:
TOXICITY DATA: 71 ug/kg oral-child TDLo; 21 ug/kg oral-human TDLo; 380 ug/kg/19 days-intermittent oral-woman TDLo; 4500 mg/kg oral-rat LD50; 1850 mg/kg oral-mouse LD50; 870 mg/kg intraperitoneal-rat LD50; 1810 mg/kg intraperitoneal-mouse LD50; reproductive effects data (RTECS).
CARCINOGEN STATUS: None.
ACUTE TOXICITY LEVEL: Moderately toxic by ingestion.
TARGET EFFECTS: Central nervous system depressant.
AT INCREASED RISK FROM EXPOSURE: Persons with liver or renal impairment, acute narrow-angle glaucoma, hypersensitivity to benzodiazepines, personality disorders, or history of drug abuse.*
ADDITIONAL DATA: The use of alcoholic beverages may enhance the toxic effects. Interactions with medications have been reported. Poisoning may impair tasks requiring alertness. May cross the placenta and may be excreted in human breast milk.*

* May be based on general information on benzodiazepines.

HEALTH EFFECTS AND FIRST AID

INHALATION:
LORAZEPAM:
ACUTE EXPOSURE- No data available.
CHRONIC EXPOSURE- No data available.

FIRST AID- Remove from exposure area to fresh air immediately. If breathing has stopped, perform artificial respiration. Keep person warm and at rest. Treat symptomatically and supportively. Get medical attention immediately.

SKIN CONTACT:
LORAZEPAM:
ACUTE EXPOSURE- No data available.
CHRONIC EXPOSURE- No data available.

FIRST AID- Remove contaminated clothing and shoes immediately. Wash affected area with soap or mild detergent and large amounts of water until no evidence of chemical remains (approximately 15-20 minutes). Get medical attention immediately.

EYE CONTACT:
LORAZEPAM:
ACUTE EXPOSURE- No data available.
CHRONIC EXPOSURE- No data available.

FIRST AID- Wash eyes immediately with large amounts of water or normal saline, occasionally lifting upper and lower lids, until no evidence of chemical remains (approximately 15-20 minutes). Get medical attention immediately.

INGESTION:
LORAZEPAM:
See information on benzodiazepines. In addition, LDH elevation may occur. Partial airway obstruction may result from overdoses. Reproductive effects have been reported in animals and humans.

BENZODIAZEPINES:
NARCOTIC.
ACUTE EXPOSURE- The possible effects may include headache, nausea, vomiting, epigastric distress, diarrhea, incontinence, drowsiness, fatigue, dizziness, weakness, muscle relaxation, ataxia, dysarthria, change in salivation, slurred speech, a bitter taste, dilated pupils, diplopia, nystagmus and blurred vision. Irritability, impaired mental and psychomotor function, hallucinations, impaired recent memory, and anterograde amnesia may occur. Joint and chest pain have been reported. With larger doses, especially in severe intoxications, there may be an initial excitement and then sedation which may progress to stupor and possibly coma. Hypotension and tachycardia or bradycardia may occur. Rarely, respiratory or circulatory depression and death occur.
CHRONIC EXPOSURE- In addition to the effects of acute exposure, repeated ingestion of benzodiazepines has been reported to cause a low incidence of other effects including paradoxical reactions such as anxiety and stimulation, skin rashes, urticaria, edema, and blood dyscrasias including agranulocytosis some of which may be hypersensitivity reactions. Hepatic reactions and jaundice, menstrual irregularities, anovulation, and impaired sexual function may also occur. Prolonged use of benzodiazepines may produce psychological or physical dependence. Abrupt cessation may result in withdrawal: Benzodiazepines may cross the placenta and may be excreted in breast milk and may result in neonatal withdrawal. An association between congenital malformations and use of minor tranquilizers during pregnancy has been suggested. Reported malformations include oral cleft, inguinal hernia, cardiac defects, microcephaly and retardation, pyloric stenosis, and duodenal atresia.

FIRST AID- Remove by ipecac emesis followed by administration of activated

charcoal. Airway-protected gastric lavage is necessary in patients with depressed respiration. Maintain blood pressure (Dreisbach, Handbook of Poisoning, 12th Ed.). Administration of gastric lavage should be performed by qualified medical personnel. Get medical attention immediately.

ANTIDOTE:
No specific antidote. Treat symptomatically and supportively.

REACTIVITY

REACTIVITY:
Stable under normal temperatures and pressures.

INCOMPATIBILITIES:
LORAZEPAM:
OXIDIZERS (STRONG): Fire and explosion hazard.

DECOMPOSITION:
Thermal decomposition products may include toxic oxides of nitrogen and carbon and toxic and corrosive fumes of chlorides.

POLYMERIZATION:
Hazardous polymerization has not been reported to occur under normal temperatures and pressures.

STORAGE AND DISPOSAL

Observe all federal, state and local regulations when storing or disposing of this substance.

****Storage****

Storage of controlled substances must comply with applicable security requirments in 21 CFR 1301.71, 1301.72, 1301.73, 1301.74, 1301.75 and 1301.76.

Store away from incompatible substances.

CONDITIONS TO AVOID

May burn but does not ignite readily. Avoid contact with strong oxidizers, excessive heat, sparks, or open flame.

SPILL AND LEAK PROCEDURES

WATER SPILL:
The California Safe Drinking Water and Toxic Enforcement Act of 1986 (Proposition 65) prohibits contaminating any known source of drinking water with substances known to cause cancer and/or reproductive toxicity.

OCCUPATIONAL SPILL:
Sweep up and place in suitable clean, dry containers for reclamation or later disposal. Do not flush spilled material into sewer. Keep unnecessary people away.

PROTECTIVE EQUIPMENT

VENTILATION:
Provide local exhaust or general dilution ventilation system.

RESPIRATOR:
The following respirators are recommended based on information found in the physical data, toxicity and health effects sections. They are ranked in order from minimum to maximum respiratory protection.
The specific respirator selected must be based on contamination levels found in the work place, must be based on the specific operation, must not exceed the working limits of the respirator and must be jointly approved by the National Institute for Occupational Safety and Health and the Mine Safety and Health Administration (NIOSH-MSHA).

Any dust and mist respirator.

Any air-purifying respirator with a high-efficiency particulate filter.

Any powered air-purifying respirator with a dust and mist filter.

Any powered air-purifying respirator with a high-efficiency particulate filter.

Any type 'C' supplied-air respirator operated in the pressure-demand or other positive pressure or continuous-flow mode.

Any self-contained breathing apparatus.

FOR FIREFIGHTING AND OTHER IMMEDIATELY DANGEROUS TO LIFE OR HEALTH CONDITIONS:

Any self-contained breathing apparatus that has a full facepiece and is operated in a pressure-demand or other positive-pressure mode.

Any supplied-air respirator that has a full facepiece and is operated in a pressure-demand or other positive-pressure mode in combination with an auxiliary self-contained breathing apparatus operated in pressure-demand or other positive-pressure mode.

CLOTHING:
Employee must wear appropriate protective (impervious) clothing and equipment to prevent repeated or prolonged skin contact with this substance.

GLOVES:
Employee must wear appropriate protective gloves to prevent contact with this substance.

EYE PROTECTION:
Employee must wear splash-proof or dust-resistant safety goggles to prevent eye contact with this substance.

Emergency eye wash: Where there is any possibility that an employee's eyes may be exposed to this substance, the employer should provide an eye wash fountain within the immediate work area for emergency use.

CREATION DATE: 03/13/89 REVISION DATE: 03/24/93

Appendix B — Calculation of Wastewater Treatment Plant Loading/Removal

ESTIMATED LOSSES TO WASTEWATER

Basis of Estimate

- 1993 Production Volume of (total of 2 mg/mL and 4 mg/mL products)

  (A decline in production is forecasted after 1994 due to the expiration of the patent for Ativan® Injection.)

- hour batch run time including clean up.
- loss to wastewater
- 170,000 GPD Plant Discharge
-
- 1994 Market estimates

  Total: mg lorazepam

Concentration in Plant Effluent

0.20 mg/L

Removal at ON-SITE WWTP

84% as BOD
84% as COD

Expected Environmental Concentration

0.03 mg/L

Appendix C — Five-Year Production Pro Forma

Appendix C

Year	4 mg Units	2 mg Units	1 mg Units
1994			
1995			
1996			
1997			
1998			

A decline in production estimates is forecasted after 1994 because the patent for Ativan® Injection expired. The unit declines reflected through 1997 are the anticipated impact of multisource competition.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 18140/S003

STATISTICAL REVIEW(S)

JUN 14 1995

Statistical Review and Evaluation

NDA#: 18-140, Amendment to Supplement SE1-003

Applicant: Wyeth-Ayerst Laboratories

Drug: Ativan® (lorazepam) Injection

Indication: Status epilepticus

Documents reviewed: Vols. 15-24, 27 dated August 8, 1994

Medical Officer: John Feeney, M.D.

I. Background

The sponsor has submitted data from four controlled clinical trials (415/416, 411, 100, DMT) in support of the use of Ativan Injection for the initial anticonvulsant treatment of status epilepticus (SE).

The sponsor first submitted data in support of the present indication in 1981. The submission included data from three of the four investigators in Trial 100. The Agency issued a Not Approvable letter on July 21, 1986. Data from Trial 100 and from uncontrolled studies were submitted to the Agency on February 19, 1987, and April 6, 1988. Based on these submissions, the Agency sent a Not Approvable letter to Wyeth-Ayerst Laboratories dated December 6, 1989.

As part of a comprehensive update of the clinical evidence in support of the SE indication, data from two new double-blind controlled trials, 415/416 and 411, have been included in the present amendment The present submission also includes data from all four investigators from Trial 100 as well as data from patients who were excluded from previous analyses. In addition, results from the open-label study DMT have been included.

This statistical review of the efficacy of Ativan Injection for the initial treatment of SE will examine the results of trials 415/416, 411 and 100.

II. Trial Design/Methods

Table 1 presents design features for the four controlled trials.

A. Trial 415/416

Trial 415/416 was a randomized, double-blind parallel groups multicenter inpatient trial. Patients with SE were randomized in equal numbers to one of three dose strengths of Ativan 2 ml IV: 4 mg (high dose), 2 mg (medium dose) or 1 mg (low dose). If the first dose of blinded test drug was not effective within 10 minutes, the patient received a 4 mg open-label dose in 2 mg increments, with a 2-minute pause to assess the effect of the first 2 mg. If the open-label dose was not effective, another 4-mg open-label dose was given 10 minutes later (20 minutes after time 0), in the manner just described.

A positive response was defined prospectively as cessation of clinical or EEG seizure activity within 10 minutes of dose administration with continued cessation for at least 30 minutes. This is the sponsor's "10/30 rule".

The primary efficacy variable, per protocol, was the percentage of patients responding to the first injection. Secondary efficacy variables were:

- the percentage of patients responding after the second or third injections;
- the median and mean response latency times in minutes (time interval from the last dose of test drug to the last convulsive episode following which the patient regained consciousness); and
- the number and percentage of patients responding transiently but experiencing a relapse before maintenance treatment becomes effective.

Treatment groups were to be compared in a sequential pairwise fashion designed to preserve an overall (family-wise) α=0.05 type I error rate. Reponses were to be initially compared between the Ativan high and low dose treatment groups. If the result was statistically significant at α=0.05, the medium and low dose treatment groups were to be compared, also at α=0.05. If the high vs low dose comparison was not statistically significant, the medium and low doses would not be compared and neither comparison would be declared significant at α=0.05. The primary statistical method was the Mantel-Haenszel procedure for 2x2 tables stratified by center. If the minimum expected cell size requirement for the procedure was not met as specified by Mantel and Fleiss [ref 1], then a permutation test for stratified 2x2 tables would be used [ref 2].

The primary analysis was to be performed on the subset of patients who met all inclusion, exclusion and diagnostic criteria and who received the entire 2 ml injection of test drug. This subset of patients formed the "evaluable" patient population. Additionally, the only patients that were to be included in the comparison between any two treatment groups were those patients from investigators who had at least one evaluable patient in each of the treatment groups being compared.

Results from secondary analyses were to be summarized and statistical testing conducted where appropriate.

Forty (40) patients were to be randomized to each of the three treatment groups for a total sample size of 120 patients.

B. Trial 411

Trial 411 was a randomized, double-blind parallel groups multicenter inpatient trial. Patients with SE were randomized in equal numbers to 2 ml (4 mg) Ativan IV or 2 ml (10 mg) Valium IV. One (1) ml of blinded test drug was to be administered slowly over a one-minute interval, with administration of another 1 ml if seizure activity persisted or recurred. If seizures continued or recurred after 10-15 minutes, a second blinded 2 ml dose was to be administered in the same stepwise manner as the first dose. If the second dose did not control seizures within 10 minutes (20-25 minutes after time 0), other measures to control SE were to be employed.

A positive response was defined prospectively as "cessation of seizure activity and recovery of consiousness". There was no mention of whether or how this definition would be modified if seizure activity returned.

According to the protocol, "the primary efficacy parameters are proportion of patients responding to the first and secind injections." This reviewer interpreted this statement to mean there were two co-primary efficacy variables: (1) the proportion of patients responding to the first dose and (2) the proportion of patients responding to the first or second doses ("overall response"). The secondary efficacy variable was response latency time.

The designated primary statistical method was the chi-square test. Survival analysis techniques were to be used to analyze the secondary efficacy variable. All tests of hypotheses were to be one-sided at the 5% level of significance.

Statistical analyses were to be performed on the subset of patients who received one or two doses of test drug and were observed for a minimum of 12 hours after the last injection. Patients could be re-enrolled in the trial after for a second time if seven days had elapsed since their previous treatment with the test drug.

Forty (40) patients were planned for each treatment group, for a total sample size of 80 patients.

C. Trial 100

Trial 100 was a randomized, double-blind parallel groups multicenter inpatient trial. Patients with SE were randomized in equal numbers to 2 ml (4 mg) Ativan IV or 2 ml (10 mg) Valium IV. Two (2) ml of blinded test drug was to be administered slowly over a two-minute interval. If seizures continued or recurred after 10 minutes, a second blinded 2 ml dose was to be slowly administered. If seizures were not controlled 10 minutes after the second dose, other measures were used to control SE. Patients could be administered a loading dose of phenytoin even if seizures had not recurred 30 minutes after the first administration of the test drug.

The protocol did not specify primary and secondary endpoints. The case report forms required injection time, seizure cessation time, and latency time for dose(s) of the test drug and other drugs given in the emergency room. Duration of seizure control, as measured from the time seizures ended after treatment with the test drug to the time that additional anticonvulsant therapy was given, was also required on the case report form. The investigator was asked to evaluate the effectiveness of the test drug using a satisfactory or unsatisfactory rating.

The protocol did not specify a statistical method for the analysis of efficacy variables.

The protocol stated that "This study will include but not be limited to 30 patients". According to Final Report GMR-24447, "A total of at least 90 patients was to be enrolled".

III. Results

A. Trial 415/416

1. Sponsor's Results

Trial 415/416 was conducted from October 1991 to May 1993 at six (6) U.S clinical centers (protocol 415) and seven (7) Canadian clinical centers (protocol 416). Protocols were identical except for minor differences, primarily in drug packaging.

Due to the large differences in the numbers of patients assigned to the treatment groups at some centers, it appears that randomization was not stratified by center. An interim analysis was planned but not carried out because enrollment was nearly completed when the analysis was scheduled to begin.

One-hundred nineteen (119) patients (48 females, 71 males; 11 to 81 years) were randomized and treated. These patients comprised the intent-to-treat (ITT) patient population, for a total of 130 episodes of SE. Eight patients were re-enrolled in the trial for a second episode of SE; three patients were enrolled a third time. The evaluable patient populations consisted of 99 to 109 patients, depending on the treatment comparison performed. Table 2 shows demographic characteristics.

Efficacy analyses were performed for four patient populations:

1. ITT, first episode only
2. ITT, all episodes
3. evaluable, first episode only
4. evaluable, all episodes.

Patients were considered as responders if seizure activity stopped within 10 minutes of completion of the dose and did not recur for 30 minutes.

The protocol did not address the important issue, in view of the number of centers affected, of whether/how to modify the Mantel-Haenszel statistical results for "noninformative" centers, i.e., centers whose 2x2 (treatment group vs response) tables had a zero margin. A zero margin occurs for tables with at least one row with all zeros (no patients in one of the treatment groups) or at least one column with all zeros (all patients in both treatment groups having positive or negative responses).

For the ITT analyses, the sponsor identified 8 centers (**415**: 02, 05, 07; **416**: 02, 03, 04, 05, 07) that were noninformative for at least one of the following Ativan treatment comparisons: high vs low dose, medium vs low dose, and high vs medium dose (Table 4). These eight centers were designated as noninformative for *all* Mantel-Haenszel analyses. To prevent the loss of information from these centers, the sponsor combined the three U.S. centers into a single center. The five Canadian centers were combined into a second center.

Response rates to the first dose for the ITT, first-episode population were 25/41 (61%), 21/37 (57%) and 25/71 (76%) for the Ativan low, medium and high dose treatment groups, respectively. P-values were 0.085 (high vs low dose), 0.723 (medium vs low dose) and 0.056 (high vs medium dose). The following table summarizes the results for each of the four efficacy analyses:

TRIAL 415/416: RESPONSE TO FIRST DOSE [a]

	Intent-to-Treat Population			Evaluable Population		
Ativan Injection	Response[b] (%)	P value vs 2 mg	P value vs 1 mg	Response[b] (%)	P value vs 2 mg	P value vs 1 mg
First Episode						
4 mg	31/41 (75.6)	0.056	0.085	30/36 (83.3)	0.037	0.169
2 mg	21/37 (56.7)		0.723	21/33 (63.6)		0.599
1 mg	25/41 (61.0)			24/33 (72.7)		
All Episodes						
4 mg	35/48 (72.9)	0.089	0.086	33/40 (82.5)	0.069	0.219
2 mg	23/39 (59.0)		0.982	23/35 (65.7)		0.921
1 mg	25/43 (58.1)			24/35 (68.6)		

a: Some centers were combined in the analysis (Mantel-Haenszel test)
b: Raw response rate based on responses collapsed across investigators. Sample size based on three-way comparison.

For the Mantel-Haenszel test without combining centers, the p-value was 0.113 for the ITT, first-episode population. For the same population, a chi-square test yielded p=0.154

The sponsor conducted an additional Mantel-Haenszel efficacy analysis for treatment comparisons not specified in the protocol. The analysis, motivated by the similarity in the observed response rates in the low and medium dose treatment groups, combined responses for these treatment groups and compared the result with the response rate for the high dose treatment group. The resulting p-value was 0.045.

A stratified permutation test [ref 2] was used to analyze the response to the (blinded) first or (open-label) second dose, the "overall response", which constituted a new (i.e., not in the protocol) response variable. The permutation test was used because the sponsor determined that the sample size, using the "rule of five" by Mantel and Fleiss [ref 1], was too small to support the Mantel-Haenszel procedure. Results for the ITT first-episode analyses were p=0.012 (high vs low dose), p=0.259 (medium vs low dose) and p=0.247 (high vs medium dose).

The sponsor also conducted analyses based on generalized estimating equations (GEEs) [ref 3]. Response to first dose was the the dependent variable in the model. Treatment group was an independent variable. Observations within a center were considered to be correlated for which the sponsor specified an "exchangeable" correlation structure. Unlike the stratified Mantel-Haenszel procedure, the GEE procedure does not require at least one patient in each treatment group at each center, and at least one responder and one nonresponder at each center. A disadvantage of the technique is that the minimum sample size required to justify the asymptotic approximations is not known. Results for the ITT first-episode analyses were p=0.029 (high vs low dose), p=0.760 (medium vs low dose) and p=0.019 (high vs medium dose).

The sponsor used a modified Bartholomew procedure [ref 4] which tests the optimal pairwise contrast, based on the data, without inflating the Type I error rate. (A contrast is a linear combination of treatment effects where the coefficients sum to zero.) The p-value for the ITT, first-episode population was 0.081.

Survival analyses of time to response to first dose were not statistically significant for the low vs high dose comparison (p>0.10 for all analyses).

The sponsor analyzed the primary response variable for the ITT first-episode and evaluable first-episode populations by sex, age (<39.5 vs > 39.5) and race (white vs other) subgroups. The Breslow-Day test for the homogeneity of odds ratios was used to analyze interactions of response with sex and race variables, logistic regression for the age variable. No significant differences in response comparing the Ativan high and low dose treatment groups were found for either population (ITT: p=0.829, 0.474 and 0.636, respectively).

2. Reviewer's Analysis

This reviewer conducted additional analyses of the response to first dose using the primary statistical analysis method, the Mantel-Haenszel analysis stratifying on center. The motivation for conducting the analyses was to use other methods for treating results for noninformative centers. The treatment comparison of interest was the Ativan high vs low dose, the sponsor's prospectively defined initial treatment comparison.

This reviewer used two methods for combining results for the noninformative centers: (1) all noninformative centers were combined into a single center; and (2) noninformative centers were combined by protocol number. Depending on the response data from the noninformative centers,

these methods might result in the loss of some or all information.

Unlike the method used by the sponsor, in which a center was designated as noninformative for *all* pairwise comparisons if it was noninformative for *any* of the three possible pairwise comparisons, this reviewer designated a center as noninformative if and only if it had a zero margin for the particular pairwise comparison of interest (high vs low dose). This method resulted in a different set of noninformative centers for the high vs low dose treatment comparison (**415**: 05; **416**: 02, 04, 07). (The sponsor found eight such centers.)

P-values were 0.077 and 0.072, respectively, for methods (1) and (2).

Canadian center 05 was classified as noninformative by the sponsor, but did not have a zero margin for any 2x2 table of pairwise comparisons. Because of this misclassification, the sponsor's first-episode ITT analysis was repeated using seven noninformative centers instead of eight. The p-value was 0.074.

Patients ranged in age from 11 to 81. One patient, who received Ativan 4 mg, fell outside the allowable age range from 18 to 85. This 11 year-old female responded to the first dose.

Three patients, all from center 416-01 (see Table 4), participated in both trials (411 and 416). In 416, the patients were assigned to different randomized treatment groups. Responses were 0,1,1 for the low, medium, and high dose treatment groups, respectively (1=response, 0=no response). Exclusion of data from these patients resulted in only slightly higher p-values for all analyses. (In 411, two of the patients were randomized to Ativan; both responded to the first dose. The third patient, randomized to Valium, was a non-responder.)

Four investigators from Trial 411 also participated in Trial 415/416 (**416**: 01, 03, 04 and 06). Analyses were conducted to assess the impact on the results of Trial 415/416 of removing these four investigators. After removing the patients at these four centers, the remaining sample size was n=54 for the Ativan high vs low dose comparison (Table 4). Methods (1) and (2) for combining noninformative centers outlined above were similarly applied to these analyses. The high vs low dose treatment comparison yielded three (**415**: 05; **416**: 02, 07) noninformative centers. P-values were 0.251 and 0.259, respectively.

Time to reponse to first dose is an unreliable endpoint; too many of the values are missing. Nineteen (19) patients in the low and high dose treatment groups who responded to the first dose had missing data on time to response. This represents more than 1/3 the total number of responders (56) in these two treatment groups. Any analysis of this endpoint will be potentially biased.

B. Trial 411

1. Sponsor's Results

Trial 411 was conducted from November, 1989, to January, 1981, at nine (9) Canadian clinical centers.

Sixty (60) patients were randomized and treated. Two of these patients were not enrolled in the trial, for reasons the sponsor does not explain. (There is no reference to the two patients anywhere in the case report tabulations.) Fifty-eight (58) patients (32 females, 26 males; 9 to 86 years) comprised the ITT patient population, for a total of 62 episodes of SE. Four patients were re-enrolled in the trial for a second episode of SE. The evaluable patient population consisted of 55 patients with a total of 59 episodes. The three nonevaluable patients were retrospectively judged by the sponsor, using a blinded selection procedure, not to have SE. Table 3 shows demographic characteristics of the ITT population.

Efficacy analyses were performed for four patient populations:

1. ITT, first episode only
2. ITT, all episodes
3. evaluable, first episode only
4. evaluable, all episodes.

Patients were considered as responders if seizure activity stopped within 10 minutes of completion of the dose and did not recur for 30 minutes.

Although the protocol called for a chi-square analysis of the response to first dose, a primary efficacy variable, the sponsor used the Mantel-Haenszel procedure for 2x2 tables, stratified by investigator, for the analysis. Three centers (01, 03 and 08) were designated as noninformative due to one or more zero margins (Table 5). The sponsor combined the three noninformative centers into a single center for the analysis, although there was no prospective plan for doing so.

A stratified permutation test [ref 2] was used to analyze the response to the first or second dose, the "overall response". A permutation test was used for overall response because the sponsor determined that the sample size was too small to support the Mantel-Haenszel procedure [ref 1].

There was a statistically greater response to first dose of Ativan (24/30; 80%) than to the first dose of Valium (16/28; 57%), p=0.044, for the ITT analysis. Overall response occurred in 28 of 30 (93%) patients randomized to Ativan and 24 of 28 (86%) of patients randomized to Valium. The observed difference for this ITT analysis was not statistically significant (p=0.394). The following table summarizes the results for each of the four efficacy analyses. Although the protocol specified one-sided p-values, the sponsor presented two-sided p-values for all analyses:

TRIAL 411: RESPONSE TO TREATMENT [a]

Response	Intent-to-Treat Population				Evaluable Population			
	Lorazepam	Diazepam	Difference(%)	p value (two-sided)	Lorazepam	Diazepam	Difference (%)	p value (two-sided)
First Episode								
1st Dose[b]	24/30 (80.0)	16/28 (57.1)	22.9	0.044	24/29 (82.8)	14/26 (53.8)	28.9	0.009
Overall[c]	28/30 (93.3)	24/28 (85.7)	7.6	0.394	27/29 (93.1)	22/26 (84.6)	8.5	0.231
All Episodes								
1st Dose[b]	27/34 (79.4)	16/28 (57.1)	22.3	0.043	27/33 (81.8)	14/26 (53.8)	28.0	0.010
Overall[c]	31/34 (91.1)	24/28 (85.7)	5.5	0.419	30/33 (90.9)	22/26 (84.6)	6.3	0.410

a: Expressed as number of patients responding/number of patients treated (%).
b: Analysis based on the Mantel-Haenszel procedure with investigator as a stratification factor.
c: Analysis based on a permutation test with investigator as a stratification factor.

The sponsor analysed the primary efficacy variable using the Mantel-Haenszel method without combining noninformative centers. The p-value for the ITT, first-episode population was 0.042. A chi-square test, the protocol-specified statistical analysis method, yielded p=0.060.

Survival analysis of time to response to first dose was not statistically significant (p=0.237).

The sponsor analyzed the primary response variable for the ITT first-episode and evaluable first-episode populations by sex, age (≤40 vs > 40) and race (white vs other) subgroups. The Breslow-Day test for the homogeneity of odds ratios was used to analyze interactions of response with sex and race variables. The sponsor does not mention which analysis method was used for age, though it may have been logistic regression, which was used for Trial 415/416. No significant differences in response were found for either population (ITT: p=0.877, 0.351 and 0.420, respectively).

2. Reviewer's Analysis

The originally intended sample size was 80 patients, to be enrolled over a period of 15 months. By the trial's end, 58 patients had been enrolled over a period of approximately 14 months. According to the sponsor, "enrollment was discontinued early so that the investigators could participate in another study [Protocol 416]". In a facsimile transmission to the FDA dated January 13, 1995, the sponsor said it decided to terminate the trial early because it did not think the study as designed had enough power to demonstrate the superiority of Ativan to Valium. According to the sponsor, the decision to terminate was not data-driven.

Patients ranged in age from 9 to 86. Nine patients, all of whom received Ativan, fell outside the allowable age range from Eight of the nine patients responded to the first dose:

Age	Treatment group	Response to first dose?
9	Ativan	Yes
67	Ativan	Yes
71	Ativan	No
74	Ativan	Yes
78	Ativan	Yes
80	Ativan	Yes
83	Ativan	Yes
86	Ativan	Yes

This reviewer confirmed the results of the analyses for the ITT, first-episode populations: Mantel-Haenszel with noninformative centers combined (p=0.044), Mantel-Haenszel with no noninformative centers combined (p=0.043 vs p=0.042 for sponsor), and chi-square test (p=0.060).

The medical reviewer pointed out inconsistencies between the primary endpoint and time to response endpoint for five patients that may call into question the reliability of the primary endpoint for these patients. Three patients were categorized as responders to the first dose, yet response times were 15, 20 and 20 minutes. These response times exceeded the 10-minute upper limit that defined first-dose responders. Two patients categorized as not responding to the first dose but responding to the second dose had response times of 4 and 8 minutes. These are probably times from the *first* dose, because other second-dose responders had times too large (e.g., 37, 45, 28 minutes) to have been measured from the second dose. These two patients may have responded to the first dose.

The net result for the three "false positives" (2 Ativan, 1 Valium) and two "false negatives" (1 Ativan, 1 Valium) is, compared to the sponsor's data, one fewer Ativan responder. The Mantel-Haenszel analysis of response to first dose for the ITT, first-episode population yielded p=0.138 and p=0.145 when centers were combined and not combined, respectively.

The medical reviewer asked the sponsor to clarify the categorization of these five patients with respect to the primary endpoint. Until the sponser responds, these analyses should be considered only speculative.

C. Trial 100

1. Sponsor's Results

Trial 100 was conducted from May, 1979, to September, 1982, at four (4) U.S. clinical centers.

One hundred one (101) patients were randomized and treated. One patient's medical record was missing. Efficacy data were missing for two other patients, leaving ninety-eight (98) patients (23 females, 74 males, 1 sex unreported; 18 to 96 years) to comprise the ITT patient population, for a total of 101 episodes of SE. The evaluable patient population consisted of 95 patients with a total of 96 episodes of SE. Twenty-three (23) patients were outside the upper age range stipulated by the protocol due to age being unknown at the time of enrollment or protocol violation.

Efficacy analyses were performed for four patient populations:

1. ITT, first episode only
2. ITT, all episodes
3. evaluable, first episode only
4. evaluable, all episodes.

For this submission, the sponsor re-analyzed efficacy data using two primary efficacy variables: (1) the proportion of patients who responded to the first dose and (2) the proportion of patients with overall response. Response was defined retrospectively and presumably -- the sponsor does not specify otherwise -- in an unblinded fashion. The sponsor used the same criterion applied to Trials 415/416 and 411, namely the 10/30 criterion. Complementary analyses were conducted which attempted to duplicate the criterion used originally by the investigators to assess treatment response. This criterion, called the 0/0 criterion, was cessation of seizure activity, judged clinically or by EEG, without consideration of time to response or duration of response. Also, since a few patients who responded to the first dose also received a second dose, the sponsor excluded patients who received a second dose in a second complementary analysis called the 0/*no second dose* criterion.

The Mantel-Haenszel procedure for 2x2 tables, stratified by investigator, was used to analyze the response to first dose, overall response and investigator's judgment. For the stratification, the sponsor combined Dr. McCutcheon's two patients with patients from the next smallest center (Dr. Ramsey, n=12) to qualify for the minimum sample size requirement.

Although the response to first dose and overall response using the 10/30 criterion were numerically greater with Ativan compared to Valium, there were no statistically significant differences for any of the four patient populations. All p-values were at least as large as 0.225. Similar results were obtained for the 0/0 criterion (all p-values$\geq$ 0.180) and the 0/*no second dose* criterion (all p-values$\geq$ 0.136). The following table summarizes the results for each of the four efficacy analyses for the 10/30 criterion:

TRIAL 100: RESPONSE TO TREATMENT (10/30 CRITERION) [a]

	Intent-to-Treat Population				Evaluable Population			
Response	Lorazepam	Diazepam	Difference(%)	p value	Lorazepam	Diazepam	Difference (%)	p value
First Episode								
1st Dose[b]	34/49 (69.4)	28/48 (58.3)	11.1	0.277	34/49 (69.4)	26/45 (57.8)	11.6	0.275
Overall	35/49 (71.4)	31/48 (64.6)	6.8	0.507	35/49 (71.4)	28/44 (63.6)[c]	7.8	0.504
All Episodes								
1st Dose[b]	35/50 (70.0)	16/28 (58.0)	12.0	0.225	35/50 (70.0)	26/45 (57.8)	12.2	0.250
Overall	36/50 (72.0)	32/50 (64.0)	8.0	0.414	36/50 (72.0)	28/44 (63.6)	8.4	0.475

a: Expressed as number of patients responding/number of patients treated (%).
b: Analysis based on the Mantel-Haenszel procedure with investigator as a stratification factor.
c: One (1) diazepam-treated patient was evaluable for the first dose but not for the second dose.

2. Reviewer's Analysis

This reviewer did not conduct an independent analysis of efficacy data from Trial 100.

D. Reviewer's Meta-Analysis of Two Trials: 411 and 100

This reviewer conducted a meta-analysis of Trials 411 (n=58: 30 Ativan 4 mg, 28 Valium 10 mg) and 100 (n=97: 49 Ativan 4 mg, 48 Valium 10 mg). A meta-analysis was considered appropriate because both trials had similar designs (parallel group, same active control). The endpoint for the meta-analysis was the proportion of patients responding to the first dose within 10 minutes with continued cessation for at least 30 minutes (the 10/30 criterion). The patient population was ITT, first-episode. The test statistic chosen prospectively by this reviewer was a weighted combination of the log(odds ratio). The p-value for the analysis was 0.046.

IV. Summary of Required Subgroup Comparisons

For Trial 411, the sponsor analyzed the primary response variable for the ITT first-episode and evaluable first-episode populations by sex, age (≤40 vs > 40) and race (white vs other) subgroups. No significant differences in response were found for either population (ITT: p=0.877, 0.351 and 0.420, respectively).

For trial 415/416, the sponsor analyzed the primary response variable for the ITT first-episode and evaluable first-episode populations by sex, age (<39.5 vs > 39.5) and race (white vs other) subgroups. No significant differences in response comparing the Ativan 4 mg and Ativan 1 mg treatment groups were found for either population (ITT: p=0.829, 0.474 and 0.636, respectively).

V. Analysis of Generalized Tonic and Simple Partial Status

The medical reviewer deems the protocol-defined endpoint, response to first dose, to be especially difficult to determine for absence status and partial complex SE. These SE seizure

types do not possess a definite time cutoff. At the request of the medical reviewer, this reviewer conducted statistical analyses of patients with either the generalized tonic (GT) or simple partial (SP) status epilepticus. Table 6 shows response rates for GT status only and (GT or SP) status for Trial 415/416. Table 7 shows response rates for GT status only and (GT or SP) status for Trial 411. The chi-square test, with and without continuity correction, was used to compare response rates between treatment groups.

In Trial 415/416, patients presenting with either GT or SP status had greater response to first dose of Ativan 4 mg (22/25; 88%) compared to Ativan 1 mg (20/33; 62%) ($p<0.05$). In Trial 411, patients receiving Ativan showed a somewhat greater response to first dose than patients receiving Valium (15/17 (88%) vs 8/14 (57%)). The chi-square p-value was 0.034 when uncorrected for the discreteness of the underlying probability distribution, and 0.074 with the continuity correction. It is noted that, in both trials, 88% of patients with GT or SP status responded to the first dose of Ativan 4 mg.

VI. Conclusions

The sponsor has submitted efficacy data for 4 controlled clinical trials. Trial DMT was open-label and not considered as contributing significantly to the efficacy assessment. The remaining trials, 415/416, 411 and 100, were evaluated primarily with respect to the primary endpoint, response to first dose, for the intent-to-treat, first-episode populations.

Trial 411 demonstrated statistical superiority (p-values approximately 0.05) of Ativan 4 mg to an active control (Valium 10 mg). These results were confirmed when the data were augmented by data from Trial 100 (meta-analysis: $p=0.046$), which by itself did not show Ativan to be superior to Valium.

Trial 415/416 failed to replicate the significant result in 411/100 (p-values between 0.05 and 0.10 for the primary -- high dose vs low dose -- comparison). In addition to the absence of a statistically significant treatment difference between the Ativan 4 mg and 1 mg treatment groups (a difference of only six outcomes in 41 patients), also troubling is the lack of proper ordering in dose-response (**2 mg** less effective than **1 mg** less effective than **4 mg**), and the potential dependence in the results between Trials 416 and 411 because they had four investigators in common.

Response to first dose was positive for patients with generalized tonic or simple partial status in the two pivotal trials, 411 and 415/416. Although there may be clincial justification for removing patients with complex partial or absence status from the analyses, this type of analysis (both retrospective and subgroup) frequently overstates the significant of treatment differences, inflating the false positive error rate. The true statistical significance of the observed treatment effects should be confirmed by conducting a prospective trial in patients with generalized tonic or simple partial status.

This reviewer acknowledges the practical difficulties of conducting trials in patients with status epilepticus. Foremost among these difficulties is the ethical requirement of using active controls and the logical imperative, for reasons of "assay sensitivity", of showing statistical superiority of the test drug to the active control. However, the statistical evidence presented by the sponsor does not meet the standard requirement, that is, demonstration of effectiveness at the two-sided 5% level of significance in more than one adequate well-controlled trial.

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Mathematical Statistician

concur: Dr. Nevius SEN 6-12-95

Dr. Dubey 6-14-95

cc: Arch NDA 18-140, Amendment to Supplement SE1-003
HFD-120
HFD-120/Dr. Leber
HFD-120/Dr. Katz
HFD-120/Dr. Feeney
HFD-120/Mr. David
HFD-713/Dr. Dubey [File: DRU 1.3.2]
HFD-713/Group 2 file
HFD-713/Dr. Sahlroot

This review consists of 14 pages of text and 7 numbered tables.

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Table 1
Controlled Clinical Trials

Trial/Dates	Number of Centers	Design	Treatment Groups (n)
415/416 10/91-5/93	6 US 7 CAN	Randomized, double-blind, dose response, parallel groups. ER patients received up to 3 doses (first only was blinded) of test drug within 20 minutes.	1. Ativan 1 mg (41) 2. Ativan 2 mg (37) 3. Ativan 4 mg (41)
411 11/89-1/91	9 CAN	Randomized, double-blind, active control, parallel groups. ER patients received 1 or 2 blinded doses of test drug within 10 to 15 minutes.	1. Ativan 4 mg (30) 2. Valium 10 mg (28)
100 5/79-9/82	4 US	Randomized, double-blind, active control, parallel groups. Patients received 1 or 2 blinded doses of test drug within 10 minutes.	1. Ativan 4 mg (49) 2. Valium 10 mg (48)
DMT 1/82-6/87	1 US	Randomized, open label, active control, parallel groups. All patients received a single dose of test drug. Nonresponders at 15 minutes or responders with recurrence of SE were crossed over to the other treatment.	1. Ativan 0.1 mg/kg (38) 2. phenytoin 18 mg/kg (41)

Table 2
Trial 415/416: Demographic Characteristics

Characteristic	Ativan Injection 1 mg (n=41)	Ativan Injection 2 mg (n=37)	Ativan Injection 4 mg (n=41)
Age (yr)			
Mean ± SD	42.7 ± 15.9	45.3 ± 17.0	41.3 ± 18.3
Range			
Sex, no., (%)			
Male	26 (63)	25 (68)	20 (49)
Female	15 (37)	12 (32)	21 (51)
Race, no, (%)			
White	24 (59)	25 (68)	28 (68)
Black	7 (17)	7 (19)	7 (17)
Arabic	1 (2)	1 (3)	0 (0)
Hispanic	3 (7)	2 (5)	3 (7)
Native American	2 (5)	1 (3)	3 (7)
Oriental	2 (5)	1 (3)	0 (0)
Other	2 (5)	0 (0)	0 (0)
Weight (kg)			
Mean ± SD	67.0 ± 11.3	63.8 ± 15.2	73.0 ± 16.6
Range			
Height (cm)			
Mean ± SD	170.0 ± 7.8	170.7 ± 9.9	167.8 ± 11.6
Range			
Primary Diagnosis, no, (%)			
Generalized Tonic-Clonic	29 (71)	24 (65)	22 (54)
Generalized Absence	2 (5)	0 (0)	2 (5)
Complex Partial	5 (12)	9 (24)	14 (34)
Simple Partial Status	4 (10)	4 (11)	3 (7)
Nonconvulsive Status	1 (2)	0 (0)	0 (0)
Prestudy Treatment, no, (%)			
Diazepam	5 (12)	2 (5)	2 (5)
Phenytoin	1 (2)	1 (3)	0 (0)

Table 3
Trial 411: Demographic Characteristics

Characteristic	Ativan (n=30)	Valium (n=28)	Total (n=58)
Age (yr)			
Mean ± SD	46.8 ± 22.5	38.6 ± 13.1	42.8 ± 18.9
Range			
Sex, n (%)			
Male	13 (43.3)	13 (46.4)	26 (44.8)
Female	17 (56.7)	15 (53.6)	32 (55.2)
Weight (kg)			
Mean ± SD	70.0 ± 21.3	72.6 ± 22.5	71.3 ± 21.5
Range			
Race, n (%)			
White	26 (86.7)	25 (89.3)	51 (87.9)
Other	4 (13.3)	3 (10.7)	7 (12.1)

Table 4
Trial 415/416: Response to First Dose, by Investigator

Investigator (Protocol-Center)	Ativan [a]			Total n
	1 mg	2mg	4 mg	
Investigators in 416 who also participated in 411				
McLachin (416-06)	3/4	4/5	5/5	14
Pillay (416-04)	0/2	.	.	2
Purves (416-03)	0/2	0/2	2/3	7
Andermann (416-01)	5/6	5/5	5/6	17
subtotal	8/14 (57%)	9/12 (75%)	12/14 (86%)	40
Investigators in 416 not participating in 411, and investigators in 415				
Asconape (415-01)	0/1	1/1	3/4	6
Barkley (415-02)	1/1	.	0/1	2
Langendorf (415-03)	4/7	1/6	1/2	15
Unwin (415-05)	0/1	0/2	0/2	5
Pierre-Louis (415-07)	2/2	1/1	3/4	7
McGoldrick (415-10)	9/12	8/10	9/9	31
Grandmaison (416-02)	.	0/1	1/2	3
Jones (416-05)	1/2	1/3	2/2	7
Young (416-07)	0/1	0/1	0/1	3
subtotal	17/27 (63%)	12/25 (48%)	19/27 (70%)	79
All investigators	25/41 (61%)	21/37 (57%)	31/41 (76%)	119

[a] expressed as number of patients responding/ number of patients treated.

Table 5
Trial 411: Response to First Dose, by Investigator

Investigator (Center)	Ativan 4 mg [a]	Valium 10 mg [a]	Total n
Investigators in 411 also participating in 416			
McLachin (05)	3/4	5/5	9
Pillay (06)	6/7	4/6	13
Purves (07)	3/4	0/2	6
Andermann (09)	5/5	5/6	11
subtotal	17/20 (85%)	13/19 (68%)	39
Investigators in 411 not participating in 416			
Bruni (01)	1/1	.	1
Guberman (02)	2/3	0/3	6
Langevin (03)	.	1/1	1
St.-Hilaire (08)	0/1	0/2	3
Reiher (10)	4/5	2/3	8
subtotal	7/10 (70%)	3/9 (33%)	19
All investigators	24/30	16/28	58

[a] expressed as number of patients responding /number of patients treated.

Table 6
Trial 415/416: Response to First Dose for Generalized Tonic or Simple Partial Status Epilepticus

Seizure type	Ativan 1 mg	Ativan 4 mg	Chi-square P-value (continuity-adjusted)
GT[a]	18/29	19/22	0.054 (0.108)
GT / SP[b]	20/33	22/25	0.021 (0.044)

[a] Generalized tonic status epilepticus
[b] Generalized tonic or simple partial status epilepticus.

Table 7
Trial 411: Response to First Dose for Generalized Tonic and Simple Partial Status Epilepticus

Seizure type	Valium 10 mg	Ativan 4 mg	Chi-square P-value (continuity-adjusted)
GT [a]	8/14	15/17	0.049 (0.120)
GT / SP [b]	12/22	20/24	0.034 (0.072)

[a] Generalized tonic status epilepticus
[b] Generalized tonic or simple partial status epilepticus.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 18140/S003

ADMINISTRATIVE DOCUMENTS

EXCLUSIVITY SUMMARY for NDA # 18-140 SUPPL # SE1-003

Trade Name Ativan Injection Generic Name Lorazepam

Applicant Name Wyeth-Ayerst HFD- 120

Approval Date 9-5-97

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it an original NDA?

YES /___/ NO /✓/

b) Is it an effectiveness supplement?

YES /✓/ NO /___/

If yes, what type? (SE1, SE2, etc.) SE1

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES /✓/ NO /___/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES /✓/ NO /___/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

3

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use?

YES /___/ NO /✓/

If yes, NDA # _____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /✓/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /✓/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

2. Combination product. N/A

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /✓/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

   For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

   (a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /✓/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:**

_____

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /✓/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain: _____

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /✓/

If yes, explain: _____

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # 345B-415-05/416-CA

Investigation #2, Study # 345B-411-CA

Investigation #3, Study # _____

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES /___/	NO /✓/
Investigation #2	YES /___/	NO /✓/
Investigation #3	YES /___/	NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study # _____

NDA # _____ Study # _____

NDA # _____ Study # _____

b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1	YES /___/	NO /✓/
Investigation #2	YES /___/	NO /✓/
Investigation #3	YES /___/	NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study # _____

NDA # _____ Study # _____

NDA # _____ Study # _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #1, Study # 345B-415-US/416-CA

Investigation #2, Study # 345B-411-CA

Investigation #__, Study # _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # YES /✓/ NO /___/ Explain: _____

Investigation #2

IND # YES /✓/ NO /___/ Explain: _____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

N/A

Investigation #1

YES /___/ Explain _____ NO /___/ Explain _____

Investigation #2

YES /___/ Explain _____ | NO /___/ Explain _____

_____ | _____

_____ | _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /✓/

If yes, explain: _____

_____

_____

_____

_____
Signature

Title: Project Manager

7/29/96
Date

_____
Signature of Division Director

9/5/97
Date

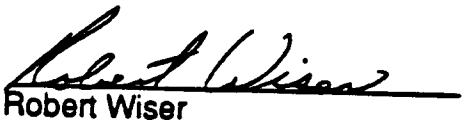
cc: Original NDA Division File HFD-85 Mary Ann Holovac

NDA No. 18-140
Supplement No. 003

PATENT INFORMATION UNDER SECTION 505(b)

ATIVAN® INJECTION (lorazepam injection) is not claimed in any U.S. Patent. In the opinion of applicant and to the best of applicant's knowledge, there is now no U.S. Patent which claims the drug referred to in this application or which claims a use of the drug for which the applicant is seeking approval

WYETH-AYERST LABORATORIES

By: 
Robert Wiser
Chief Patent Counsel

Ativan® Injection - NDA No. 18-140 - Supplement 003

Patent/Exclusivity Information

New Indication: Treatment of Status Epilepticus

1)	Active ingredient(s)	Lorazepam
2)	Strength(s)	2 and 4 mg/ml (Vials and Tubex® cartridge-needle Units)
3)	Trade Name	ATIVAN® INJECTION
4)	Dosage Form (Route of Administration)	Intravenous Injection
5)	Applicant Firm Name	Wyeth-Ayerst Laboratories
6)	NDA Number	18-140
7)	Approval Date	
8)	Exclusivity - Date first ANDA could be submitted or approved and length of exclusivity period	Pursuant to Section 505(j)(4)(D)(iii) and 505(c)(3)(D)(iii) of the Federal Food, Drug and Cosmetic Act, no ANDA may be approved with an effective date which is prior to 3 years after the date of approval of this NDA Supplement.
9)	Applicable patent numbers and expiration date of each	None

Ativan® (lorazepam) Injection
NDA No. 18-140

Item 15 B. Certification Required by Generic Drug Enforcement Act of 1992

Wyeth-Ayerst hereby certifies that it did not and will not knowingly use in any capacity the services of any person debarred under subsection (a) or (b) of section 306 of the Federal Food Drug and Cosmetic Act in connection with this supplemental application (S-003) for NDA No. 18-140 for Ativan® Injection.

Signed: Joseph N. Bathish

Joseph N. Bathish
Vice President
Worldwide Regulatory Affairs

MEMORANDUM

DATE: August 7, 1996

FROM: Deputy Director
Division of Neuropharmacological Drug Products/HFD-120

TO: File, NDA 18-140/S1-003

SUBJECT: Further Supervisory Review of a Supplement for the Use of Ativan in Patients With Status Epilepticus

BACKGROUND

In my review of this supplement dated 3/26/96, I concluded that it could be considered approvable if several issues were adequately addressed by the sponsor. Specifically, the issues I felt needed to be addressed were:

1) the timing of the 2 infusions of the first dose in Study 411

2) the use of maintenance therapy in Study 411 and Study 415/416

3) the potential discrepancy between the results of analyses of responders as defined in the protocol compared to the analysis presented utilizing a non-protocol specified definition of responder in Study 411

4) the effects on the outcome of potential misclassification of 5 patients as either responders or non-responders in Study 411

The first 3 concerns were communicated to the sponsor in a telephone call on 4/10/96. The sponsor responded to this request with submissions dated 6/5/96 and 7/1/96. The fourth request above was not addressed in either of these 2 documents; a separate request for this information was made on 8/1/96, and was addressed in a fax from the sponsor dated 8/6/96. Dr. Feeney has reviewed the 6/5 and 7/1/96 responses in his review dated 7/16/96. I have the following comments.

COMMENTS

1) As Dr. Feeney points out, essentially all Ativan responders received both infusions of the first dose, while only about half the responders in the Valium group received both infusions. However, as he also notes, all non-responders in both groups received both infusions of the first dose, allaying any concerns that patients randomized to treatment with Valium did not receive a potentially sufficient first dose.

2) Data submitted by the sponsor demonstrates that maintenance therapy was not differentially distributed between the treatment groups in either study.

3) The sponsor has documented that there were no patients who were responders by one definition that were also not responders according to the other definition; i.e., this re-classification maneuver had no effect on the outcome.

4) Dr. Feeney has not seen the sponsor's response to this question. In this case, 3 patients were classified as responders with latencies to response greater than 10 minutes (15, 20, 20), and 2 patients were classified as non-responders to the first dose, but responders to the second dose, who were reported to have had response latencies of 4 and 8 minutes.

According to the sponsor, the explanation lies in the fact that for the first 3 patients, the response times are reported as minutes from the initiation of the first infusion of the first dose. In all 3 cases, the latency to response from the end of the second infusion of the first dose was under 10 minutes. Since we have been considering response to first dose as the primary measure of effectiveness, this explanation is satisfactory (recall that the allowable duration between infusions of the first dose was unspecified; for example, in one of these 3 cases, the inter-infusion interval was 18 minutes; this was allowable by protocol).

Regarding the 2 other patients, the latencies reported were also from the initiation of the first dose. In these cases, however, the second dose was given earlier than the protocol dictated, so the response seen occurred after the second dose. Despite the fact that the second dose was given

inappropriately early, the sponsor's characterization of these patients as non-responders to the first dose is appropriate.

RECOMMENDATIONS

Given the sponsor's responses to our concerns, I recommend that the division issue the attached Approvable letter.

Russell Katz, M.D.

Cc:
NDA 180140/S-003
HFD-120
HFD-120/Leber/Katz/Feeney/David
HFD-713/Sahlroot
rk 8/7/96

MEMORANDUM

DATE: March 26, 1996

FROM: Deputy Director
Division of Neuropharmacological Drug Products/HFD-120

TO: File, NDA 18-140/S1-003

SUBJECT: Supervisory Review of NDA 18-140, Supplement for the Use of Ativan in Patients With Status Epilepticus

BACKGROUND

Wyeth-Ayerst, sponsor of approved NDA 18-140 for the use of Ativan (lorazepam) as a preanesthetic agent, submitted a supplement to the NDA in 1981 for its use as a treatment of status epilepticus. The application included results of active control trials that failed to demonstrate a difference between treatment groups, and, as a result, a Not Approvable letter was sent in 1986. Although the sponsor responded, the critical deficiencies were not adequately addressed, and a second Not Approvable letter issued in 1989.

The most recent amendment was submitted on August 8, 1994, with several additional submissions. The application now includes the results of 2 clinical trials that are adequate and well-controlled by design to address the question of the effectiveness of Ativan as treatment for status epilepticus. In addition, results of 2 other trials have been submitted. The current submission has been reviewed by Dr. John Feeney, Medical Officer in the Division, and by Dr. J.Todd Sahlroot, Mathematical Statistician, of the Division of Biometrics. Dr. Feeney has concluded that the supplement should be approved for the use of Ativan as treatment for generalized tonic-clonic status and simple partial status. Dr. Sahlroot has concluded that the application should not be approved. In this memo, I will briefly describe the results of the trials, and present my recommendations.

STUDY 411

This was a randomized, multi-center, double blind, parallel group, active control trial performed in Canada in which patients with status epilepticus were randomized to receive either Ativan or Valium intravenously. Patients with generalized tonic-clonic, simple partial, complex partial, or absence status were eligible, and some seizure activity prior to treatment had to be witnessed.

By protocol, patients were to receive treatment according to the following regimen:

Ativan 2 mg or Valium 5 mg initially to be followed by an additional **2 mg Ativan or 5 mg Valium** only if seizure activity persists or recurs. The (potential) total dose of 4 mg of Ativan or 10 mg of Valium is considered the first dose. If seizures continue or recur after a 10-15 minute observation period, a second dose of study medication is to be given in the same regimen as the first dose. If seizures are not controlled within 10 minutes after the second dose, additional measures to control seizures should be employed.

Maintenance therapy (e.g., IV phenytoin) could be initiated within 15 minutes after study medication (either the first or second dose) is effective.

Patients who received treatment were permitted to be re-randomized to treatment for additional episodes of status if the episodes occurred at least 7 days apart.

By protocol, patients were to be considered responders if there was cessation of seizure activity and recovery of consciousness. The primary effectiveness parameters were declared to be the proportion of patients responding to the first and second injections. These parameters were to be analyzed using the chi-square test. Other data were collected, including latency to response, time of completion of each injection, etc., and other measures to be compared included number of patients responding transiently but experiencing a relapse before maintenance treatment has become effective.

RESULTS

A total of 58 individuals were randomized at 9 centers (30 Ativan, 28 Valium); 4 of these patients were randomized more than once for additional episodes of treatment, yielding a total of 62 episodes of status. According to the sponsor, 3 patients were incorrectly treated (2 with pseudoseizures, 1 with status due to hypoglycemia-these were prospective exclusion criteria). The sponsor argued that only the first episode treated for any given patient should be included in the analysis, because any additional episodes do not represent independent data. Given these data and considerations, the sponsor constructed 4 data sets:

1) Intent to Treat, first episode only (N=58; 30 A, 28 V)

2) Intent to Treat, all episodes (N=62; 34 A, 28V)

3) Evaluable, first episode only (N=55; 29 A, 26 V)

4) Evaluable, all episodes (N=59; 33 A, 26 V)

The sponsor did not present the results of the protocol specified efficacy measure; namely the proportion of patients responding to the first and second dose, with responder defined as one in whom there was noted a cessation of seizures with recovery of consciousness. Further, the data that would be necessary to compute these proportions were not submitted. (It should also be noted that the exact nature of the primary outcome variable is not clear; for example, did the sponsor intend to analyze responses to either dose separately, or perform a single analysis on the total number of patients who responded to either the first or second dose?)

Rather, the sponsor chose to present the proportion of patients responding to the first dose as one anaysis, **and** the proportion of patients responding to either the first or second dose as another primary analysis, **using the following definition of a responder:**

A responder to a given dose is a patient in whom seizures stopped within

10 minutes of the dose, and in whom this cessation persisted for at least 30 minutes. This definition is the one prospectively designated as primary in the second multi-center trial to be described later.

Proportions of responders using this definition were presented for the 4 cohorts described above. The following displays the Percent Responders for the intent-to-treat population for the first dose of the first episode:

	Percent Responders	P-value
Ativan	24/30 (80%)	
Valium	16/28 (57%)	0.04

The p-value displayed represents the results of a Mantel-Haenszel test. The protocol specified chi-square analysis yielded a p-value of 0.06. Similar results were obtained for the response to first dose when all 62 episodes were included in the analysis. In general, analyses of the Evaluable patients, as presented by the sponsor, were highly significant.

Analyses of the proportion of patients who responded to either the first or second dose (one reasonable interpretation of the protocol specified primary outcome-given the caveat that this **still** is not the definition of responder given in the protocol) showed no significant differences between treatments. No analyses of response to second dose alone were presented.

As Dr. Feeney points out on page 7 of his review, however, 5 patients appear to have been misclassified by the sponsor as either being responders or non-responders to the first dose. Specifically, for 3 patients, times to response were listed as 15, 20, and 20 minutes, yet they were classified as responders (recall that the protocol stated that a responder to a given dose was one in whom seizures ceased within 10-15 minutes of the dose, and the definition of a responder actually utilized also required that the onset of seizure cessation be within 10 minutes of dose administration). By either definition of responder, these 3 should not have been classified as responders. In addition, as Dr. Feeney points out, 2 patients were listed as non-reponders, whereas their times to response were 4 and 8 minutes after drug administration.

As Dr. Sahlroot describes in his review on page 10, the net effect of correctly reclassifying these 5 patients results in 1 fewer Ativan responder. The Mantel-Haenszel analysis applied to this new data set for response to the first dose for the intent-to-treat population results in a p-value of 0.14.

As stated in the protocol, investigators were permitted (though not obligated) to initiate maintenance therapy approximately 5 minutes after a dose was judged to be effective. However, we have received no data from the sponsor regarding this concomitant drug use. That is, we do not know the number of patients, if any, that received such maintenance therapy, nor, of course, do we know in which patients such therapy was given, the timing of such therapy, dose, drug, etc. It should be noted that Dr. Feeney has requested information from the sponsor about concomitant drug use, as well as further clarification regarding the misclassification of the 5 patients described above; we have not received their response.

While the use of such medication could not, by definition, have affected the proportion of patients classified as responders as defined by the protocol, the use of such medication at the time described in the protocol could possibly have affected the number of patients ultimately classified as responders using the retroactively applied definition of a 30 minute seizure free interval, because the maintenance therapy could have contributed to seizure control during that interval. The amount of time that the maintenance therapy could have potentially been "on board" could vary. At the minimum, suppose that seizures stopped 1 minute after study drug administration in a particular patient. Maintenance therapy could have been given at 15 minutes, and therefore could potentially have been on board for the last 16 minutes of the seizure free interval (seizure free interval in this case runs from time 1 minute to time 31 minutes after study drug with 14 minutes between study drug and maintenance therapy). On the other hand, if seizures stopped at 10 minutes after study drug administration, and maintenance therapy was initiated 5 minutes later, the maintenance therapy would have been "on board" for 25 of the 30 minutes of no seizure activity for a responder. Although it could be argued that the maintenance therapy could not be exerting any anti-seizure effect as rapidly as within 25 minutes of its infusion, there is no

evidence to support that contention. Indeed, in a recent action taken by the Agency with regard to fosphenytoin (an intravenously administered prodrug for phenytoin), its approval as a treatment for status epilepticus was contingent upon the achievement of equivalent plasma levels of unbound phenytoin as those resulting from IV phenytoin within minutes of the injection. In other words, it was considered necessary, for the treatment of status epilepticus, for "therapeutic levels" of phenytoin to be achieved within a few minutes of administration, reflecting the view that, in the absence of evidence to the contrary, we must assume that phenytoin might be exerting a beneficial effect very soon after its administration. Given, then, the possibility of the maintenance therapy contributing to seizure control during the 30 minutes required for a patient to be classified as a responder, knowledge of the use of such therapy in each treatment group should be critical for a complete assessment of the effects of the study drug in this trial.

Dr. Feeney, on page 16 of his review, discusses the potential unreliability of assessing seizure cessation in patients with complex partial and/or absence status. He suggests that the end of an episode of generalized tonic-clonic or simple partial status is a more reliable endpoint, since these latter 2 seizure types have motor manifestations, the cessation of which should be relatively easy to observe. He has performed analyses including only those patients with either GTC or simple partial status, as well as analyses including only those patients with GTC status. Analyses including only those patients with either GTC or simple partial status yielded significant p-values, and analyses including only patients with GTC status yielded p-values of between 0.05 and 0.12, depending upon the specific analysis performed (see Dr. Sahlroot's review, page 21).

STUDY 415/416

This was a multi-center, double blind, fixed dose response, parallel group study performed in the US and Canada, in which patients with status epilepticus were randomized to receive a single blinded dose of either 1, 2, or 4 mg of Ativan. If within 10 minutes of this injection seizures had not stopped, an open dose of Ativan could be given; a second open dose could be given if seizures were not controlled within 10 minutes of the

first open dose.

In this trial, the protocol designated primary outcome was the proportion of responders, defined as a patient in whom seizures stopped within 10 minutes of blinded drug administration, and in whom the seizure free interval persisted for at least 30 minutes. The primary analysis was to be a sequential Mantel-Haenszel analysis comparing the percentage of responders in the subsets of patients in the 4 mg and 1 mg groups who met all exclusion, inclusion, and diagnostic criteria. If this comparison was significant at p=0.05, a second comparison between the 2 and 1 mg groups was to be made.

In this trial, the entire dose was to be given as a single injection, in contrast to Study 411, in which the first dose was to be given in 2 increments. Also, as in Study 411, patients could be treated for more than one episode of status.

Further, the protocol states that maintenance therapy with intravenous phenytoin could be initiated 10 minutes after the blinded dose, if indicated by local practice. However, the Case Report Form (CRF) (page 116, Vol.4) states:

> No other antistatus medication will be given until 10 minutes after the first dose of lorazepam has proven ineffective.

RESULTS

A total of 119 patients were enrolled at 6 US and 7 Canadian centers. A total of 130 episodes of status were treated.

Again, the sponsor presented results for 4 cohorts, analogous to those for Study 411, distributed as follows:

	1 mg	2 mg	4 mg
1) Intent to Treat, first episode	41	37	41
2) Intent to Treat, all episodes	48	39	43

3) Evaluable, first episode	36	33	33
4) Evaluable, all episodes	40	35	35

The following results are presented for the proportion of responders to the unblinded dose for the intent to treat, first episode only cohort:

4 mg- 31/41 (76%)

2 mg- 21/37 (57%)

1 mg- 25/41 (61%)

As discussed by Dr. Sahlroot (pp 5-7), the p-value for the primary comparison (high dose vs low dose) varies dependent upon the analysis performed, but generally ranges from 0.07-0.085. Results for the Evaluable patient subset (the protocol specified primary cohort), intent to treat, first episode only cohort yields a p-value of 0.17.

Analyses comparing the 4 mg group to the 2 mg group (a procedure the protocol explicitly stated would not be performed if the primary comparison did not reach significance at 0.05) yielded p-values ranging from 0.04-0.06, for the Evaluable and Intent to treat populations, respectively.

Again, as in Study 411, the use of concomitant maintenance therapy is unaddressed by the sponsor. In this trial, however, even the rule for permitting such use is unclear. The protocol states that it may be given 10 minutes after the study drug, but the case report form states that it may only be given 10 minutes after the first dose is determined to be ineffective. If the CRF rule was actually utilized, there would be no concern about an effect of concomitant therapy on the determination of a responder, since, by definition, a patient could only receive such therapy if they were not a responder. On the other hand, if investigators employed maintenance therapy in patients who were seizure free for 10 minutes (as the protocol suggests they could), then, as in Study 411, such use could

have effected response rates. For this reason, knowledge of the use of maintenance therapy is critical for a complete assessment of this trial as well.

The sponsor also performed a post hoc Mantel-Haenszel analysis comparing proportion of responders in the 4 mg group to the proportion of responders in the 1 and 2 mg groups combined. Presumably, the nominal p-value was 0.045. Dr. Sahlroot has not independently performed this analysis.

Finally, Dr. Sahlroot has performed an analysis of responder rate in the 4 mg group compared to the 1 mg group for the subgroup of patients who had GTC status and the subgroup of patients who had either GTC or simple partial status, for the reasons described above for Study 411. He obtained nominal p-values of 0.1 and 0.4 for these comparisons, respectively.

STUDY 100

In previous submissions, the sponsor had submitted partial results of this study, which was essentially similar in design to Study 411. Specifically, they had previously submitted results of 3 of the 4 centers in this trial. In this most recent amendment, they submitted the complete results, which are described by Dr. Sahlroot on pp. 10-12 of his review. He has not independently performed an analysis of this trial; as presented by the sponsor, while there were slight numerical differences favoring Ativan, no statistically significant differences were seen in this study of approximately 100 patients.

SUMMARY

The sponsor has submitted the results of 3 trials that are adequate by design to establish the effectiveness of Ativan as a treatment for acute status epilepticus. Studies 411 and 100 each compared Ativan to Valium, while Study 415/416 compared several doses of Ativan.

Study 100 does not demonstrate the effectiveness of Ativan by the usual standards.

Study 411 appears, as presented, to support the effectiveness of Ativan. Specifically, an analysis of the percent responders in the intent to treat population for the first dose of the first episode yields a p-value of 0.04. However, certain information, critical to a complete assessment of this trial, is not available.

There are 3 areas of concern. First, and perhaps least important, the sponsor has provided no details about the actual administration of the first dose. Recall that the first dose was to be given in 2 portions, the second half to be given if seizures persist. No time frame was given in the protocol detailing how long the treating physician was to wait before making the determination that the second half of the first dose was to be given. Given that decisions about timing of dosing, maintenance therapy, etc. played an important part in the interpretation of this study, it would be useful to have the information about the timing of the 2 halves of the first dose.

More significant, however, is the lack of data about maintenance therapy. There is no evidence presented to establish that intravenous phenytoin could not have had antistatus effects within the time frames utilized to judge effectiveness in these trials. Because there exists the possibility that maintenance therapy was differentially employed in the 2 treatment groups, this information is critical to our adequate understanding of the results of the trial.

Importantly, the sponsor did not analyze the protocol specified outcome. The definition of a responder in the protocol was not utilized. Although the definition they did use was the one prospectively specified in Study 415/416, and appears perfectly reasonable on clinical grounds, it would be important to see if there are any discrepancies between the protocol specified outcome and the one actually analyzed. (This trial was discontinued early, ostensibly because the sponsor decided that it did not have sufficient power to detect a difference between Ativan and Valium. The sponsor states that this decision was not data driven. It is interesting to speculate, however, about whether this study was examined, after its completion, to identify possible outcomes that appeared nominally significantly positive. The use of such a retrospectively identified outcome as the primary outcome of a second

study would be perfectly appropriate; however, statistical significance in the second study would not constitute independent replication of a result by the usual definition). It should also be noted that, regardless of definition of reponder used, the protocol specified that response to first and second dose would be the primary analysis, a statement that is vague at best.

Finally, as Dr. Feeney notes, several patients were misclassified either as responders or non-responders. A re-analysis of the data using the correct classifications results in a loss of statistical significance. Obviously, complete and accurate response information is necessary to adequately analyze this trial.

In Study 415/416, the results as presented almost reach the usual standards of statistical significance. Hwever, the same problem of absent information regarding concomitant maintenance IV phenytoin exists. In this trial, however, the rules for such use are unclear, there being a potential difference between what the protocol and the CRF says. Again, complete information about this issue is critical.

Regarding the question of the unreliability of determining the endpoint of certain types of status, and the nominally positive findings on some analyses of the subgroups of patients with motor manifestations, I agree with Dr. Sahlroot (p. 13 of his review) that conclusions based on retrospectively identified subgroups are dangerous, and that this finding would need to be prospectively confirmed in a well-controlled trial.

RECOMMENDATIONS

It is possible that Studies 411 and 415/416 may ultimately be found to establish the effectiveness of Ativan as a treatment of status epilepticus. However, in the absence of the information described in the Summary section above, I cannot recommend the approval of this supplement at this time.

JAN 10 1995

NDA: 18-140 Submission Date: August 8, 1994

Generic Name, Strength(s), and Formulation: **Lorazepam 2 mg/mL and 4 mg/mL Injection for Intravenous and Intramuscular Administration.**

Brand Name: Ativan® Injection

COMPLETED

JAN 10 1995

Sponsor: Wyeth-Ayerst Laboratories
Philadelphia, PA

Reviewer: Safaa Ibrahim, Ph. D.

Type of Submission: Review of Labeling

REVIEW OF LABELING

BACKGROUND:

Lorazepam (Ativan®) injection is a benzodiazepine with antianxiety, anticonvulsant, and sedative effects. It interacts with the γ-aminobutyric acid (GABA)-benzodiazepine receptor complex, which is widespread in the brain of human as well as other species. Ativan® injection is indicated in adult patients for preanesthetic medication, producing sedation, relief of anxiety, and a decreased ability of recall events related to the day of surgery. It is intended for intravenous and intramuscular administration and is available in strengths of 2 mg/mL and 4 mg/mL.

The sponsor submitted a supplemental new drug application (SNDA) on August 28, 1981 for the use of Ativan® Injection in the treatment of status epilepticus. This SNDA was not approvable from the clinical standpoint since the data submitted did not provide sufficient evidence of efficacy pertaining to this new indication. A non-approvable letter was issued on December 6, 1989 to this effect.

The current submission contains updated clinical information pertaining to the use of Ativan® Injection for the treatment of status epilepticus. Also included in the current submission was the firm's proposed draft of the annotated labeling for Ativan® Injection pertaining to the new indication (Appendix I). The Division of Biopharmaceutics was asked to review the pharmacokinetically relevant portionsof the draft labeling as well as the journal articles submitted in support of this labeling. Appendix II is a revised version of the labeling as written by the Division of Biopharmaceutics.

COMMENTS:

(To be sent to the Medical Reviewer)

1. The Medical Reviewer is requested to review and verify the following from the sponsor's proposed draft labeling (See Appendix I):

(a) Paragraphs 3, 4, 5, and 6 on page 3.
(b) On page 8, the last sentence of Drug Interactions paragraph (When dexamethasone is given .....occur.).

2. Labeling changes were made in the Clinical Pharmacology/pharmacokinetics, Precautions/Drug Interactions, and Dosage and Administration sections; see pharmacokinetic labeling write-up in Appendix II.

3. Concurrent administration of lorazepam with valproate to 6 healthy male subjects resulted in decreased total clearance of lorazepam by 40% and decreased formation clearance of lorazepam-glucuronide by 55% as compared to lorazepam administered alone. Accordingly, lorazepam plasma concentrations were about two-fold higher for at least 12 hours post-dosing during valproate treatment. Lorazepam dosage should be reduced to 50% of the normal adult dose when this drug combination is prescribed in patients.

4. Coadministration of lorazepam with oral contraceptive steroids to healthy females was associated with a 55% decrease in half-life, a 50% increase in the volume of distribution, thereby resulting in an almost 3.7-fold increase in total clearance of lorazepam as compared to control healthy females. It may be necessary to increase the dose of Ativan® in female patients who are concomitantly taking oral contraceptives. This dosing adjustment should also be based on the clinical response.

5. Concurrent administration of lorazepam with probenecid to 9 healthy volunteers showed a prolongation of lorazepam half-life by 130% and a decrease in its total clearance by 45%. Ativan® dosage needs to be reduced by 50% when coadministered with probenecid.

(To be Sent to the firm)

6. The sponsor is requested to incorporate the changes in the proposed draft labeling and adopt the labeling as amended by the Division of Biopharmaceutics (See Appendix II).

RECOMMENDATION:

The sponsor is requested to adopt the pharmacokinetic labeling as outlined in Appendix II.

Please convey this Recommendation and Appendix II to the firm.

Safaa Ibrahim, 1/10/95
Safaa S. Ibrahim, Ph.D.
Pharmacokinetics Evaluation Branch I

RD/FT initialed by R. Baweja, Ph.D. R. Baweja 1/10/95.

cc: NDA # 18-140 (Suppl.), HFD-120, HFD-426 (Ibrahim, Baweja, Fleischer), Chron, Drug, HFD-19 (FOI), and Reviewer Files.