CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number: NDA 20646

Trade Name: GABITRIL

Generic Name: TIAGABINE HYDROCHLORIDE

Sponsor: ABBOTT LABORATORIES

Approval Date: SEPTEMBER 30, 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION: NDA 20646

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CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: NDA 20646

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-646

Abbott Laboratories
Pharmaceutical Product Division
Attention: James D. Steck
100 Abbott Park Road; D-491, AP6B-1SW
Abbott Park, Illinois 60064-3500

SEP 30 1997

Dear Mr. Steck:

Please refer to your new drug application dated November 3, 1995, received November 6, 1995, and to your amendment dated March 31, 1997, received April 1, 1997, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Gabitril (tiagabine hydrochloride) tablets, 4mg, 12mg, 16mg, and 20mg.

Reference is also made to the Agency's Approvable Letter dated October 31, 1996.

We acknowledge receipt of your additional correspondence and amendments dated:

October 29, 1996	June 5, 1997	August 21, 1997	September 10, 1997
November 8, 1996	July 24, 1997	August 29, 1997	September 10, 1997
December 19, 1996	August 1, 1997	September 2, 1997	September 19, 1997
May 21, 1997	August 5, 1997	September 8, 1997	September 26, 1997
June 2, 1997	August 8, 1997	September 9, 1997	

The User Fee goal date for your original submission was November 6, 1996. The User Fee goal date for your amendment is October 1, 1997.

This new drug application provides for the use of tiagabine hydrochloride as adjunctive therapy in adults and children 12 years and older in the treatment of partial seizures.

We have completed the review of this application, including the submitted draft labeling, 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. Accordingly, the application is approved effective on the date of this letter.

Labeling

The final printed labeling (FPL) must be identical to the enclosed marked-up draft labeling. Marketing the product with FPL that is not identical to this draft labeling may render the product misbranded and an unapproved new drug.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FINAL PRINTED LABELING" for approved NDA 20-646. Approval of this submission by FDA is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of the drug become available, revision of that labeling may be required.

Chemistry, Manufacturing, and Controls

In your March 31, 1997 submission, you proposed 24 month expiration dating for your product with the following degradant specifications :

At present, you have not submitted sufficient evidence to permit us to conclude that drug product containing the proposed levels of the above degradants will be safe in use. Our reasoning is as follows.

According to the ICH Harmonized Tripartite Guideline-Impurities in New Drug Products; Recommended for Adoption on 11/6/96 by the ICH Steering Committee, the maximum amount of any individual degradant that may be considered acceptable without requiring qualification in products with daily dose between 10 and 100 mg/day (the daily dose range for tiagabine) is 0.5% or 200 μg (total daily dose), whichever is smaller.

The recommended daily dose described in your proposed labeling is up to 56 mg/day (although 80 mg/day is mentioned), 0.5% of which is 280 μg. The maximum permissible degradant level (without requiring qualification) associated with the maximum dose proposed in your labeling would therefore be 200 μg, or 0.25%. Because your proposed limits for the degradants are al than this limit, they must all be "qualified" before these proposed specifications are approved.

In support of qualification, you have submitted information about the level of degradants in various tablet strengths to which patients in several studies have been exposed, as well as the results of a 3 month toxicity study in rats which examined the effects of up to 10 times the dose of each of the 3 degradants to which patients would be exposed under the proposed specifications. Further, you have submitted the results of a 2 year carcinogenicity study in mice, in which species is a metabolite, the results of which you conclude establish the safety of in this species at levels up to thousands of times greater than levels to which humans would be exposed.

Although these data represent partial qualification of the degradants, we do not consider them sufficient to establish the safety of the product with a 24 month expiry.

The human data are also not sufficient. Levels of in the product used in these studies did not generally exceed 0.25%. Levels of in this product were generally greater than 0.25%, some as high as but it is not likely that the 4 mg tablets used provided exposure to 60 mg of tiagabine and its associated degradant. Specific information on total daily dose in these patients is not available to us.

Further, it should be noted that your animal reproduction/teratogenicity and mutagenicity studies were all performed with drug substance, and, hence, these studies did not examine the effects of the degradants in question. Also, the mouse carcinogenicity study exposed the animals to high levels of only

Although we do not believe a 24 month expiry is yet supported, our review of your data has permitted us to conclude that an 18 month expiry will provide a product that can meet alternative satisfactory specifications (as discussed in a telephone conference on September 18, 1997 between members of your staff and of the Division of Neuropharmacological Drug Products) and would not necessitate additional animal or human qualifying data. Labeling will need to limit the maximum human daily dose to 56 mg.

In the referenced telephone conversation, a specification of was discussed for the degradant. Your letter of September 19, 1997 to Dr. Leber showed that many lots of the 4 mg tablet would exceed and asked for a specification of I have accepted your request because only the 4 mg tablet exceeds the limit with any frequency, and this tablet size will not ordinarily result in a exposure even at degradant. The larger tablets sizes are regularly under

Consequently, you are approved with the following expiration dating and degradant specifications:

We also request that you monitor the levels of degradant in the stability samples on a monthly basis and submit the results for review at the indicated expiration date.

We recognize that you are still very much interested in obtaining approval of your originally proposed expiration dating and degradant levels. Toward this end, we recommend that you perform the following studies to support your original proposals.

1) A complete standard battery for genotoxicity testing of pharmaceuticals performed with the combination of the 3 degradants.

2) A 3 month toxicology study which follows the design of your 3 month rat study with degraded drug, comparing a non-toxic dose of undegraded tiagabine to tiagabine containing a mixture of degradation products, but using very high doses relative to those to which humans will be exposed.

3) A teratology study in rats which compares the middle and high doses of undegraded tiagabine which were used in you r original teratology study to the same doses in the presence of a high level of the mixture of degradants.

Our staff will be happy to discuss appropriate designs of these studies with you.

Other

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

Please submit one market package of the drug product (containers and cartons only) when it is available.

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 Jacqueline H. Ware, Pharm.D., Regulatory Management Officer, at (301) 594-2850.

Sincerely yours,

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURE

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20646

APPROVABLE LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-646

OCT 31 1996

Abbott Laboratories
Pharmaceutical Product Division
Attention: David C. Furlano, Ph.D.
100 Abbott Park Road
Abbott Park, Illinois 60064-3500

Dear Dr. Furlano:

Please refer to your November 3, 1995, new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Gabitril™ (tiagabine hydrochloride) 4mg, 12mg, 16mg, and 20mg tablets.

We acknowledge receipt of your additional correspondence and amendments dated:

November 13, 1995
November 17, 1995
November 29, 1995
December 1, 1995
December 5, 1995
December 14, 1995
December 22, 1995
January 17, 1996
January 18, 1996
January 19, 1996
January 24, 1996
January 31, 1996
February 5, 1996
February 8, 1996
February 15, 1996
February 21, 1996
March 1, 1996
March 7, 1996
March 12, 1996
March 14, 1996
March 22,1996
March 27, 1996
April 3, 1996
April 8, 1996
April 12, 1996
May 6, 1996
May 15, 1996
May 16, 1996 (2)
May 22, 1996
June 4, 1996
June 25, 1996
June 26, 1996
June 28, 1996 (2)
July 2, 1996 (3)
July 8, 1996 (2)
July 10, 1996
July 11, 1996
July 15, 1996
July 17, 1996
July 18, 1996
July 24, 1996
July 31, 1996
August 7, 1996
August 19, 1996
August 23, 1996
September 6, 1996
September 11, 1996
September 17, 1996
September 24, 1996

We have completed the review of this application as submitted with draft labeling, and it is approvable.

Although we have reached a general conclusion that the NDA may eventually be approved, additional work remains to be done. We do not fully understand the nature of the adverse events associated with the use of tiagabine. In particular, there are adverse mental status changes in patients, some of sufficient severity to cause premature discontinuation of treatment, that you have not described adequately. These are not of a kind likely to lead to non-approval of the application, but, until we have a clearer understanding of their nature, severity, and course, we will be unable to write informative labeling for Gabitril™. The steps needed to correct this deficiency are described below.

In sum, before this application may be approved, it will be necessary for you to conduct further analyses, provide information, and agree to adopt as labeling for Gabitril™, the draft package insert attached to this letter, which also contains detailed suggestions and requests.

Package Insert

The attachment to this letter provides a draft of the labeling that the Agency asks you to adopt for Gabitril™ Tablets upon its approval. Although sections of this proposal are taken verbatim from the labeling proposed by you in the NDA, other sections have been extensively revised and/or expanded to include new subsections. Please note that we have embedded throughout the text of the attached draft labeling, "Notes to Sponsor:", requesting further revisions or clarification of the label. We have the following specific comments and requests for the following sections of labeling.

1. Indications Section

The attached draft labeling includes language in this section that permits a claim for Gabitril™ as adjunctive treatment for partial seizures in patients above the age of 12. We have several comments about this.

a) Partial Seizures

Based upon the reports submitted to the NDA and our own analyses, we believe a claim for partial seizures can be approved despite the fact that two of your three major studies were intended primarily to evaluate tiagabine's effect on complex partial seizure rates.

There are, however, some residual concerns that should be addressed prior to final approval. In particular, investigator verbatims included on the case report forms sometimes report that, in Study M91-603, a number of patients did not count all partial seizures from the beginning of the study. While we have no evidence that these errors of omission occurred in a systematic pattern, (i.e. introduced a bias in the estimate of treatment effect), we would like assurance that they did not introduce such a bias. Specifically, you should review the verbatims to determine whether or not the incidence of incomplete reporting of partial seizures differs by treatment assignment. We also seek assurance that similar under-reporting did not occur in M91-605 and M92-775; accordingly, please conduct a similar analysis for these two trials. Should under-reporting be either extensive or differentially associated with one treatment, further analyses may be required.

Redacted 1

page(s) of trade secret and/or confidential commercial information

2. Warnings section

a) Withdrawal Seizures

Before this section can be revised, considerable additional work must be completed. In particular, we need to know precisely the number and kind of seizure events that occurred when treatment was withdrawn in study M91-603. As discussed earlier in our comments pertaining to the partial seizure claim, your method of classifying seizures in the NDA was based upon the unjustified assumption that all generalized seizures had a partial onset. In addition, you failed to enumerate, during the withdrawal period of study M91-603, any seizure type that was not required for entering the trial (e.g., absence seizures, myoclonic seizures).

Accordingly, please enumerate each seizure type observed in the withdrawal phase. For each patient, record whether and, if so, how often each seizure type occurred during the withdrawal and baseline phases. Then, by seizure type and treatment, report the number of individual patients who had a change in seizure frequency (either increased, decreased, or no change). Our goal is to construct a table of the following kind which shows the shift in seizure frequency. In this instance, seizure frequency should be compared in terms of seizure frequency per 28 days adjusted for days at actual risk both the baseline and the withdrawal period. In preparing this table, we ask that you compare seizure rates in the withdrawal period for each of its four weeks. If the rates across these four weeks are more or less uniform (i.e., show no time dependent interval hazard), the table can be constructed using the overall rate for the full four weeks of the withdrawal. If, however, the hazard reveals a time dependency, we will have to explore with you the best way to present this information.

	Rx 1			Rx 2		
Sx type	Decrease	No change	Increase	Decrease	No change	Increase
GTC						
PS						
CPS						
Etc.						

b) Alterations in Mental Status

Alterations in mental status, some so severe as to require discontinuation of tiagabine treatment, have been reported in association with its use. The actual incidence of clinically important mental status changes is unknown, but your ISS implies that as many as 425, perhaps more, of the some 2500 patients treated with tiagabine might have had a change in mental status. Accordingly, Gabitril™ product labeling must describe and discuss the differential diagnosis of tiagabine associated mental status changes in a Warnings Statement.

The Warnings statement we seek should enumerate, using clinically meaningful terminology, the kinds of mental status change that have been observed, their incidence, and the pathogenetic mechanisms that may be responsible for them (e.g., delirium, stupor, absence seizures, etc.). Mechanism is of particular importance because the management of a drug induced untoward event may depend upon it (e.g., excess sedation may require only reduction in the dose of drug administered; absence seizures may require the addition of another AED)

Unfortunately, the clinical information provided in the reports made to the NDA is unlikely to be adequate to allow the construction of the kind of Warnings statement that we believe is essential to the prudent and safe use of Gabitril™.

The terms employed to describe mental status changes in the reports made to the NDA are often ambiguous and vague. The usage of some reporting terms is almost idiosyncratic. For example, multiple patients are reported as having aphasia, a term ordinarily used to describe a disorder of language arising as a consequence of focal, structural neurological injury; accordingly, we do not understand why it has been used to describe what we take to be reversible mental status changes. Similarly, other reports describe mental status changes in ways that provide little insight as to their actual nature. (e.g., confusion, thinking abnormal, psychosis, etc.).

Accordingly, as an initial step, you need to identify any patient who has suffered any kind of mental status change. Your search of the database should not be based on the restricted set of COSTART terms that you used to identify the cohort of 425 patients that you evaluated in an effort to uncover cases of absence seizures, but should be based on all terms that might possibly identify a patient with a mental status change.

Once these cases are identified, you will need to characterize, in clinically understandable terms, the mental status changes affecting them. While it is possible that you may be able to perform this classification using case report forms currently in your possession, the task may well require you to interview the original source (i.e., the clinical reporter) to ascertain the true nature and characteristics of the events (i.e., course, severity, outcome) in question.

Determining the source, kind and quality of evidence used to classify patients with putative mental status changes is an important part of the task, especially in regard to the goal of identifying the mechanism or mechanisms through which tiagabine might have caused these changes.

In particular, you will need to ascertain and report to us about the extent to which individuals with mental status changes were evaluated for the presence of absence seizures. Our interest in absence seizures is, as noted, heightened because their management may differ from that of mental status change induced by other mechanisms, e.g., CNS depression (the former might require a new antiepileptic drug; the latter a dosage reduction).

We are particularly concerned that many more of the patients than the 9 cases you identified might have had absence seizures (i.e, patients with seizures might have been mistakenly classified as cases of stupor, confusion, coma, aphasia, etc.)

Accordingly, you need to document, in more detail than in your initial submission, the strategies, methods and procedures you used to identify, evaluate, and classify individual patients presenting with mental status changes. For example, the 9 patients with spike-wave EEG changes appear to have been identified only because they were reported, as such, by 5 investigators. Your staff was evidently concerned that other patients with mental status changes might have had absence seizures. The NDA did not make clear, however, how this possibility was assessed.

3. Description and How Supplied Sections

Please note that we have not included in labeling a description of the 20 mg tablet. As you know, the lack of strict bioequivalence between a 20 mg single dose given with 5, 4 mg tablets used in the clinical trials and the proposed 20 mg tablet (specifically, the latter results in a greater C_{max} than the former) raises concerns about the safety of this proposed tablet strength. We have not found the information you have submitted to establish the safety of the 20 mg tablet compelling and, accordingly, we cannot approve the 20 mg tablet dosage strength at this time. We note your intention to perform an additional bioequivalence study with these formulations in the fasted state. As you see, we have permitted the lower dosage strengths.

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

In addition to the issues noted above, we have the following additional requests.

Chemistry, Manufacturing and Controls

Biopharmaceutics

We ask that the following final dissolution methodology and specification be adopted for Gabitril™ tablets:

Apparatus:
Agitation:
Medium:
Profile Times:
Assay:
Specification:

Prospective Pregnancy Registry

We urge that you create and maintain a registry of women who were exposed to tiagabine during their pregnancy. The value of this registry lies primarily in its capacity to prospectively enroll registrants before they are aware of fetal outcome. Our staff will be happy to discuss with you the specific design elements of this registry.

Pediatric Studies

We strongly urge you to perform adequate and well controlled investigations in children with epilepsy at the earliest possible time. Our staff would be happy to discuss appropriate study methodologies with you.

Safety Update

Under 21 CFR 314.50(d)(5)(vi)(*b*), we request that you update your NDA by submitting all safety information you now have regarding your new drug. Please provide updated information as listed below:

1. Retabulate all safety data including results of trials that were still ongoing at the time of NDA submission. The tabulation can take the same form as in your initial submission. Tables comparing adverse reactions at the time the NDA was submitted vs now will greatly facilitate review.

2. Retabulate drop-outs with new drop-outs identified. Discuss, if appropriate.

3. Provide details of any significant changes or findings, if any.

4. Summarize worldwide experience on the safety of this drug.

5. Submit case report forms for each patient who died during a clinical study or who did not complete a study because of an adverse event.

Please also update the new drug application with respect to reports of relevant safety information, including all deaths and any adverse events that led to discontinuation of the drug and any information suggesting a substantial difference in the rate of occurrence of common but less serious adverse events. The update should cover all studies and uses of the drug including: (1) those involving indications not being sought in the present submission, (2) other dosage forms, and (3) other dose levels, etc.

Other

Also, 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

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 your other options under 21 CFR 314.110. In the absence of such action FDA may take action to withdraw the application.

The drug may not be legally marketed until you have been notified in writing that the application is approved.

Should you have any questions, please contact: Jacqueline H. Ware, Pharm.D.
Project Manager
Telephone: (301) 594-5526

Sincerely yours,

10/31/96

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

attachment(1)

cc: Original NDA 20-646
HFD-120/Div. Files
HFD-2/M.Lumpkin
HFD-8092
HFD-120/JWare
HFD-120/Leber/Katz/McCormick/Burkhart/Balian
HFD-120/Fitzgerald/Fisher
HFD-120/Blum/Rzeszotarski
HFD-860/Mahmood/Hossain
HFD-710/Chi/Sahlroot
HFD-101/L.Carter
DISTRICT OFFICE
HFD-40/DDMAC (with draft labeling)
HFD-560/D.Bowen (with labeling - for OTC Drug Products Only)

drafted: JHW/September 13, 1996/tiagael1
edit: 9/30/96;10/3/96; 10/22/96
Final: 10/22/96

APPROVABLE (AE)
New NDA