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