SECTION 7.2.5 STUDY M90-481

SECTION 7.2.5.1 PROTOCOL SYNOPSIS

TITLE Phase II Study of Tiagabine: Efficacy and Safety in Adjunctive Treatment of Partial Seizures

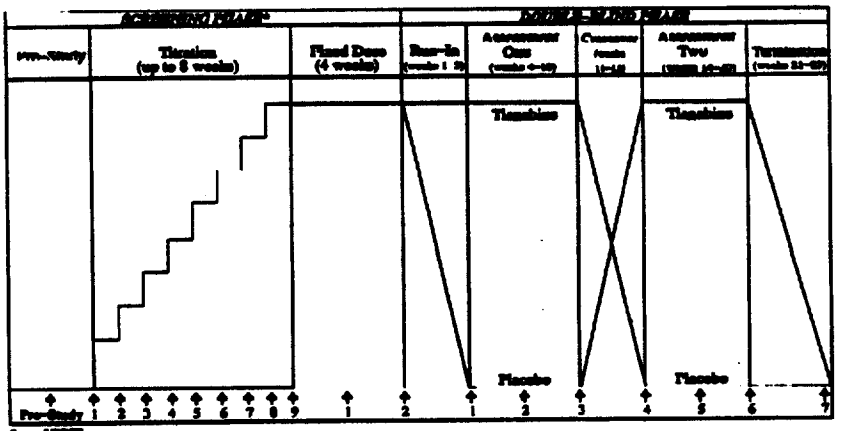
OBJECTIVE

The objective of this study is to determine the safety and efficacy of tiagabine as therapy for complex partial seizures when it is used in combination with other antiepileptic drugs.

STUDY DESIGN

This is a multicenter (6) double-blind, placebo-controlled, fixed-dose, balanced, two-period crossover antiepileptic drug trial following an enrichment design.

STUDY SCHEMATIC



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* NOTE: The Termination Period of 2 weeks length which ended the Screening Phase for patients who prematurely discontinued or who failed to meet the criteria for randomization is not shown

Figure 1. Study Schematic: Safety and Efficacy of Tiagabine HCl as Adjunctive Treatment for Complex Partial Seizures

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PROTOCOL

Enrollment

Patients with complex partial seizures with or without secondary generalization are recruited for this trial. Planned is recruitment of 100 patients from 4-6 centers to permit randomization of approximately 60 patients into the Double-Blind Phase. Patient assignment to treatment sequence groups during the Double-Blind Phase is random and balanced (1:1) within each study center.

Inclusion Criteria

- **Diagnosis of complex partial epilepsy.** This diagnosis must be supported by: Observed ictal events consistent with complex partial seizures that are documented by reliable observers such as family members, friends, or medical personnel and,
  One of the next two:

--An ictal EEG demonstrating a focal abnormality in a patient clinically having a complex partial seizure.
--An interictal EEG demonstrating unilateral or bilateral asynchronous activity consistent with complex partial seizures.
Or in the absence of a demonstrable EEG abnormality as defined above:
CT or MRI evidence of a focal CNS lesion consistent with complex partial seizures.

- Frequency of at least 6 complex partial seizures occurring alone or in combination with any other seizure types within the 8-week period preceding Prestudy Visit P1.
- Stable regimen of between 1 and 3 of the following antiepileptic drugs: phenytoin, carbamazepine, phenobarbital, primidone, clobazam, clonazepam, oxcarbazepine, valproate or vigabatrin. (Vigabatrin and oxcarbazepine are only acceptable in countries where regulatory approval has been received.)

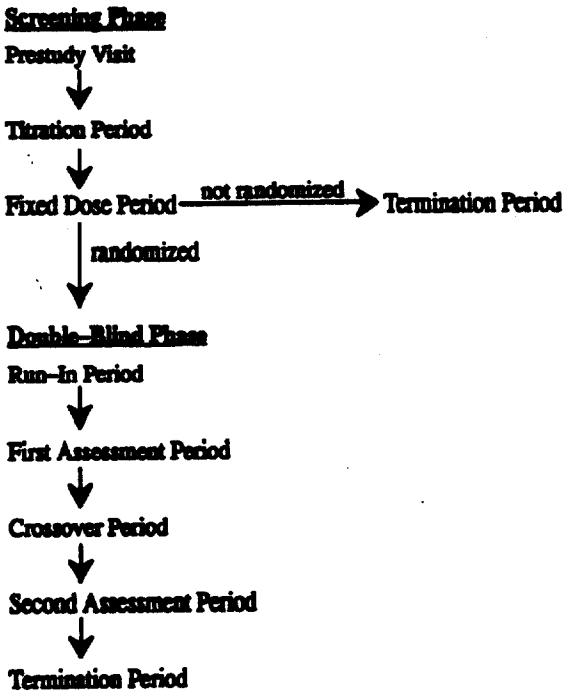
Exclusion Criteria

- Pseudoseizures,active CNS infection, demyelinating disease, degenerative neurologic disease, or any progressive CNS disease that may confound interpretation of the study results.
- Medical disease manifesting with signs and symptoms that may confound interpretation of the study results or a medical or neurological disorder requiring frequent changes in medication (including dosage changes, clinically significant illness within the previous three months.
- Patients taking concomitant non-antiepileptic medications which may confound interpretation of the study results.
- Patients who have taken an investigational drug (excluding tiagabine) either within the 30 days of the commencement of the 8-week baseline period or between the baseline period and the start of dosing with tiagabine.
- Patients with a history of clinically significant psychiatric illness, psychological or behavioral problems.

SCHEDULE The study consists of a screening phase and a double blind phase. Eligible patients enter the **open label Titration Period** in which tiagabine is administered in gradually increasing doses (8-52 mg/day). Dose escalation continues until patients either show a clear reduction in seizure frequency or develop unacceptable adverse events. Thereafter the dosage of tiagabine will be held as constant as possible during the **open label Fixed Dose Period.** Patients who experience a 25% reduction in their total seizure frequency and who require no changes in the total daily dose of their concomitant antiepileptic drugs, and who adequately tolerated tiagabine in the Screening Phase enter the Double-Blind Phase.

The **Double-Blind Phase** of the study has a placebo controlled, fixed-dose, two-period crossover design. When patients enter this phase they are randomized (1:1) to two different sequences of drug administration: placebo-tiagabine or tiagabine-placebo. The dose of study drug will be selected by the investigator, individualized for each patient, and based on the information collected for that patient during the Screening Phase. In the Double-Blind Phase, study drug dosing will be held constant during the Assessment Periods. Run-in, Cross-over, and Termination Periods are also included to permit gradual introduction and withdrawal of potentially active study drug. Efficacy will be determined by comparing the **complex partial seizure** frequencies during tiagabine and placebo Assessment Periods.

STUDY SEQUENCE



STATISTICAL METHODS

All tests will be two-tailed and a Type I error rate of 0.05 will be used throughout.

Efficacy Analyses -- Double Blind Phase

Seizure occurrences during the First and Second Assessment Periods will be used for the efficacy analyses comparing add-on tiagabine and add-on placebo treatments. The primary efficacy variable will be the weekly complex partial seizure frequency calculated from seizures which occurred during an assessment period (see explanation below). Complex partial seizures occurring alone or in combination with any other seizure types will be included to calculate their seizure frequency.

Methods for Analyses

The primary efficacy analysis will be a nonparametric analysis of the weekly complex partial seizure frequency for two-period crossover studies and application of it to multi-center studies using the van Elteren method.

Seizure Frequency Calculation

This calculation method is identical to study M92-565.

Additional Analyses

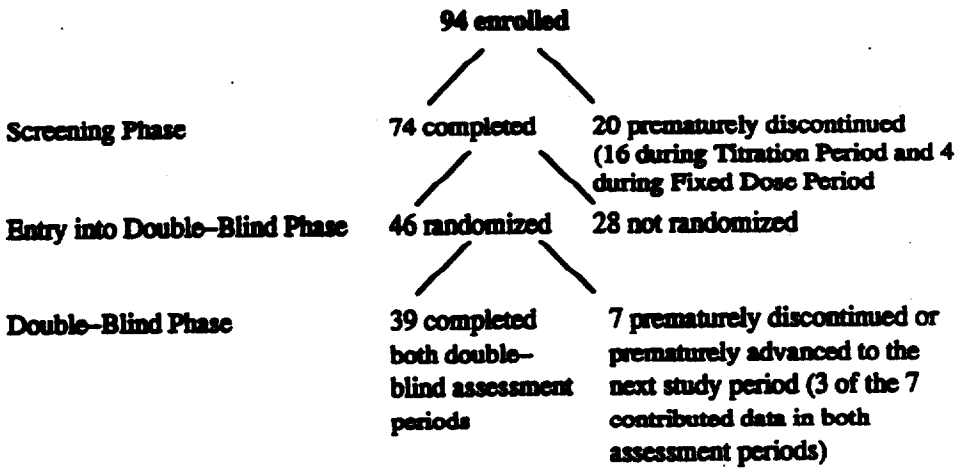
Efficacy analyses will also be performed for seizure types other than complex partial

seizures. The analysis for a particular seizure type will include patients who had at least one seizure of that type during either the Screening Phase or the Double-Blind Phase.

SECTION 7.2.5.2 STUDY CONDUCT

Tiagabine HCl was administered in gradually increasing doses by the protocol from 8 mg/day to a maximum of 52 mg/day during the open label phase. Dose escalation continued until patients showed either a clear reduction in seizure frequency or unacceptable side effects. Then the doses of tiagabine were maintained without change during the 4-week Fixed dose (open label) period. Qualified patients (25% reduction in seizures compared to an historical baseline) were randomized to receive one of two treatment sequences, either tiagabine/placebo or placebo/tiagabine during assessment periods 1 and 2.

Ninety four patients were enrolled in this study and all received tiagabine HCl.There were 74 patients who completed the fixed dose period and of these 46 entered the Double Blind phase. The following is an overall summary of patient disposition.



PREMATURE CROSSOVER

In this study patients who had a clear, sustained increase in seizure frequency were allowed to prematurely crossover from Assessment Period 1 to Assessment period 2. This practice only affected one patient who had been randomized to the P/T sequence.

DEMOGRAPHICS AND PATIENT CHARACTERISTICS

The sponsor obtained data on patient demographics and disease characteristics in this study. The mean age for all patients enrolled was 36.7 years (range 19-71). Sixty one (65%) of the patients were male and all patients were Caucasian.The mean number of years with epilepsy for all patients were 24.5 years, and the mean number of AEDs ever taken was 7 (median also 7, range 1-7). The most common epilepsy etiologies in the 94 patients screened was idiopathic. In addition to

complex partial seizures, 54% of the enrolled patients were reported to have experienced tonic clonic seizures and 26% to have experienced simple partial seizures in the 8 weeks prior to screening. The sponsor notes that in some instances the seizure description suggested that the complex partial seizure was preceded by a simple partial seizure but it was coded only as a complex partial seizure by the investigator (i.e., patients 5006, 5007, 5009, 5026, 4007, 4008, 4001, 4015,6011, 6013,6018, 6025, 6027, 6014, 6016, and 6024). There will be more discussion of seizure classification presently.

MEDICATIONS

This study permitted daily doses up to a maximum of 52 mg; The average total daily dose during the Double-Blind Phase was 33.4 mg (0.46 mg/kg) (ranges = 12-52 mg and 0.15-0.82 mg/kg, respectively). See following table for distribution.

DOUBLE BLIND PHASE STUDY DRUG ADMINISTRATION		
	Randomized Pt dataset N=46	Intent to treat dataset N=42
TDD (mg) Mean(SD)	33.4 (11.9)	34.8 (11.43)
Range	12-52	20-52
Distribution		
12	1	0
16	1	0
20	5	5
24	11	9
32*	12	12
40	6	6
52	10	10

*median TTD of Tiagabine for the DB phase was 32 mg.

CONCOMITANT AEDS

Thirty-four (74%) of the 46 randomized patients were taking carbamazepine prior to entering and throughout the study; seven (15%) were on carbamazepine monotherapy, and 27 (59%) were on carbamazepine in combination with other AEDs. The next most common concomitant AEDs, as monotherapy or polytherapy, were vigabatrin (30%), phenytoin (24%), and valproate (22%). The most common concomitant AED polytherapy combinations were carbamazepine and vigabatrin (13%) and carbamazepine and phenytoin (9%).

Concomitant AED plasma concentrations, expressed as the percent of the Fixed Dose Period average concentration, from samples collected at the Week 3 and Week 7 evaluations of the First and Second Assessment Periods were calculated for the intent-to-treat dataset. Analyses for carbamazepine, phenytoin, valproate and vigabatrin showed no statistically significant treatment differences in the plasma concentrations of carbamazepine, phenytoin (at Week 7), valproate and vigabatrin or in the time since the previous dose for any of the four concomitant AEDs. A treatment difference of 18.5% (p = 0.049) was noted in phenytoin plasma concentrations at Week 3, in that phenytoin concentrations compared to the Fixed Dose Period average concentrations were 15.9%

higher in the tiagabine HCl treatment period and 2.6% lower in the placebo treatment period.

PROTOCOL VIOLATIONS

Adherence to the protocol was largely the rule, however, there were some notable deviations. These included change in doses of concomitant AEDs, use of prn antiepileptics for increased seizure activity, errors in randomization and failure in counting of seizures.

CONCOMITANT AEDS AND DEVICES

For most patients the total daily dose of concomitant AEDs remained constant for patients throughout the Double-Blind Phase. However, patient 4018 took a reduced dose of carbamazepine during the placebo phase for 9 days, resuming the original dose prior to the end of the Assessment Phase.

In addition, five patients took diazepam and one patient took paraldehyde for acute treatment of seizures in addition to their stable concomitant AED regimens during assessment periods 1 and 2. Details of the additional AED usage are summarized below:

DIAZEPAM USE DURING ASSESSMENT PERIODS 1 AND 2●
(NUMBER OF DAYS)

PATIENT	TIAGABINE HCL	PLACEBO
4002	12	16
4010	3	36
4011	NONE	1*
4015	1	NONE
4021	5	3

●All treatment periods for these patients were 49 days, except for Patient 4010 whose placebo treatment period was 47 days.
*Patient also received paraldehyde on this day.

Except for Patient 4010, whose diazepam usage was longer during placebo (36 days) than tiagabine HCl treatment (3 days), additional concomitant AED usage appeared to be similar across the two treatment periods.

ERRORS IN RANDOMIZATION:

One patient (4018) received the wrong number and while he should have been randomized to tiagabine-placebo sequence, in fact received the placebo tiagabine sequence. According to the General Comments Patient 9005 was also given the wrong sequence--that intended for 9006.

FAILURE IN COUNTING SEIZURES :

Cases of *status epilepticus* were excluded from all seizure rate calculations due to difficulty in assigning a specific seizure count to them. Fortunately none of the episodes of *status epilepticus* occurred during the assessment periods.

There were four patients who failed to provide seizure counts during either or both assessment periods. (Patients 5015, 7010, 6025, and 7004) .

PATIENTS LACKING SEIZURE COUNTS DURING ASSESSMENT PERIODS

PID	PBO	TGB
5015*	14 days	0
7004*	49 days	0
4005	49 days	5 days
6006	49 days	15 days
	TGB	PBO
7010*	50	0
6125*	0	0

*Not included in sponsor's ITT dataset

Those patients who had no seizure data during the second period were excluded from the intent to treat population.

SECTION 7.2.5.3 SPONSOR'S RESULTS

The sponsor's efficacy results for this study will be summarized in the following format:

(1)COMPLEX PARTIAL SEIZURES:. 4- WEEK SEIZURE RATE DURING AN ASSESSMENT PERIOD.

(2)ALL PARTIAL ONSET SEIZURES: 4-WEEK PARTIAL ONSET SEIZURE RATE

(3) TONIC CLONIC SEIZURES, : 4-WEEK PARTIAL ONSET SEIZURE RATE DURING AN ASSESSMENT PERIOD.

(1) COMPLEX PARTIAL SEIZURES:. 4- WEEK SEIZURE RATE DURING AN ASSESSMENT PERIOD. The primary efficacy variable was the weekly (here converted to 4-week) **complex partial seizure** rate during an Assessment Period. Patients in the intent-to-treat dataset experienced a median 1.8 fewer (mean = 3.1 fewer) complex partial seizures per 4 weeks while receiving tiagabine HCl than while receiving placebo as shown in the following table.

	TiagabineHCl	Placebo	Tiagabine HCl Minus Placebo Treatment Difference	
Median	6.3	9.1	-1.8	p=.054
Mean	3.5(19.28)	16.6(24.02)	-3.1(10.88)	

The weighted treatment comparison for the nonparametric analysis favored tiagabine HCl and was nearly statistically significant ($p = 0.054$). The unweighted treatment comparison for the nonparametric analysis and the weighted and unweighted treatment comparisons of the parametric analysis favored tiagabine HCl and were all statistically significant ($p \leq 0.008$).

A statistically significant investigator by treatment interaction in square-root transformed complex partial seizure rates indicated that the mean 4-week treatment differences were not consistent across investigators, however, as shown below:

		Tiagabine HCl Minus Placebo Treatment Difference	
Investigator	Number of Patients	Median	Mean (SD)
Chadwick	6	-3.6	-4.7 (4.13)
Dam	6	-3.4	-7.8 (11.66)
Duncan	12	0.9	2.4 (6.44)
Morrow	4	-7.7	-17.7 (24.36)
Richens	14	-1.7	-1.1 (5.77)

Investigators Chadwick, Dam, Morrow and Richens showed lower mean 4-week seizure rates for tiagabine HCl than for placebo, while Investigator Duncan showed a slightly higher mean 4-week seizure rate for tiagabine HCl than for placebo.

The 4-week complex partial seizure rate during the tiagabine HCl treatment period was expressed as a percent reduction from the placebo treatment period rate for each patient. Eleven (26%) of the 42 patients in the intent-to-treat dataset experienced a reduction of 50% or more.

(2) ALL PARTIAL ONSET SEIZURES: 4-WEEK PARTIAL ONSET SEIZURE RATE

The 4-week partial onset seizure rate during an Assessment Period was considered a secondary efficacy variable. Patients in the intent-to-treat dataset experienced a median 1.8 fewer (mean = 2.4 fewer) partial seizures per 4 weeks while receiving tiagabine HCl than while receiving placebo as shown in the following table.

N= 42	Tiagabine HCl		Placebo		Tiagabine HCl Minus Placebo Treatment Difference	
Median	6.31		0.3		-1.8	p≤.018
Mean	17.4	(36.5)	19.8	(30.04)	2.4(18.11)	

Both the weighted and unweighted treatment comparisons were statistically significant ($p \leq 0.018$) and favored tiagabine HCl in the nonparametric and parametric analyses.

(3) TONIC CLONIC SEIZURES, : 4-WEEK PARTIAL ONSET SEIZURE RATE DURING AN ASSESSMENT PERIOD.

Another secondary efficacy variable was the 4-week tonic clonic seizure rate during an Assessment Period. Patients in the intent-to-treat dataset who experienced at least one seizure with a tonic clonic component during the study (n = 27) experienced a median 1.0 fewer (mean = 4.2 fewer) tonic clonic seizures per 4 weeks while receiving tiagabine HCl than while receiving placebo.

N=27	Tiagabine HCl		PBO	Tiagabine HCl Minus Placebo Treatment Difference		
Median	1.1		2.3		-1.0	p=.009†
Mean(SD)	3.7	8.35	7.9	19.56	-4.2(11.7)	

†nonparemetric analysis

The treatment comparison was statistically significant in favor of tiagabine HCl in both the nonparametric (p = 0.009) and parametric (p = 0.009) analyses.

The 4-week tonic clonic seizure rate during the tiagabine HCl treatment period was expressed as a percent reduction from the placebo treatment period rate for each patient. Seventeen (63%) of the 27 patients in the intent-to-treat dataset experienced a reduction of 50% or more.

SECTION 7.2.5.4. FDA ANALYSIS

The methodological problems described for study M92-565 particularly with regard to blinding and possible withdrawal effects apply to this study also, which is an identical design. (Please refer to the previous study for comments)

ANALYSIS OF CARRYOVER EFFECT: An analysis of carryover effect was conducted by Dr.Sahlroot for this study. (Please refer to the statistical review)). The results indicated no statistically significant carryover effect for either period for the main seizure types analyzed. This was true for both parametric and nonparametric tests on the primary efficacy variable.

ANALYSIS OF MISSING DATA: As noted there were 4 patients who did not contribute data for at least one Assessment Period of this trial. Of these three patients had some data.

Patients with Data missing during one or both Assessment Periods		
Patient	Assessment Period with missing data	Treatment
5015	2	tiagabine
7004	2	tiagabine
7010	2	placebo

The approach to these was not to exclude them from the ITT dataset as the sponsor has done, but rather to incorporate these into the analyses by imputing seizure rates for the missing assessment period. The patient with data missing from both Assessment Periods was not used. The median seizure rates by seizure type were determined using the se of all patients with data. The appropriate median seizure rates were then imputed for each patient with missing data. The p-values for trial M90-481 were .031 for complex partial seizures and 0.027 for all partial onset seizures combined.

In addition to this, worst case analyses were also done , using "0" for missing placebo rates and an arbitrarily large number for missing tiagabine seizure rates. For these analyses, p-values were not significant (p>.25).

ANALYSIS OF THE EFFECT OF ELEVATED PHENYTOIN LEVELS
While there was no evidence for a Tiagabine-Phenytoin interaction based on the drug interaction studies which were conducted independently, the AED trough plasma level data in this study indicated that in one of the tiagabine treated periods there appeared to be a statistically significant increase in phenytoin levels compared to placebo phase (18%). Eleven patients received phenytoin during this study. While it was not necessarily assumed to be the result of a drug-drug interaction, the effect of these elevated levels on the overall demonstration of efficacy in this trial was examined. The effect was noted only during Assessment Period 3 . Week 7 data indicated only a 1% increase in PHT concentrations.

Mean seizure rate reductions (placebo rate minus tiagabine rate)was 1.7 for PHT treated patients and 1.84 for patients not receiving phenytoin. It is assumed that this elevation occurring only during one period of the study had any effect on the outcome.

DISCUSSION
This was a small double blind crossover trial evaluating Tiagabine in the adjunctive treatment of Partial Complex seizures. In this study the median dose achieved was 32 mg. Results on the for all Partial Onset Seizures (combined) were statistically significant but did not hod up to the analyses for missing data. The results were not significant for the primary outcome measure, partial complex seizures (p=0.054) using the weighted vanElteren test. Tests for carryover effects were negative and imputed seizure rates for dropouts provided some assurance that the dropouts did not unduly influence the results.

As pointed out , flaws in the conduct of this trial may have contributed to the small differences seen between treatment groups. Certainly the trend to treat seizures with additional medication as they increase in frequency could be responsible for reducing the difference between treatment groups.

SECTION 7.2.6 STUDY 93-090

SECTION 7.2.6.1 PROTOCOL SYNOPSIS

TITLE: The safety and Efficacy of Tiagabine HCl Monotherapy in the Treatment of Partial Seizures: High Dose versus Low Dose.

OBJECTIVE:to evaluate the efficacy and safety of two dosage levels of tiagabine when administered as monotherapy treatment for patients with partial epilepsy. The safety and efficacy of tiagabine 36 mg/day was compared to tiagabine 6 mg/day.

STUDY DESIGN: This is a multicenter, double-blind, randomized, parallel group, study in patients with complex partial with or without secondarily generalized tonic-clonic seizures.

ENROLLMENT

Approximately 120 patients were projected for randomization to each treatment group, thus requiring that approximately 275 patients be enrolled at approximately 35 centers. The patients were to be randomized in a 1:1 ratio to either the high or low dose tiagabine HCl within each center.

Key Inclusion Criteria

•Diagnosis of **complex partial seizures with or without secondary generalization.** Complex partial seizures may occur alone or in combination with simple partial and/or secondary generalized tonic clonic seizures. This diagnosis must be supported by the following:

•Observed ictal events consistent with complex partial seizures with or without secondary generalization that are documented by reliable observers such as family members, friends, or medical personnel and,

and at least one of the next two:

•An ictal EEG at some time in the past demonstrating a focal or localized ictal pattern either at the beginning of the seizure or throughout the seizure, in a patient clinically having a complex partial seizure with or without secondary generalization.

•An interictal EEG at some time in the past demonstrating focal abnormalities (spikes, sharp waves, slowing) consistent with complex partial seizures.

•A least 4 complex partial seizures occurring alone or in combination with any other seizure types within the 8-week period preceding the screening visit. Each of the two 4-week periods must contain at least one complex partial seizure.

•Stable regimen of one U.S. marketed antiepileptic medication.

•Ability to maintain an accurate seizure diary.

• CT scan or MRI of the brain performed since being diagnosed with epilepsy.

Key Exclusion Criteria

•Pseudoseizures within the past 6 months.

•History of status epilepticus.

•Active CNS infection, demyelinating disease, degenerative neurologic disease, or any progressive CNS disease that may confound interpretation of the study results or any medical or neurological disorder requiring frequent changes in medication (including dosage changes).

•Substance Abuse

•Patients who have previously participated in a tiagabine HCl study and received at least one dose of study drug or who have taken a non-U.S. marketed (investigational) drug within 30 days prior to the Screening Visit.

•Significant psychiatric illness, psychological or behavioral problem, including active psychosis or suicidal ideation which would interfere with their ability to participate in the study.

Study Schedule

The study will consist of two phases: an 8-week **prospective Baseline Phase** including a Screening Visit and a 21-week Double-Blind Phase.Patients meeting entry criteria will be required to maintain an accurate seizure diary throughout the study. During the Baseline Phase, the daily dose of the concomitant AED will be maintained. Upon

completion of the Baseline Phase, patients with at least four **complex partial seizures** (include seizures with a complex partial component) with at least on in each of 4-week period will be advanced to the Double Blind Phase. Upon entering the Double-Blind Phase, eligible patients will be randomized to receive either 36 mg or 6 mg tiagabine HCl per day.

The first six weeks of the Double-Blind Phase comprise the Titration Period. After the second week of the Titration Period patients I begin tapering off of their baseline AED to achieve tiagabine HCl monotherapy (total of four weeks). The next 12weeks comprise the Fixed Dose Period during which the patient receives a constant dose (high or low) of tiagabine HCl alone.

STUDY DRUG ADMINISTRATION: Patients will take tiagabine HCl with food three times per day, (with at least six hours separating each dose); this will be reinforced with written instructions.

Efficacy Analyses

The primary efficacy variable for comparing the high dose and low dose of tiagabine treatments will be the reduction from Baseline Period to Experiment Period (the combined interval of the Titration Period and Fixed-Dose Period) in 4-week **complex partial seizure rates**. Complex partial seizures occurring alone or in combination with any other seizure types will be used to calculate this rate. The comparison of high dose and low dose groups will use both parametric and nonparametric methods. In addition, the reduction in 4-week complex partial seizure rate from Baseline Period to Experiment Period excluding the first six weeks of the period will be compared for the high dose and low dose groups.

Analysis Method

The van Eltern, a nonparametric method which extends the use of the Wilcoxon two-sample test to the multicenter case, will be the primary analysis method.

SECTION 7.2.6.2 STUDY CONDUCT

This randomized, double-blind, parallel-group trial of high-dose (36 mg/day) versus low-dose (6 mg/day) tiagabine monotherapy was conducted at 22 centers throughout the United States. The trial was in general conducted in a manner consistent with the design of the protocol.

PATIENT ACCOUNTABILITY:

One hundred ninety-eight patients (198) entered the Double-Blind Phase of the study. Of these 198 patients, 102 were randomized to receive tiagabine 6 mg/day and 96 were randomized to receive tiagabine 36 mg/day. Fifty-seven (57) patients (29%) completed the study (34 in the 6 mg/day group and 23 in the 36 mg/day group). Of the 141 patients prematurely discontinued from the study, 79 (40%) discontinued during the Titration Period (34 in the 6 mg/day group and 45 in the 36 mg/day group), 57 (29%) discontinued during the Fixed-Dose Period (29 in the 6 mg/day group and 28 in the 36 mg/day group), and 5 (3%) discontinued during the Termination Period (5 in the 6 mg/day group and none in the 36 mg/day group). The discontiuations due to lack of efficacy were approximately equal in both treatment groups and accounted for about half of the droupouts. The remainder were due to adverse events (46%) personal, and other.

SECTION 7.2.6.2 SPONSOR'S RESULTS

There was no statistically significant difference between the two groups in the median four-week complex partial seizure rates in the intent-to-treat (ITT) dataset.

There were no statistically significant differences between the two treatment groups in the median four-week seizure rates for simple partial, secondarily generalized tonic-clonic, or combined partial seizures.

Further, a high rate of premature patient discontinuation from the study precluded an appropriate comparison of efficacy between the 6 mg/day and 36 mg/day monotherapy dosage regimens.

Summary : By the sponsor's admission this study did not successfully demonstrate efficacy of tiagabine 36 mg monotherapy in the treatment of Partial seizures. Therefore the FDA did not conduct an independent analysis of the data.

SECTION 7.2.7 STUDY M90-511

SECTION 7.2.7.1 PROTOCOL SYNOPSIS AND STUDY CONDUCT

TITLE: Safety And Efficacy Of Tiagabine HCl Monotherapy For The Inpatient Treatment Of Complex Partial Seizures: A Placebo-controlled Study

OBJECTIVE: This study was designed to obtain information on the safety and efficacy of tiagabine HCl monotherapy administration for the treatment of complex partial seizures.

The study was conducted as an inpatient, single center, randomized, double-blind, placebo-controlled, parallel-group antiepilepsy drug trial. Patients with difficult to control complex partial seizures undergoing evaluation for epilepsy surgery were enrolled. The study was intended as the initial tiagabine HCl monotherapy study in the clinical development program.

The study consisted of an Open Phase, a Double-Blind Phase, and a Washout Phase. Eligible patients were admitted to the hospital and remained there for the duration of the study. Following admission to the hospital, patients entered a 7-day Double-Blind Phase and were dosed every 4 hours with tiagabine HCl or matching placebo. Patients were assigned to one of two strata, those with and without a history of convulsive status epilepticus. Within each stratum, the treatment assignment was balanced (1:1) between placebo and tiagabine HCl. Concurrent marketed antiepilepsy drugs (AEDs) were abruptly discontinued with the start of study medication. Study medication was discontinued on Day 8.

The protocol specified that patients had the right to withdraw from the study at any time. The protocol further specified that patients may be prematurely discontinued from the

study if they met any of the following criteria for convulsive (generalized tonic-clonic) seizures during the study:

- Convulsive status epilepticus.
- Three convulsive seizures within any 24 hour period.*
- Two convulsive seizures within any 3 hour period.*

* (Includes only those occurring after initiation of the first dose of study medication).

The protocol also specified that patients be discontinued from the study if they met the following criteria for total frequency of clinically important seizures compared to their baseline rate:

Baseline Rate (seizures/day)[a]	Criteria for Premature Discontinuation	
	(seizures/day)[b]	(seizures/48 hours)[b,c]
≤ 0.25	> 4.0	> 5.0
> 0.25 to ≤ 0.50	> 5.0	> 7.0
0.50 to ≤ 1.00	> 6.0	> 8.0
> 1.00	≥ 6 x baseline rate	≥ 4 x baseline rate

[a]The baseline rate was calculated by the following formula:

A/28=

A=Number of clinically important seizures of all types in the 28 days preceding Day 1 (including the time preceding the initiation of study medication dosing on Day 1).

[b] Seizures/day were determined at 1000 hours on Days 2-8 by determining the total number of clinically important seizures in the preceding 24 or 48 hours, respectively.

[c] If the patient's seizure rate was decreasing in second 24 hrs. compared to first 24 hrs. in the 48 hr. period being considered, the patient could be continued in the study, even if seizure rates exceeded those listed.

Eleven patients were enrolled into the study and received study medication. One of the eleven patients had a history of convulsive status epilepticus and received tiagabine HCl. A total of seven patients received tiagabine HCl and four patients received placebo.

Three patients, all from the tiagabine HCl group, completed the study. The remaining eight patients were prematurely discontinued from the study. Of the eight patients, six patients (2 tiagabine, 4 placebo) prematurely discontinued for protocol-prescribed escape criteria; two patients (tiagabine) prematurely discontinued for adverse events.

Efficacy analyses planned in the protocol were not performed because of the small number of patients enrolled in the study, since the statistical power for demonstration of efficacy was calculated on the basis of enrollment of 40 patients.

Tiagabine HCl monotherapy was administered (every 4 hours in gradually increasing doses) to epilepsy patients with difficult to control partial seizures. Only three patients were able to complete this study. The sponsor's conclusion that tiagabine monotherapy

SECTION 7.2.8 SUMMARY OF EFFICACY FINDINGS

The sponsor's claims will be addressed below.

Tiagabine is effective the adjunctive treatment of partial seizures with and without secondary generalization.

The sponsor has made the claim that Tiagabine is effective as adjunctive therapy in the treatment of partial onset seizures (POS) at doses in the range of 32 to 56 mg daily given as BID, TID, or QID dosing regimens. The tables (Tables 1 and 2) on the following page summarize the studies which support this claim (highlighted). Studiy M91-603 supports the sponsor's claim that 32 and 56 mg are effective in the adjunctive therapy of POS. The results of study M91-605 and 775, while they show a trend in favor of this claim, are not statistically significant. While the two crossover studies very weak studies, both in design and conduct, the findings from studies M90-481 and M91-565 provide some confirmation of the results from the parallel studies (See table 2). Study 565 is supportive for the treatment of partial onset seizures using 32 mg (given as QID). And M90-481 is supportive of this claim at a median dose of 52 mg. The treatment effects, if one were to accept the two "supportive studies" is still very small, but of the same magnitude as seen in M91-603.

With regard to complex partial seizures, the primary outcome variable for most of the controlled epilepsy there were statistically significant reductions in 4-week seizure rates supported by study M91-605 at a dose of 32 mg (given as BID) and M91- 603 at a dose of 32 mg (given as QID) during tiagabine treatment compared to placebo treatment. Confirmation is provided by the very weak study M90-481.

The sponsor's analyses of secondary generalization in any of the five studies were not sufficient to support this claim.

TABLE 1 SUMMARY OF RESULTS OF THE THREE PARALLEL CONTROLLED TRIALS OF TIAGABINE VS. PLACEBO IN THE TREATMENT OF PARTIAL SEIZURES
SPONSOR'S DATA

Seizure Type /Study	0 mg (Pbo)	16mg Rate∆	30 mg Rate ∆ PER ABBOTT †	30 mg 50%	32 mg (8QID) Rate∆	32 mg (16BID) (Rate∆)	32/56 mg Comb Rate∆	56 mg Rate∆
M91-603	-.3 N=90	-1.2 N=61 p=.24 p=.49			-2.7 N=86 p=.018 p=.036		-2.9 N=143 p<.001 p=.001	-3.3 N=55 p<.001 p<.001
M91-605	-.3 N=105				-1.2 N=103 p=.056 p=.17	-1.6 N=106 p=.097 p=.19		

Seizure Type /Study	0 mg (Pbo)	16mg Rate Δ	30 mg Rate Δ PER ABBOTT †	30 mg 50%	32 mg (8QID) Rate Δ	32 mg (16BID) (Rate Δ)	32/56 mg Comb Rate Δ	56 mg Rate Δ
M92-775	0.1/6.5% N=77		-1.1† N=77 p=.014	14.3%¥ N=77 p=.169				
PARTIAL COMPLEX								
M91-603	-.7 N=90	-.8 N=61 p=.44 p=.46			-2.2 N=86 p=.03 p=.089		-2.6¥ N=143 p=.007 p=.018	-2.8 N=55 p=.028 p=.05
M91-605	-.2 N=105				-1.2¥ N=103 p=.018 p=.104	-1.6¥ N=106 p=.055 p=.26		
M92-775	-.1/14.7% N=75		-1.3† N=72 p=.019	20.6% N=75 p=.371				

¥denotes primary outcome measure for that study

†data analyzed after unblinding and after initial negative results were available

TABLE 2 SUMMARY OF RESULTS OF THE THREE PLACEBO CONTROLLED CROSSOVER TRIALS OF TIAGABINE IN THE TREATMENT OF PARTIAL SEIZURES SPONSOR'S DATA

Median TDD	32 mg (8 mg qid)	52 mg* (13 mg qid)
PARTIAL ONSET		
M91-565	-2.4 N=26 p=.002 p=.005	
M90-481		-1.8 N=42 p=.018 p=.004
PARTIAL COMPLEX		
M91-565	-2.8 N=28 p≤.009 p≤.009	
M90-481		-1.8 N=42 p=.054 p=.008

Efficacy results were not affected by demographic characteristics, disease characteristics, or concomitant medications.
The sponsor performed analyses of selected subgroups of patients from Studies M91-603 and M91-605 revealed that the efficacy of tiagabine, measured by the proportion of patients achieving 50% or more reduction from baseline in 4-week CPS seizure rate, was not affected by demographic characteristics (gender, race, age, weight), disease characteristics (psychiatric history, history of partial seizures with secondary generalization, number of AEDs ever taken), concomitant AEDs, or selected concomitant medications (NSAIDs, benzodiazepines, anti-depressants).

Efficacy was due to tiagabine rather than changes in dose or concentration of concomitant AEDs.
In the parallel-group, add-on studies the mean daily dose and trough plasma concentrations of AEDs remained relatively unchanged from the Baseline Period to the Experiment Period. Similarly, the average daily dose and the plasma concentrations of AEDs did not differ between the tiagabine treatment period and the placebo treatment period in the crossover, add-on studies. Consequently, tiagabine administration was primarily responsible for the observed reduction in seizures found in these studies.

Tiagabine was also evaluated as monotherapy.
The were two parallel-group monotherapy studies (M90-511 and M93-090) did not provide sufficient evidence for a monotherapy claim. In study M93-090 there was no statistically significant difference between the two treatment groups in the change from baseline in 4-week seizure rate (the primary prospective outcome measure). Study M90-511 enrolled too few patients to determine efficacy.

Conclusion: Taken in sum these five adjunctive therapy studies provided weak evidence for the efficacy of Tiagabine HCl 32 mg in the adjunctive treatment of partial onset seizures.

Recommendation: This drug should be considered approvable for the adjunctive treatment of partial onset seizures. The sponsor should be required to perform a more thorough analysis of study M91-603 for potential withdrawal seizures.

REVIEW AND EVALUATION OF CLINICAL DATA: SAFETY

Application Information

NDA # 20-646, Safety Update II and Response to Approvable Letter

Sponsor: Abbott Laboratories

Drug Name

Generic Name: Tiagabine hydrochloride

Trade Name: Gabitril

Drug Characterization

Pharmacological Category: Antiepileptic

Proposed Indication: Add-on Therapy for the Management of Partial Seizures

NDA Classification: S

Dosage Forms, Strengths, and Routes of Administration: Oral Administration, 4, 12, 16 and 20 mg Strengths available.

Reviewer Information

Safety Reviewer: James F. Knudsen, Ph.D., M.D.

Review Completion Date: 07/25/97

Table of Contents

Table of Contents (continued)

Introduction

The letter to the sponsor dated October 31, 1996, the NDA (20-646) for Gabitril (Tiagabine HCL) tablets was approvable. The approvable letter requested submission of additional information. More specifically, in order to write an informative labeling, additional information regarding withdrawal seizures and alterations in mental status changes were requested. There have been various communications and submissions between the FDA and the sponsor regarding the mental status issue, including the proposal submitted, and accepted by the FDA in the December 19, 1996 letter confirming the general plan to re-evaluate the mental status adverse events.

The FDA also requested that the sponsor update the NDA by submitting a safety update providing new safety information (regarding tiagabine) accumulated since the cut-off date for the four-month safety update submitted March 1, 1996 and reviewed by John D. Balian, M.D. (review completion date July 25, 1996).

The sponsor submitted a safety update as well as responded to the issues in the approvable letter regarding the labeling, including withdrawal seizures and alterations in mental status. The submission comprises 20 volumes, and is the subject of the present review.

Safety Update

Background

This report is the second update (Safety Update II) for NDA 20-646, which was submitted on November 4, 1995. As outlined and agreed to in the accepted proposal submitted to the FDA Division of Neuropharmacological Drug Products on October 29, 1996, Safety Update II is an abbreviated safety update focusing on results which have changed since Safety Update I based on new/revised data.

The new safety information consists of data received since the Safety Update I cutoff dates (November 30, 1995, for Abbott-sponsored studies and August 31, 1995, for sponsored studies). The cutoff date for Safety Update II is August 31, 1996, for both Abbott-sponsored and sponsored studies; however, the cutoff date for pregnancies extends to October 15, 1996, and to December 31, 1996, for deaths. Compared to Safety Updated I, Safety Update II also includes, according to the sponsor,

- Data from two additional pharmacology studies (one Abbott, Study M96-448; one Study M96-444)
- Data from one additiona sponsored long-term study (Study M94-179)

- Data from one sponsored single-blind, short-term study in children (Study M93-043) where final results were not available as of the Safety Update I data cutoff
- Additional data from 788 patients in seven long-term studies (two sponsored by Abbott, five by) which were ongoing at the cutoff for Safety Update I

Also, some new/revised data are provided for Abbott short-term Studies M91-603 (TIA-106) and M91-605 (TIA-109). Unlike the original ISS and Safety Update I, primary adverse events leading to discontinuation are identified and included for all Phase II/III studies. Data from the 20-mg tablet bioavailability Study M96-546 were not included in Safety Update II since results were not available prior to the Safety Update II data cutoff. However, the report of this study, including safety information, is included in the response to the tiagabine NDA approvable letter.

Therefore, in this submission, the safety profile, was updated based primarily on data from subjects/patients with tiagabine exposure since Safety Update I in 11 clinical trials sponsored by Abbott Laboratories and These studies are displayed in the sponsor's table, which follows. A summary of these studies is provided in Appendix 1 of this review for the reader.

Ongoing or Newly Completed Studies Providing Data New in Safety Update II

Sponsor	Study	Type	Status	Number of New Unique Tiagabine-Treated Subjects/Patients
Abbott	M91-604	Long-term	Ongoing	51 patients
	M92-813	Long-term	Ongoing	1[1] patient
	M96-448	Clinical Pharmacology	Complete	22 subjects
	M91-578	Long-term	Ongoing	
	M92-873	Long-term	Ongoing	
	M93-043	Short-term	Complete	
	M93-047	Long-term	Ongoing	
	M93-065	Long-term	Ongoing	
	M93-092	Long-term	Ongoing	
	M94-179	Long-term	Ongoing	11[2] patients
	M96-444	Clinical Pharmacology	Complete	14 subjects

[1] With compassionate exception, this patient was allowed to reenter the study following a 14- month interruption in tiagabine treatment.
[2] Incomplete data was available for 19 additional patients with adverse events.

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Extent of Exposure

Overall, a total of 2531 patients have participated in 19 epilepsy studies (one new to safety update II) representing an increase of 63 unique patients since Safety Update I. Of these 63 unique patients, 51 were from Study M91-604, 11 were from Study M94-179 (new in Safety Update II), and one was from long-term Study M92-813. The new patient in Study M92-813 was previously enrolled in that study but was discontinued per Abbott requirement due to continued felbamate therapy. With compassionate exception, the patient was allowed to re-enter the study for seizure control 14 months after discontinuation; since re-entry occurred following a 14-month gap in tiagabine exposure, the patient was considered as an additional unique patient for the purpose of data summarization. Summary of patient accountability located in Appendix 2 of this review.

A total of 590 patients and subjects have received tiagabine in clinical pharmacology studies (an additional 36 subjects since Safety Update I). Twenty-two (22) enrolled in Study M96-448, a 2 mg tablet bioavailability study, and 14 enrolled in Study M96-444, an erythromycin interaction study. Each of these clinical pharmacology studies is new in Safety Update II. Data from the 20 mg tablet bioavailability Study M96-546 is not included in Safety Update II since results were not available prior to the Safety Update II data cutoff. However, a report for this study (in Vols. 7-8) including safety information for 60 patients is included in the response to the tiagabine NDA approvable letter and is reviewed.

Overall, there is an increase of 99 subjects/patients (33%) from safety update I (an additional 63 patients in epilepsy studies and 36 subjects in clinical pharmacology studies) incorporated in safety update II. It is noted by the sponsor (section 8.11.1.0 Introduction, Vol. 14) that the new long-term study and data from the short-term study in children (M93-043) and ongoing epilepsy studies account for an additional 600 patient-years of exposure (3831 patient-years). This is a 19% increase over the 3231 patient-years reported in safety update I in which there were 18 clinical trials for which a total of 2468 unique patients had been exposed to tiagabine in phase II/III epilepsy studies. The additional exposure (Sponsor's section 8.11.3.0, Vol. 14) occurred in 9 phase II/III studies (one new to safety update II), representing the treatment of 63 additional unique patients as well as 788 patients in ongoing long-term epilepsy studies continuing tiagabine treatment beyond the period covered in Safety Update I.

The following table (Sponsor's Table I, Vol. 14) provides an overview of all studies.

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Overview of Studies Evaluated for Safety and Number of Patients/Subjects Included within Each Group of Studies

Study Group	Studies Included, by Sponsor	Treatment Groups	Number of Patients Update II (Update I, if different) Abbott	Novo	Combined
Placebo-Controlled, Parallel-Group, Add-On Epilepsy Studies	Abbott: M91-603, M91-605	Placebo:	198	77	275
	M92-775	Tiagabine:	417	77	494
Low- Versus High-Dose Monotherapy Studies	Abbott: M93-090	Tiagabine Low (6 mg):	102	0[4]	102
	Not applicable[4]	High (36 mg):	96	0[4]	96
Long-Term Epilepsy Studies[2]	Abbott[3]: M91-604, M92-813	Tiagabine:	1489 (1437)	759 (748)	2248 (2185)
	M91-578, M91-595, M91-710, M92-873, M93-047, M93-065, M93-092, M94-179				
All Epilepsy Studies[1,2]	Abbott[3]: M90-481, M90-511, M91-603, M91-604, M91-605, M92-813, M92-855, M93-090	Tiagabine:	1701 (1649)	862 (851)	2531 (2468)
	M91-565, M91-578, M91-595, M91-710, M92-775, M92-873, M93-043, M93-047, M93-065, M93-092, M94-179				
Clinical Pharmacology Studies[5]	Abbott: M89-319, M89-398, M90-425, M90-426, M90-463, M90-496, M90-518, M91-560, M91-590, M92-792, M92-809, M92-810, M93-083B, M92-793, M93-009, M93-080, M93-081, M93-089, M94-155, M94-156, M94-157, M94-170, M94-171, M94-244, M96-448	Tiagabine Single Dose Subjects:	221 (199)	61	282 (260)
		Patients:	53	0[4]	53
	M91-607, M91-712, M93-044, M93-045, M93-066, M93-079, M93-087, M93-088, M94-188, M96-444	Tiagabine Multiple Dose Subjects:	94	96 (82)	190 (176)
		Patients:	57	8	65

[1] Thirty-two patients in studies had previously been enrolled in Abbott studies.

[2] One long-term extension study conducted in Japan is not included in this list. Up to 60 patients were expected to receive tiagabine in this study; however, safety data was not included in the database for analysis.

[3] One Phase II study and one long-term extension study conducted in Japan are not included in this list. Up to 100 patients were expected to receive tiagabine in these studies; however, data was not included in the database for analysis.

[4] Two Phase I studies (R&D/95/402 and R&D/95/403) conducted in Japan are not included in this list. A total of 24 subjects received tiagabine in these studies; however, safety data was not included in the database for analysis.

[5] The long-term Study M91-604 included patients from add-on studies M91-603, M91-605 and M92-825; patients from monotherapy studies M92-855 and M93-090, and pediatric patients from Phase I Study M94-244. Study M92-813 incorporated results of Study M92-813C, a Canadian study.

[6] No Novo studies.

Cross reference: Appendix C.1.1.1

In all epilepsy studies a total of 1274 patients (50%) have now been treated with tiagabine for more than one year compared with 1236 (50%) in safety update I. A total of 832 (33%) have been treated for more than 2 years compared with 698 (28%) in safety update I. Furthermore, 541 (21%) patients have been treated for more than 3 years as of the data cutoff for safety update II, compared with 161 (7%) in safety update I. Of the patients treated with tiagabine for more than 1 year, 11% (139/1274) had a most frequent daily dose of 80 mg or greater (section 8.11.3.0, Table 4, volume 14).

Review of Deaths

Among the 3091 tiagabine-exposed patients in all epilepsy studies, 35 patients have died, representing an increase of four since Safety Update I, (enumerated in Appendix 3 of this review). The four additional deaths of tiagabine-treated patients are Patients 50403 and 50807 in the long-term, ongoing, Study M91-604; Patient 6710 in Study M92-813C, and Patient 1304 in Study M92-813 (long-term, ongoing). Patient 6710 had been off tiagabine for approximately three months at the time of death and patient 1304 had been off 5 months. These deaths will not be part of the mortality rate calculations.

The revised number of deaths from safety update I was 27 (because 4 patients were off tiagabine and not counted) and for safety update II, 2 for a total of 29 deaths/3091 or a crude mortality rate of 0.94% or 0.71/100 Pys, (Pys of exposure 3831, or 600 more than safety update I).

Two (one new in Safety Update II) of the 35 deaths of tiagabine-treated patients were considered by the investigator to possibly be related to study drug administration: Patient 51503 (reported in Safety Update I) and Patient 50807 (new in Safety Update II), both in study M91-604. Narratives of the four deaths which occurred since Safety Update I were provided in Appendix D.3.1, volume 16 and were reviewed, summaries follow.

Patient 50403 was a 14YOM who was receiving 80 mg/d of tiagabine and 400 mg/d of phenytoin. He was hospitalized on treatment day 1486 after suffering a tonic clonic seizure following abdominal pain and vomiting. He died of heart arrest. Autopsy revealed volvulus and intestinal gangrene. Limited information precludes assessment of the etiology of these events.

Patient 50807 was a 44YOM (according to narrative summary) receiving 32 mg/d of tiagabine, at onset of event (day 827). He also received phenytoin and valproate. The patient was hospitalized for DVT on treatment day 1058 and experienced severe pneumonia on treatment day 1123. Patient discontinued tiagabine on treatment day 1170 due to the CNS neoplasm (an astrocytoma). Pneumonia resolved, with antibiotic treatment, on day 1177. Patient subsequently died of the CNS neoplasm. (The narrative summary varies from the description given in section 8.11.8.3 entitled Deaths, Vol. 14).

Patient 6710, a 58YOM, had been off tiagabine for roughly 3 months at time of death from multi-organ failure secondary to pneumonia and sepsis. He had been discontinued from tiagabine therapy on treatment day 846 due to the difficulty of dose administration through a J tube which had been used in the context of complications resulting from cerebral hemorrhage and aspiration (day 813).

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Patient 1304, a 25YOM, was hospitalized 5 months after discontinuing tiagabine. He died of AVM and coma.

From the narrative summaries, there is no evidence that tiagabine was associated with the 4 deaths reported in the safety update II. There are no new reports of sudden, unexplained deaths, a topic discussed in Dr. Balian's medical review date July 25, 1996, and Dr. Leber's memorandum of October 22, 1996.

Review of Dropouts

Prior to Safety Update II, data identifying the primary adverse events leading to discontinuation had not been included in databases received for studies; thus, analyses of primary adverse events resulting in premature discontinuation were based on Abbott studies only. However, this information was provided in . databases for Phase II/III studies received for Safety Update II, so analyses of primary adverse events leading to discontinuation for Phase II/III studies are presented based on data from Abbott and studies. As a result, a notable difference from Safety Update I compared to Safety Update II in the overall number of discontinuations for adverse events is exhibited. For Safety Update I, the proportion of discontinuations in tiagabine-treated patients for adverse events in Abbott epilepsy studies was 19% (310/1649). In Safety Update II, the proportion of discontinuations in Abbott and epilepsy studies combined is 21% (522/2531). Adverse events identified as the primary reason for discontinuation were presented in sponsor's Table 40 (Vol. 14) for all Abbott and epilepsy studies. Separate tabulations were also provided for adverse events not restricted to primary. More than one primary adverse event leading to discontinuation was reported for seven patients in studies (one patient reporting each set of events listed): nervousness and thinking abnormal; speech disorder and thinking abnormal; ataxia and vertigo; dyspnea and headache; depression and hostility; arthralgia and rash; and agitation, confusion, and suicide attempt. Thus, a total of 530 primary adverse events are tabulated in Table 40 (volume 14) for the 522 patients who discontinued. The most frequent events leading to premature discontinuation were associated with the nervous system (383/2531; 15%) and were: dizziness (1.7%), somnolence (1.6%), depression (1.3%), confusion (1.1%), and asthenia (1.1%).

In the placebo-controlled, parallel group add-on epilepsy studies (2 Abbott and 1 study), 14% (69/494) of the tiagabine-treated patients and 7% (18/275) of the placebo-treated patients had an adverse event identified as the primary reason for discontinuation. Compared with safety update I, this represents an increase of 2% in the tiagabine-treated group with no change for placebo. Adverse events identified as the primary reason for premature discontinuation occurred most frequently in the nervous system in which 10% (48/494) of tiagabine and 3% (8/275) of placebo-treated patients discontinued. Data are from sponsor's Appendix Table C.1.7.16 (Vol. 15).

In the table which follows (sponsor's Table 41, Vol. 14), the only adverse events associated with discontinuation in 1% or more of tiagabine-treated patients for which the incidence was approximately 2x the placebo were confusion and somnolence.

Adverse Events Identified as the Primary Reason for Premature Discontinuation of Two or More Tiagabine-Treated Patients in Placebo-Controlled, Parallel-Group, Add-On Epilepsy Studies

	Number of Patients Discontinued for the Adverse Event			
	Safety Update I [1,2]		Safety Update II [1,2]	
Body System COSTART Term	Placebo N=198	Tiagabine N=417	Placebo N=275	Tiagabine N=494
Any AE Resulting in D/C	14	50	18 [14]	69 [63]
Body as a Whole				
Abdominal Pain	0	2	0	3
Infection	0	2	0	2
Digestive System				
Vomiting	1	2	1	3
Nervous System				
Asthenia	0	2	2 [1]	4
Ataxia	1	4	1	4
Confusion	0	6	0	8 [7]
Depression	0	2	0	2
Diplopia	0	1	0	2 [1]
Dizziness	1	3	1	4
Headache	1	0	1	2
Hostility	1	1	0	3
Nervousness	0	2	0	2
Somnolence	2	6	2	8 [6]
Thinking Abnormal	0	2	0	2

[1] Safety Update I based on Abbott studies only; Safety Update II based on both Abbott and Novo studies
[2] Includes discontinuations during the titration, fixed-dose, and termination periods
[3] Includes discontinuations during the titration, fixed-dose, and termination periods. Numbers during titration and fixed-dose periods only are given in brackets where they differ from those including the termination period.
Cross Reference: Appendix C.1.7.16.

Line listings of adverse events identified as resulting in premature discontinuation are in Appendix D.3.2 (volume 16). This document served as a primary source for identification of patients to review in greater detail. Narratives for all patients who discontinued study drug prematurely due to adverse events are provided in Appendix D.4.1 (volume 16).

The sponsor's table of premature discontinuations presented above varies from the dropout table in Balian's medical review (Balian's review Appendix Table 8.6.2) even though the denominators (tiagabine patients n=494 and placebo patients n=275) for the 3 pooled

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studies, 2 U.S. (Abbott), non U.S. ( ) are the same in both tables. In Balian's table the adverse events for which ≥ 1% of tiagabine treatment patients dropped out and for which the incidence was at least 2x the placebo included the following, in alphabetical order: ataxia (2%), confusion (2%) ,dizziness (4%), headaches (1%), nervousness (1%), somnolence (2%), speech disorder (1%), and tremor (1%). For the reader's convenience, a copy of Balian's table is provided in Appendix 4 of this review. As noted previously in the present review (sponsor's table), only confusion and somnolence met the criteria of premature discontinuation in 1% or more tiagabine-treated patients and at least 2x the incidence in placebo-treated. Furthermore, in the revised labeling (tab 3.1, volume 1, section ADVERSE REACTIONS, pg. 17 of 25) the sponsor mentions that the most common adverse events considered the primary reason for discontinuation in the two U.S. studies (excludes study) were confusion (1.2%), somnolence (1.0%) and ataxia (1.0). Which datasets to pool may, interalia reconcile some of the confusion with respect to apparent differences in the incidences of adverse events reported in the present submission and previously. Dr. Balian may not have restricted his tabulations of adverse events to primary reasons for discontinuation.

The percentages of patients who discontinued for a given adverse event in the long-term epilepsy studies in the safety update II (18%, 396/2248) were similar to those reported in Safety Update I (15%, 234/1489). The line listings for the patients who discontinued for adverse events Appendix D.3.2 (volume 16) since safety-update I served as a primary resource for identifying specific patients to review in greater detail. The narrative summaries of the patients with mental status changes were reviewed (Appendix D.4.1., Vol. 16). The limited amount of reported data in these summaries precludes any overall assessment with respect to drug attribution and the adverse event.

The majority of the premature discontinuations were because of nervous system related adverse events, 13% (292/2248), unchanged from safety update I. The largest difference between safety update I and II in adverse events leading to discontinuations were observed for somnolence, which increased from <1% to 2%, and dizziness which increased from <1% to 2%.

From the line listings, three cases were identified which received further scrutiny. These cases do not appear in safety update I. Patient number 30902 (study M91-604), a 25 YOM (Hispanic) discontinued treatment with tiagabine (16mg/day) an treatment day 1359. On treatment day 1271 patient was stated to have experienced the event retroperitoneal fibrosis (RTF). He had previously been exposed to higher doses (112mg/day) of tiagabine. Other antiepileptic drugs used by patient within 7 days of the adverse event were listed as phenytoin (500mg/day; start day - 113) and carbamazapine (2000 mg/day; start day 1069). The reporter considered the event to possibly be related to treatment with tiagabine with carbamazepine treatment as an alternative etiology. There is no further information in the narrative summary. Because of insufficient data it is not possible to determine the

significance of this case report, or a cause and effect relationship. However, neither carbamazapine nor phenytoin are associated with (RTF). Other manifestations of RTF due to caval compression such as claudication due to aortic or iliac arterial compression did not appear as adverse event terms leading to discontinuation.

Patient number 3205 (study M93-047) a 53YOM with no past recorded medical history of an allergic diathesis, discontinued tiagabine (32mg/day) treatment after 2 years because of pemphigoid blisters, (diagnosis confirmed by skin biopsy). The investigator assumed the rash as possibly related to tiagabine therapy. The patient was treated with local and systemic steroids. Tiagabine was tapered and stopped. Carbamazepine (1400mg/day) was reported to be in use within 7 days of the event. According to the sponsor the event was originally classified as vesiculobullous rash (COSTART term). After re-evaluation it was decided to change the event as unexpected. An association with tiagabine treatment cannot be excluded. The rash "largely" cleared with discontinuation of tiagabine and use of steroids and antibiotics. Pemphigoid may be a manifestation of a drug-induced reaction but may also be idiopathic. Vesiculobullous rash has been observed during lamotrigine clinical trials.

Patient number 2223 (study M93-047) a 18YOM discontinued tiagabine treatment (32mg/day). He experienced a "moderately severe rash" (no description or clarification) on treatment day 689. Other medications taken concurrent to onset of the event were clobazam (40mg/day) and lamotrigine (25mg/day). Patient discontinued tiagabine on treatment day 700. The event resolved on treatment day 703. Another COSTART term used in the otherwise uninformative narrative summary was NEOPL CNS which was serious and was reported 2 months after the rash. There is no additional information about this case. An association of the rash with tiagabine treatment cannot be excluded. Discontinuations in bioavailability study M96546 (not part of safety update II) are discussed in Appendix 12 of this review.

Because of the occurrence of these two skin rashes resulting in patient discontinuation from the study, as well as the description of Stevens-Johnson Syndrome as a serious event, additional information on these topics (incidences in clinical trials) is incorporated into appendix 13 of this review.

Serious Adverse Events

As of the database cutoff date for Safety Update II, 518 (20%) of the 2531 tiagabine-treated patients in epilepsy studies experienced a total of 1049 serious adverse events (no restriction with respect to treatment-emergence). This patient percentage represents an increase of 1% since Safety Update I and reflects the additional exposure time represented by Safety Update II. Of these 518 patients with serious adverse events, 164 (32%) had at least one serious adverse event which was considered by the investigator to be possibly or probably related to tiagabine administration, compared with 154 (43%) in safety update I.

The cumulative incidence of serious adverse events was 20% (518/2531) in this safety update compared with 19% (469/2468) in the previous update. The body as a whole was listed with the most frequently occurring serious adverse events with the COSTART term accidental injury accounting for the greatest proportion; unchanged from safety update I. The narrative summaries of several cases of these reports revealed that seizures often preceded the accidental injury. The nervous system was the next body system with the most frequently reported serious adverse events; the incidence was 8% (209/2531), and is unchanged from the database of safety update I.

The results of separate analysis of psychosis, weakness, confusional states and status epilepticus conducted in this safety update were similar to those reported in safety update I, and reviewed by Balian.

Overall, the following serious adverse event terms were reported with greater frequency (4 or more) in safety update II than in safety update I, ordered by decreasing frequency: reaction unavailable (N=13); depression (N=5); pneumonia (N=5); dehydration (N=4).

The line listing of all patients in the safety update meeting the criteria for having a serious adverse event was reviewed (Appendix D.5, volume 16). Cases of possible clinical significance, (e.g., not reported previously) utilizing the sponsor's narrative summaries, are summarized. Parenthetically, the narrative summaries were characterized by a paucity of information, e.g., no vital sign, laboratory, ECG data.

Case number 2102 (study M93-043) was a 9 year old identified in the line listing as a case with Stevens-Johnson syndrome, which "started" on December 1, 1995. According to the narrative summary, due to the lack of effect, the patient received his last dose of tiagabine (4mg/day x 7 days) on November 29, 1995. The maximum daily dose had been 32mg/day. Since there is no height or weight given in the narrative summary for this 9 year old, the dose/kg b.w. or M^2 can not be calculated. A chronology of tiagabine and concomitant medication administration as well as the events are presented on the following page.

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Chronology of Drug Administration in 9 Year Old With Stevens-Johnson Syndrome

Drug	Date (start to end)	Daily Dose (mg)	Comment
Tiagabine	1/3/94 - 6/15/995	24-32	
	6/15 - 11/5/95	32	
	11/6/95	30	
	11/7 - 11/19/95	16	
	11/20 - 11/22/95	8	
	11/23 - 11/29/95	4	• Stevens-Johnson syndrome <u>start</u> date 12/1/95
Clobazam	11/1/95 - 1/8/96	10	• Prednisone 12/1/95
Valproic	11/1/95 - 12/19/95	600	• <u>END</u> date of Stevens-Johnson Syndrome (12/18/95)
Phenytoin	11/7 - 11/12/95	300	
	11/12 - 12/1/95	150	

The patient previously received tiagabine from July 15, 1993 to January 2, 1994 without report in the narrative summary of any adverse event.

Valproic (600mg/day) was added to the patient's treatment regimen on 11/1/95 at a time when there were no adverse effects reported. Whether or not the addition of Valproic had any clinical effect on tiagabine blood concentrations and the subsequent adverse event is unknown. However, Valproic has been documented to significantly decrease tiagabine binding <u>in vitro</u> resulting in an increase of approximately 40% in the free tiagabine concentration. (Information from original NDA, PK data).

Phenytoin (300mg/day) was started on 11/7/95 some 24 days before the "start" of Stevens-Johnson Syndrome on 12/1/95 and at a time with tiagabine daily dosing was being reduced. Phenytoin (150mg/day dose) was stopped on 12/1/95. Cutaneous reactions induced by phenytoin usually begin 1 to 3 weeks after phenytoin is begun and resolve with drug cessation. Stevens-Johnson Syndrome has been reported with phenytoin exposure. The possible involvement of tiagabine cannot be definitely excluded.

Case number 3205 (study M93-047) had a pemphigoid bullous rash. He was discussed previously in this review (discontinuation section). Neither of the aforementioned skin reactions were reported in safety update I.

Case number 51704 (Study M91-604) is a case of a 66YOF who was hospitalized on 2 separate occasions because of accidental injuries, one associated with a fall and a second due to a concussion secondary to an automobile accident. She was receiving 80mg/day of tiagabine at the onset of both events, in addition to phenytoin (300mg/day). There is no information available in the narrative summaries to ascertain whether or not any prodromal events such as dizziness, weakness occurred before the serious events. Incidentally, the foreign labeling (Volume 13) advises caution should be shown by patients driving vehicles or operating machinery (because tiagabine may cause CNS related symptoms such as dizziness).

There were additional reports of pneumonia and myocardial infarctions in the safety update II. These cases were examined. From the limited information in the narrative summaries there was no evidence of hypersensitivity pneumonitis. Case number 2208 was a 33 YOF (study M92-813) who was hospitalized on treatment day 1287 for a severe myocardial infarction. At the onset of the event the patient was receiving tiagabine 36mg/day; other anti-epileptic medication taken concurrent to the onset of the event consisted of carbamazepine (600mg/day). The investigator considered the event to not be related to treatment with tiagabine and reported coronary artery disease as an alternative etiology. The duration of the event was seven days. The patients continuing tiagabine treatment as of treatment day 1318. The patient's screening medical history indicated no prior conditions that were significant to the event. There is no other information available about this case, consequently, it is not possible at this time to determine the significance of this report. From Balian's review of the safety update I database, in controlled trials 0.5% (2/388) of the tiagabine exposed patients and no placebo-treated patients experienced treatment emergent cardic-related events, one an M.I. (Patients 10323) and a second a prolonged QT interval (patient 11815). Overall serious events recorded as myocardiac infarct occurred in 6 patients out of 2531 tiagabine-treated.

Case number 52705 (study M91-604) a 35YOM had a serious adverse event (COSTART term) of "thinking abnormal" while on 80mg/day of tiagabine. The narrative summary indicated that the patient was hospitalized on day 1015 of treatment because of moderately severe thinking abnormal (in-coherence) and reported postictal effects as an alternative etiology to tiagabine-treated associated incoherence. The mental status-related event thinking abnormal is addressed more fully, later in this review.

Severe, not serious adverse events are discussed in the bioavailability study M96546 (not part of safety update II safety data) and are summarized in Appendix 12 of this review.

Other Safety Findings

Since the reporting of Safety Update I, minor corrections were made to the adverse event databases of the placebo-controlled, parallel-group, add-on, epilepsy studies. These minor corrections consisted of changes for two patients; Patient 10305 in Study M91-605 and Patient 11109 in Study M91-603. An updated summary of all treatment-emergent adverse events with onset during the Titration and Fixed Dose Periods (i.e., the Experiment Period) which were reported by $\geq$ 1% of patients treated with tiagabine in these studies is presented by body system, COSTART term, and treatment group in sponsor's Table 26 (Volume 14) as well as the proposed labeling.

Urinalysis of patients (the majority) in study M91-604 revealed crystals. These were identified as calcium oxalate (urine pH:acid) and in some instances uric acid and triple phosphate. From the limited data from the line listing the patients appeared to be asymptomatic. Although urine crystals are often overemphasized in importance they may be a clue to disturbances of hydration, for example, thiazide induced, hypocitraturia, due to thiazides, as well as metabolic disturbances. Crystalluria was not mentioned in the safety update I review consequently the incidence is not known. Topiramate, a recently approved antiepileptic drug has been associated with kidney stones. (PRECAUTION section of labeling for topiramate).

Examination of the line listings (Vol. 17) from study M91-604 did reveal a case which warrants comment. Patient Number 50819 was a 46 YOF (no weight/height given) with (moderate) hyperammonemia noted on day 915 of tiagabine dosing (24mg/day) and lasting 26 days. Additionally the line listing (no narrative summary) revealed that she was diagnosed with (mild) pancytopenia on day 939 of treatment, hyponatremia (day 891 of tiagabine exposure and lasting 14 days) and moderate hypotension on day 1135 of therapy (duration unknown). Among actions taken, dose of tiagabine was lowered. Amorphous urates were present in the urine. Interesting case so far but without any further information (like concomitant medications), no association with tiagabine exposure is possible. Case is ongoing.

Parenthetically some sulfa-containing drugs (tiagabine is 2-thienyl-), e.g. the sulfonamides, such as the carbonic anhydrase inhibitor acetazolamide may cause diversion of ammonia from the urine into the systemic circulation, calculus formation, and Na+/K+ wasting. With respect to the last adverse effect, preclinically, tiagabine produces saluresis and diuresis. Whether or not these events are manifested in tiagabine exposed patients is not known.

Common Drug Related Adverse Events (5% Table)

There is no change from the original NDA / safety update I, Table 10.b in Balian's medical review (page 20).

Dose Response For Common Adverse Events

The sponsor has constructed a table (Table 5, Volume 1) for the package insert (labeling) as requested by the FDA (letter of October 31, 1996) which shows adverse events by dose for the 32 and 52mg dose groups and placebo from study M91-603. As noted previously, asthenia, dizziness, tremor and thinking abnormal appeared to exhibit a positive dose relationship or association with rate of titration.

Adverse Events Over Time

An analysis of prevalence/incidence of 5 related adverse events over time was done using the Abbott data (due to differences in adverse event profiles of the 2 clinical programs). The 5 selected adverse events were: asthenia, dizziness, nervousness, thinking abnormal and tremor.

These events were selected either because their incidence was at least 5% greater among tiagabine-treated patients than placebo-treated patients in the placebo-controlled, parallel-group, add-on epilepsy studies, or because a statistically significant tiagabine positive dose response was noted in Study M91-603 (see results of Safety Update I, Balian's medical review).

Since the reporting of Safety Update I, minor corrections were made to the adverse event databases of the placebo-controlled, parallel-group, add-on, epilepsy studies. These minor corrections were described in Section 8.11.8.1.1. of Volume 14. The following table (sponsor's Table 30, Volume 14) in an updated summary of the prevalence of the selected treatment emergent adverse events. The numbers affected are bolded in the table.

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Incidence of Selected Treatment-Emergent Adverse Events in the Abbott Placebo-Controlled, Parallel-Group, Add-On Epilepsy Studies

	Incidence (%) Over Time					
	Titration Period (4 Weeks)[1]		Fixed-Dose Period (8-12 Weeks)[1]		Termination Period (13-16 Weeks)[2]	
COSTART Term	Placebo N=198	Tiagabine N=417	Placebo N=190	Tiagabine N=365	Placebo N=86	Tiagabine N=185
Asthenia	8	15	7	7	1	1
Dizziness	9	19	9	10	5	3
Nervousness	2	8	2	4	1	<1
Thinking Abnormal	0	4	3	3	0	0
Tremor	2	8	3	3	1	<1

[1] Safety Update I values for bolded numbers were: asthenia 6 and dizziness 8.
[2] Incidence during the Termination Period (not summarized in Safety Update I) is based on M91-603 patients only (placebo patients in M91-605 were allowed to begin titrating on tiagabine in the Termination Period).
Cross Reference: Appendix C.1.7.8.

An incidence of adverse events over time table was also updated by sponsor (sponsor's Table 31, Volume 14) for minor changes and is presented here.

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Prevalence of Selected Treatment-Emergent Adverse Events in the Abbott Placebo-Controlled, Parallel-Group, Add-On Epilepsy Studies

	Prevalence Over Time					
	Titration Period (4 Weeks) [N (%)][1]		Fixed-Dose Period (8-12 Weeks) [N (%)][1]		Termination Period (13-16 Weeks) [N (%)][2]	
COSTART Term	Placebo N=198	Tiagabine N=417	Placebo N=190	Tiagabine N=365	Placebo N=86	Tiagabine N=185
Asthenia	15 (8)	62 (15)	20 (11)	60 (16)	8 (9)	16 (9)
Dizziness	17 (9)	80 (19)	23 (12)	70 (19)	6 (7)	23 (12)
Nervousness	3 (2)	32 (8)	4 (2)	33 (9)	3 (3)	16 (9)
Thinking Abnormal	0 (0)	18 (4)	5 (3)	23 (6)	1 (1)	7 (4)
Tremor	3 (2)	34 (8)	8 (4)	30 (8)	1 (1)	14 (8)

[1] Safety Update I values for bolded numbers were: asthenia 59 (16), dizziness 16 (8) and 22 (12), and tremor 4 (2) and 9 (5).
[2] Incidence during the Termination Period (not summarized in Safety Update I) is based on M91-603 patients only (placebo patients in M91-605 were allowed to begin titrating on tiagabine in the Termination Period).
Cross Reference: Appendix C.1.7.7.

Adaptation or tolerance to these adverse events in tiagabine-treated patients appeared to have occurred by the end of the fixed-dose study. Although a larger percentage of tiagabine than placebo-treated patients dropped out, possibly those intolerant of the adverse events.

For long-term epilepsy studies, the prevalence of the selected adverse events was highest within the first six months of treatment. The prevalence of these adverse events decreased over subsequent six-month time intervals. Through 36 months, the results were essentially unchanged from Safety Update I. The new results through 48 months maintain a general pattern of gradually decreasing prevalence across consecutive 6-month intervals. The incidence were similar to those observed for prevalence.

The prevalence and incidence of selected treatment-emergent adverse events is presented by six-month time intervals for Safety Update II in Table 34 and 35, Volume 14.

Overdose Experience

As of August 31, 1996, 31 overdoses (25 in Safety Update I) had been reported in association with tiagabine clinical trials. In the review of clinical overdose with tiagabine, only cases reported as serious adverse events are included. Through August 31, 1996, there were 11 instances of overdose of tiagabine reported as serious adverse events; three of these instances were reported since Safety Update I. In all 11 instances, the patients had complete recovery, usually within 24 hours. An additional 11 cases (an increase of one since Safety Update I) listed in the serious adverse event database occurred in individuals not enrolled in tiagabine clinical trials who intentionally or accidentally ingested tiagabine that was supplied to a trial patient. Five other instances (an increase of two from Safety Update I) reported as serious adverse events were cases of overdose of drugs other than tiagabine by individuals in tiagabine clinical trials. Finally, four adverse events associated with the term overdose, though not considered here as clinical overdoses, were discussed in Safety Update I.

Incidentally the proposed labeling OVERDOSAGE section has been changed to reflect the total of 11 patients. The Sponsor submitted brief narratives (Appendix D.6.1, Volume 16) of the 3 new tiagabine overdoses (each in M91-604-long-term). Narrative summaries did not provide vital sign, ECG or laboratory data.

A summary of the 3 cases follows:

Patient 71201 (12 YOF) took approximately 400mg tiagabine (100, 4mg tablets) to avoid school; her teacher had made a comment in class about her epilepsy the previous week. The patient experienced generalized tonic-clonic status epilepticus, which responded to intravenous phenobarbital. She recovered completely and has been undergoing psychiatric evaluation.

Patient 90412 (18 YOM) took approximately 60mg tiagabine (five 12mg tablets) after having an argument with his mother. The patient was hospitalized with somnolence secondary to the overdose. He recovered and has been undergoing psychiatric evaluation. As of day 870 he continued tiagabine.

Patient 90424 (41 YOF) was hospitalized twice within 30 days for severe depression. She attempted suicide by taking an overdose of several medications, including tiagabine. The dosage taken is not known. The patient was hospitalized and had gastric lavage. No events occurred from the overdose. The patient recovered and was transferred to another hospital for treatment of depression. As of treatment day 761, she was continuing treatment with tiagabine.

Additionally, 11 non-patients, an increase of one since the safety update I were listed among serious adverse events as having ingested tiagabine supplied to a trial patient. The one new case reported in Safety Update II involved the 11-month-old grandson of a patient who ingested one-half of an 8mg tiagabine tablet. The child seemed drowsy and was diagnosed as having tonsillitis. The drowsiness (COSTART term somnolence) lasted two hours and was believed to be related to tonsillitis and not to the accidental ingestion of tiagabine.

Duration of Adverse Events Over Time

Minor insignificant changes have been made to safety update I values and are presented in sponsor's Tables 36 (placebo-controlled, parallel-group, add-on epilepsy studies) and 37 (long-term epilepsy studies).

Human Reproductive Data

As of October 15, 1996, 27 pregnancies had been reported by patients in tiagabine clinical trials. This represents an increase of one pregnancy since Safety Update I.

Eleven patients carried to term (an increase of two since Safety Update I), and ten of these patients delivered healthy babies. The eleventh patient (Patient 3706 in study M92-813) had a Cesarian section delivery for breech presentation, and the baby had hip dysplasia which was attributed to the breech presentation.

Withdrawal-Emergent Adverse Events

In the long-term studies, 3 patients experienced status epilepticus during abrupt or tapered withdrawal from tiagabine, three more than were reported in the previous safety update.

Literature Update

A worldwide literature review was conducted by the sponsor (report in Volume 13 from April 30, 1995 to October 30, 1996). Ten data files, including four major search services were used to identify articles. This involved 7 published articles of various types including double blind studies, open studies, case reports, animal studies, and retrospective reviews. The majority of these publications contained no retrievable safety information, e.g., side effects, laboratory abnormalities, test results, that could be specifically linked to tiagabine.

One small case-series (Schapel, G. Seizure 5:153, 1996) reported on 3 patients exposed to tiagabine. Across the 3 patients, with various combinations of concomitant medications, the most common adverse event was non-convulsive status epilepticus attributed to a paradoxical epileptogenic effect of tiagabine dose increase. Each patient experienced confusion, impaired awareness, and/or a "twilight state", a prolonged episode of unresponsiveness. Symptoms subsided with dose reduction of tiagabine. The sponsor

noted that the case review of the 3 patients suggests that the paradoxical exacerbation of epilepsy may be attributed to the patients' concomitant antiepilepsy drugs because the metabolism of tiagabine is enhanced by other enzyme-inducing agents. One patient was receiving carbamazepine and lamotrigine: one patient was receiving carbamazepine and phenytoin, and one patient was receiving lamotrigine and vigabatrin.

I see no articles which are likely to alter the safety profile of tiagabine at this time.

Foreign Regulatory Update

Tiagabine HCl (also under the trademark Gabitril) has been approved in several European countries.

The sponsor submitted copies of 2 examples of foreign labeling for Gabitril (Volume 13) which were examined. The first is the mutually agreed upon Summary of Product Characteristics (SPC) that will be used in European Union Member States. The second is an English translation of the SPC to be used in Switzerland.

The special warnings and special precautions for use (section 4.4) of the former labeling mentions the following: a risk of aggravation of absences in patients treated with Gabitril cannot be excluded;

In patients with a history of serious behavioral problems including depression and anxiety there was a risk of recurrence of symptoms during treatment with Gabitril;

Spontaneous ecchymoses have been reported and if observed blood count and platelet count is to be done.

There is no special warning section in the rather abbreviated labeling to be used in Switzerland.

Both labels note effects on ability to drive and use machines which may be compromised because of dizziness and other CNS related symptoms, especially during initial dosing.

Post-Marketing Experience

Tiagabine tablets are currently marketed in certain European countries by
As of June 30, 1997, only one non-serious spontaneous adverse drug experience has been reported to Novo-Nordisk for the marketed product. No serious spontaneous ADE reports have been received by Preliminary information from indicates that no reports were received in July, 1997.

Responses from company to the FDA Action Letter for Tiagabine.

In addition to the safety update II supplied by the sponsor as a partial response to the Agency's approvable letter for tiagabine, the sponsor has also provided, in this submission,

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a response to the Agency's request for additional analyses of withdrawal seizures and mental status-related adverse events.

For the convenience of the reader, a copy of the comments, beginning with comment 2.a, from the Agency to the sponsor and germane to the present clinical safety review is provided in Appendix 5 of this review.

Withdrawal Seizures

In response to the Agency's request in the approvable letter for a withdrawal seizure analyses enumerating seizure type observed in the withdrawal phase of study M91-603 (dose response trial in which testing was done at baseline and at fixed-dose on 156 patients), the sponsor submitted tables. These tables (Volume 2, Tables 8-12) summarize the distribution of change from baseline in 4-week seizure rates during the withdrawal period by seizure type and by treatment group, based on the experience for each week and the combined four-week experience. Copies of these tables are provided in Appendix 6 of this review.

Overall, there was no evidence to suggest an increase in seizure pattern over the 4 week period compared to placebo for any seizure type. Analysis of seizure rates during tiagabine withdrawal showed no time-dependant hazard for partial seizure types as well as for seizure types other than partial.

Alterations in Mental Status

Background

The Agency had concerns that the mental status-related adverse events noted were not adequately described and suggested a detailed examination of the kinds of such events found with tiagabine, the differential diagnosis of them, and the mechanisms by which they occur. A strategy to characterize the events and a methodical evaluation to rule out the potentially confounding presence of absence status epilepticus was suggested. Also discussed and agreed to was a detailed examination of a sample of patients with such events from double-blind placebo-controlled trials with the production of narrative summaries to better describe the events in more clinically relevant terms.

Methods

An overview of the method of analyses used by the sponsor to characterize the mental status related adverse events is provided in the Appendix 7 of the present review.

The database supplied by the sponsor in the form of appendices were examined to evaluate the characterization of mental status changes in tiagabine-treated patients relative to placebo. A discussion of these findings follows the format of the analyses designated by the sponsor as A, B, C and D.

Results

The mental status-related adverse events were defined by the sponsor as any adverse event, from the description of all nervous system adverse events, which affected level of consciousness, thought processes, behavior/personality and dizziness (excluding light-headedness). Dizziness is a non-specific term that may or may not represent impairment of consciousness or thought content.

Group A Analysis

The mental status-related adverse events (activities of associative cerebral functioning) were chosen for this analyses using criteria discussed earlier by the sponsor including thought content, thought processes, mood/behavior, and level of consciousness. Dizziness was also included because it was the most common adverse event in tiagabine clinical studies although those events clearly designated as "light-headedness" in the descriptions were excluded. For the convenience of the reader, Appendix 8 of this review contains tables which are referred to in the next 3 paragraphs.

The resulting list of adverse events grouped by medical term under these 5 categories for the 3 double-blind placebo-controlled studies (sponsor's Appendix Group A, Analysis.0, P. 39, Volume 5) reveals that the incidence of mental status related adverse events was increased with tiagabine treatment compared to placebo. The categories of mental status with the largest difference between tiagabine and placebo were dizziness (21% vs 13%) mood/behavior (21% vs 10%) and thought processing (14% vs 7%). The specific medical terms with statistical significant differences (Fisher's Exact test at 0.05 level) between tiagabine and placebo were dizziness, fatigue, somnolence, depression, insomnia, irritability, and concentration impaired.

Among the patients reporting mental status-related adverse events, 13 tiagabine-treated patients (2.6%) and 0 placebo-treated patients reported the events as severe. Nearly all of the severe events involved impairment of alertness in the form of drowsiness or tiredness (sponsor's Appendix Group A, Analysis .7, P. 124, Volume 5). There were no reports of moderate or severe thinking abnormal adverse events. Eight of the patients experienced a severe event that resulted in tiagabine therapy discontinuation.

From Appendix Group A Analysis .8 (P. 127, Volume 5) in the three double-blind, placebo-controlled, parallel-group studies, discontinuations for mental status changes occurred in 6% (31/494) of tiagabine-treated patients compared with 2% in placebo (5/275). An increase in discontinuations with tiagabine of 1% over placebo was found with confusion, and somnolence. Confusion was the most common event for discontinuation. Only 2/494

(<1%) of tiagabine-treated patients discontinued because of the thinking abnormal. Discontinued patients often had pre-existing psychiatric histories or cognitive impairment. Most patients discontinued for mental states changes that were mild or moderate in severity. The duration was usually limited to the trial period.

There was no clear dose-response within the therapeutic range recommended for add-on therapy (32-56 mg/day) but there was a greater incidence of mental status changes e.g., dizziness and nervousness, in the 36 mg/day group compared to the 56 mg/day low-dose group in the conversion to monotherapy study M93-090. In this monotherapy design, the patients had no hepatic enzyme inductions so that 36mg as monotherapy may be out of the therapeutic range (Appendix Group A, Analysis .3a and .3b, P. 81-, Volume 5). Most patients required no change in the dose or discontinuation. Somnolence, dizziness and lethargy required the greatest proportion of change.

Of the 12 mental status related events, all diminished in incidence in the fixed-dose compared to titration period. Some events were longer in duration with tiagabine including concentration impaired.

Less than 2% of the tiagabine-treated patients had a serious adverse event in which the primary reason for hospitalization was a mental status related adverse event.

Lastly an analysis of patients reporting adverse events or clusters (onset on same day or within one day after any one of the adverse events in the cluster) suggestive of non-convulsive status epilepticus (NCSE) was done by sponsor to evaluate any association of tiagabine use with unrecognized NCSE (sponsor's Appendix Table Group A, Analysis .9A, P. 129,Vol. 5). To assure broad capture, the occurrence of any adverse event consistent with a change in the level of consciousness and/or intellect and a motor symptom event was evaluated. In the 3 placebo-controlled add-on epilepsy studies (M91-603, 605 and N92-775) 2 placebo (N=275) and 18 (N=494) tiagabine-treated patients had potential NCSEs. (Sponsor's Appendix Table group A. Analysis .9B, P. 130, Vol. 5). Overall among all epilepsy trials, 181 patients come within this category of NCSE. An analysis of patients with possibly unrecognized or unrecorded NCSE showed most (89%) continued taking tiagabine and required little or no use of intravenous medication or benzodiazepines possibly suggesting that these patients did not have NCSE and that treatment of these patients did not require extraordinary therapy, (from sponsor's Appendix Table group A analysis. 9A, P.129, Vol. 5).

Group B Analysis

NCSE was further evaluated by analyzing tiagabine-treated patients in all epilepsy clinical trials who reported at least one episode of either status epilepticus or complex partial. For the reader's convenience tables relevant to this section are located in Appendix 9 of this review.

The tiagabine dose after the first episode of NCSE was assessed among 77 patients from the clinical trials of epilepsy. (Sponsor's Table 21, Vol. 2). Approximately 17% of patients (13/77) either discontinued or lowered the dose of tiagabine. The remaining 83% either had no change (74%) or increased the tiagabine dose (9%). Four patents (5%) had an IV medicine added and one patient received a benzodiazepine as treatment. Concomitant AED doses were changed in about half of the patients.

Among the 36 patients with more than one episode of NCSE (sponsor's Table 22, Vol. 2) the results were similar. Approximately 80% (29/36) of the patients had either increased tiagabine dose (8%) or had no dose change (72%). No patient required additional benzodiazepine and one required an IV medicine.

Approximately 71% of patients with NCSE had no dose change 7 days before the episode. The same was seen in 75% of patients without NCSE, (sponsor's Table 23, Vol. 2).

Group C Analysis

As an additional evaluation of the questions of mental status and tiagabine therapy, an analysis of 13 clinical cases of patients in clinical trials with mental status related adverse events and spike/wave discharge on EEG were reviewed. These patients had been reported previously as cases of unclear diagnosis. All 13 cases were reviewed by an advisory panel in September, 1996. Previously (for safety update I) nine of 13 cases had been initially reviewed in July of 1995.

In Section 8.13.17.3 (Volume 14) of safety update II, Table 87 summarizes the information available for the 13 patients with impaired mental states and non-diagnostic generalized spike-wave EEG changes. It was concluded that reports of spike/wave discharges occurring with changes in mental state occurred most often in patients with pre-existing spike/wave changes and tiagabine did not cause generalized spike wave discharges at therapeutic doses.

Group D Analyses

To further clarify the mental status-related terms, in compliance with the Agency's request, the sponsor reassessed the adverse events from which the COSTART terms were derived, evaluating the appropriateness of the mental status-related terms using data from 11 investigator sites from studies M91-603 and M91-605.

For the reader's convenience, a copy of the detailed methodology is provided in the Appendix 7 of this review. Additionally, a copy of the telephone conference call of November 26, 1996 during which the issue of the plan for evaluating alterations in mental status is discussed is also provided in the Appendix 10 of this review.

Patient narratives were constructed by the sponsor to assist in the identification of clinically meaningful descriptions of mental status-related adverse events and are included in Group D analysis Volume 6 of this safety update submission.

Of the patients treated (N=615) in the 2 double-blind, placebo-controlled studies, 40% (N=248) were studied (tiagabine,168 and placebo, 80). Among the 135 patients with treatment-emergent mental status-related adverse events, 95 were in tiagabine and 40 were in placebo. Patient narratives were generated from these groups.

Investigators were contacted over the phone and by questionnaire to obtain more clinically meaningful descriptions of the events. Changes in both COSTART and medical terms were recorded in this process although no changes were made to the original database. The resulting changes in the terms are shown in Appendix Table Group D Analysis.1., Volume 5 and for the convenience of the reader in Appendix 11 of the present review. There was little overall change in the significance between the groups. In the original data for the 11 investigators, only the COSTART term "thinking abnormal" was significantly increased over placebo and there was a relative risk of 6.67 of a tiagabine-treated patient exhibiting the event. No medical terms were significantly increased with tiagabine compared to placebo. In the new questionnaire data, only insomnia (as both COSTART and medical term) was significant versus placebo and the significance of the COSTART term thinking abnormal was lost. The relative risk was decreased to 1.62 from the original 6.67 largely because of an increase in the number of placebo patients having the event. In general, there was little other change between the two databases. It was also noted that nearly all of the events were indirectly rather than directly observed. The sponsor supplied a table (Appendix Table Group D Analysis .2) which showed all mental status-related adverse events studied in the sample and any changes to the COSTART or medical term. Several COSTART terms per original case report adverse event description, e.g., aphasia, depersonalization, amnesia were recorded per questionnaire adverse event description to the COSTART term thinking abnormal.

In conclusion, the sponsor's review of the sample of patients from two of the double-blind, placebo-controlled, add-on, parallel-group studies further defined the nature of the events occurring in association with tiagabine therapy.

Patients from the top-enrolling investigators from two pivotal mental status add-on trials were studied to ascertain the nature of related adverse events. Clarifications were obtained for several medical and COSTART terms. Asthenia was noted to be tiredness or lack of energy. Nervousness was found to be anxiety and irritability. Thinking abnormal was mental slowness or difficulty concentrating. The patients often had similar pre-existing conditions. The events were usually well-tolerated or easily managed with dosage reductions. There were few discontinuations and only one hospitalization. Difficulty sleeping or falling asleep, dizziness, and lethargy or tiredness were the most common and found in similar percentages of tiagabine and placebo-treated patients. Hostility, irritability,

trouble concentrating or mental slowness, depression, and mild memory impairment were less common. The results are quite similar to those reported previously on Group analysis A.

To gain some perspective with regards to the mental status adverse event data in tiagabine-treated patients and conceivably assist in decision making with respect to drug labeling it may be helpful to examine these data with reference to other recently approved epilepsy drugs. One of the most recently approved being topiramate. Topiramate data, because of similarities in addressing the issue of risks associated with cognitive/psychiatric or neuropsychiatric events as conveyed in the approvable letter of December 29, 1995 is mentioned in this review. Furthermore, the WARNINGS section of topiramate labeling incorporates these events and clearly, a question arises as to whether similar labeling should be implemented for tiagabine. The Division file for topiramate served as a resource. In 3 placebo-controlled tiagabine epilepsy studies the proportion of patients (14%, 69/464) that had any adverse event identified as the primary reason for premature discontinuation was similar to that reported for topiramate (17%, 89/527). Placebo rates were also similar. In pooled data from the 3 tiagabine placebo-controlled, add-on epilepsy studies (sponsor's Table 41, Volume 14) discontinuations for mental status related adverse events concerned with thought processes (confusion and thinking abnormal) occurred more frequently (2%, 10/494 vs 0%, 0/275 for tiagabine and placebo, respectively) than other adverse events. Similarly, in the topiramate pooled data from the placebo-controlled studies, the most frequent reason attributed to withdrawal was that of cognitive impairment (manifested by confusion, impaired thinking, etc.). This occurred with an incidence of 5% (27/527) and 0.9% (1/216) in the topiramate and placebo-treated groups, respectively.

Of the patients who discontinued, the mental status category mood/behavior encompassing the terms depression, hostility and nervousness accounted for 1.4% (7/494) of the withdrawals from tiagabine treatment and none from placebo. For topiramate-treated patients, 0.06% (3/527) withdrew for depression and 1.0% (2/216) and 3% (15/527) withdrew for nervousness, emotional liability and anxiety and none from placebo.

Dizziness accounted for 0.08% (4/494) of tiagabine and 0.04% (1/275) placebo patients withdrawing. Similarly, dizziness in topiramate-treated patients accounted for a small percentage of withdrawals (1.1%, 6/527) and no placebo. The mental status category level of consciousness medical adverse event term somnolence was responsible for 1.6% (8/494) of withdrawals in tiagabine-treated patients and 0.07% (2/275) for placebo. Only 0.02% (1/527) topiramate exposed patients discontinued because of somnolence, and 0.05% (1/216) placebo. Reports of psychomotor slowing resulting in discontinuation did not occur in tiagabine-treated patients whereas 4.1% of topiramate-treated patients (n=1,715 individuals) discontinued because of this event.

The table which follows of pooled data from placebo-controlled epilepsy studies enumerates those neuropsychiatric treatment-emergent mental status-related adverse events associated with the use of tiagabine (incidence of 1% or greater) and not seen at an equivalent incidence among placebo patients. The events are grouped by medical

status category. The specific medical terms in tiagabine-treated patients which showed a statistically significant increase compared to placebo (at the 0.05 level) were: dizziness, fatigue, somnolence, depression, insomnia, irritability and concentration impaired. Topiramate-treated patients showed additional impairment of cognition or mental processing relative to placebo as indicated by such specific medical terms as confusion and thinking abnormal, slow or sluggish. Data for this table have been assimilated from Appendix Group A Analysis .0, Volume 5 for tiagabine and the table in section 8.4.1.1 of the medical review of topiramate by Cynthia E. McCormick (p. 154, October 11, 1995). Psychomotor slowing; speech (e.g., hesitancy) and language problems (e.g., word-finding) were reported as adverse events in more than 10% of topiramate-treated patients and fewer than 1% of tiagabine-treated patients. In fact, 4.1% (70/1,715) of patients who received topiramate in clinical trials discontinued because of psychomotor slowing. The overall picture which emerges from these data is one in which tiagabine is associated with generalized cognitive dysfunction, albeit not with the magnitude typified by topiramate (with the obvious caveat about comparisons between drugs), even taking into consideration the differences in the mental-status related events for the two placebo groups.

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Number (%) of Patients With Mental Status-related Adverse Events				
Mental Status Category/ Medical Term	Tiagabine (N=494)	Placebo (N=275)	Topiramate+ (N=527)	Placebo (N=216)
Dizziness/ Dizziness	102 (21)	35 (13)	165 (31)	33 (15)
Level of Consciousness				
Fatigue	39 (8)	10 (4)	135 (26)	29 (13)
Somnolence	13 (3)	1 (<1)	149 (28)	21 (10)
Lethargy	16 (3)	4 (1)	- not available -	
Mood/Behavior				
Depression	16 (3)	2 (<1)	61 (12)	11 (5)
Insomnia	23 (5)	5 (2)	29 (5.5)	10 (5)
Irritability	26 (5)	4 (1)	- not available -	
Thought Process				
Concentration Impaired	19 (4)	3 (1)	69 (13)	4 (2)
Confusion	18 (4)	7 (3)	84 (16)	9 (4)
Thinking Abnormal, Slow or Sluggish	6 (1)	0 (0)	112 (21)	5 (2)

+ Placebo-controlled studies of similar design. Proportions are not clinically different from the pooled data for the placebo-controlled, add-on trials, listed in Table 2 of the labeling for topiramate (1996 version).

Clinical Section on Labeling

Abbott has attached (in Volume 1) a draft labeling with revisions and clarifications. The major change from the Division's draft labeling is the location of the mental status-related adverse events which they have placed in the PRECAUTIONS section rather than the WARNINGS section requested by the Division.

Extrapolating from the dropout, serious and treatment emergent adverse event data the proportion of cognitive/neuro-psychiatric adverse events as well as nervous system adverse events overall in the tiagabine-treated patients is less than topiramate which has a WARNING section in the label (describing the serious cognitive/neuropsychiatric events). Moreover, serious adverse events suggestive of cognitive dysfunction such as thinking abnormal, confusion, memory loss in the tiagabine safety update II epilepsy studies occurred at a rate of <1%. In contradistinction to the rates of cognitive impairment reflected by these terms for topiramate which were several orders of magnitude greater. (Information from page 189 of McCormick's review of October 11, 1995). Consequently as a result of the above evaluation in addition to comparison with labeling from the other recently approved antiepilepsy drug products, there are no objections to placement in the PRECAUTIONS section of the tiagabine label mention of mental status adverse events.

Conclusions

Abbott's responses to the safety issues in the approvable letter dated October 31, 1996 are satisfactory. In evaluation of the mental status related adverse events, Abbott believes that neither the nature nor the severity of the events warrant inclusion in the WARNINGS section of the labeling. The PRECAUTIONS section of the labeling has been selected by Abbott. After assessment of the overall incidence of neuropsychiatric adverse events (dropouts, serious, treatment-emergent) as well as dose response information combined with inspection of labeling from other antiepilepsy drugs approved in the last 5 years (gabapentin, 1993; felbamate, 1993; lamotrigine, 1994; topiramate, 1997). I support the view that the PRECAUTIONS section of the labeling is appropriate for the cognitive/neuropsychiatric adverse events (mental status adverse events).

The cumulative safety data in safety update II support the findings of the earlier update. Adverse events are generally related to the nervous system and are reversible. Additionally, two events not mentioned in the original NDA review were of possible importance. One case of Stevens-Johnson syndrome and one case of retroperitoneal fibrosis occurred in patients exposed to tiagabine. Assessment of these adverse events is inextricably complicated not only by the coexistent treatments, co-morbid diagnosis, but also by the paucity of data in each single case report. Even though tiagabine has not been shown during clinical trials to be causally associated with the rare skin rash Stevens-Johnson's Syndrome one should remain vigilant and diligent during postmarketing when exposure to tiagabine increases. During premarketing clinical trials in over 3500 individuals exposed to lamotrigine only 2-3 reports of Stevens-Johnson Syndrome occurred. However, the postmarketing experience with over 400,000 exposures has revealed more than 125 cases of this rash. Crystalluria was reported in some patients in safety update II, but the patients were reported to be asymptomatic.

Recommendations

I recommend the acceptance of the sponsor's responses to the Agency's comments/requests which were set forth in the approvable letter.

James F. Kuberg
08/25/97

8/13/97

The safety update appears to add nothing new regarding the safety profile of flagabine except for possibly [redacted] serious skin reactions. These were discussed in appendix 13 of Dr Knudsen's review.

I discuss these cases as well as my opinions regarding the sponsor's response to the Approvable letter under a separate memo.

G Burm

cc:
NDA
Division File HFD-120/
/RKatz/
/GBurkhart/
/JKnudsen/
/CSO/

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Appendix 1

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Table 2.A. Table of Studies Providing New Data by Study Design, Abbott Sponsored

Long-Term Epilepsy Studies

Abbott/[1] Study Number/Title/ Abbott Report Number	Investigator Name/ Location	Design, Blinding, Randomization	Start/ Stop Dates	Treatment/ Dose Regimen/ Formulation[1]	Number Treated[2]	Age Range (Mean)	Gender[3] Race[3]	Treatment Duration
Study M91-604/ TIA-110: An Open-Label Extension Study of Tiagabine in Treatment of Patients with Partial Seizures R&D/95/684[4]	Multi-center Study - See Study Summary (57 sites)	Open-label Non-comparative	07/1992 Ongoing[6]	Tiagabine ≤128 mg/day Variable regimen Tablets	815 (764 in Safety Update I)	3-77 (33)	M (54%) F (46%) C (89%) B (7%) O (4%)	open
Study M92-813/ TIA-114: An Open-Label Study of the Safety of Long-Term Tiagabine Administration in Patients with Epilepsy R&D/95/624[5]	Multi-center Study - See Study Summary (66 sites) [Note: Includes five sites in Canada participating in M92-813C]	Open-label Non-comparative	12/1992 Ongoing[6]	Tiagabine ≤120 mg/day (U.S.) ≤80 mg/day (Canada) Variable regimen Tablets	674 (673 in Safety Update I)	10-74 (33)	M (50%) F (50%) C (89%) B (5%) O (6%)	open

[1] Refer to Table of Investigational Formulations, Section 2.4 in the NDA
[2] Number of patients who received at least one dose of the study drug
[3] M=Male, F=Female; C=Caucasian, B=Black, O=Other.
[4] Interim report based on patient visit cut-off of 04/30/95.
[5] Interim report based on patient visit cut-off of 02/01/95.
[6] Safety Update II includes data through 08/31/96.

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Table 2.A. Table of Studies Providing New Data by Study Design, Abbott Sponsored (continued)

All Epilepsy Studies

Abbott Study Number/Title/ Abbott Report Number	Investigator Name/ Location	Design, Blinding, Randomization	Start/ Stop Dates	Treatment/ Dose Regimen/ Formulation [1]	Number Treated [2]	Age Range (Mean)	Gender [3] Race [3]	Treatment Duration
Study M91-604/ TIA-110: An Open-Label Extension Study of Tiagabine in Treatment of Patients with Partial Seizures R&D/95/684 [4]	Multi-center Study - See Study Summary (57 sites)	Open-label Non-comparative	07/1992 Ongoing [6]	Tiagabine ≤128 mg/day Variable regimen Tablets	815 (764 in Safety Update I)	3-77 (33)	M (54%) F (46%) C (89%) B (7%) O (4%)	open
Study M92-813/ TIA-114: An Open-Label Study of the Safety of Long-Term Tiagabine Administration in Patients with Epilepsy R&D/95/624 [5]	Multi-center Study - See Study Summary (66 sites) [Note: Includes five sites in Canada participating in M92-813C]	Open-label Non-comparative	12/1992 Ongoing [6]	Tiagabine ≤120 mg/day (U.S.) ≤80 mg/day (Canada) Variable regimen Tablets	674 (673 in Safety Update I)	10-74 (33)	M (50%) F (50%) C (89%) B (5%) O (6%)	open

[1] Refer to Table of Investigational Formulations, Section 2.4 in the NDA
[2] Number of patients who received at least one dose of the study drug
[3] M=Male, F=Female, C=Caucasian, B=Black, O=Other
[4] Interim report based on patient visit cut-off of 04/30/95
[5] Interim report based on patient visit cut-off of 02/01/95
[6] Safety Update II includes data through 08/11/96

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Table 2.A. Table of Studies Providing New Data by Study Design, Abbott Sponsored (continued)

Clinical Pharmacology, Bioavailability

Abbott Study Number/Title/ Abbott Report Number	Investigator Name/ Location	Design, Blinding, Randomization	Start/ Stop Dates	Treatment/ Dose Regimen/ Formulation [1]	Number Treated [2]	Age Range (Mean)	Gender [3] Race [3]	Treatment Duration
Study M96-448/ TIA-089 A Comparative Study of the Relative Bioavailability of a Test Formulation of Tiagabine Administered Fasting R&D/96/496	Cavanaugh, J., PhD., MD Abbott Clinical Pharmacology Research Unit Victory Memorial Hospital Waukegan, Illinois	Single dose Open-Label Three period Crossover Randomized	04/29/96 05/22/96	Tiagabine 2 mg x 4 QD Formulation 1	22	18-40 (27)	M (68%) F (32%)	1 day
				Tiagabine 4 mg x 2 QD Formulation 2			C (77%) B (14%) O (9%)	
				Tiagabine 4 mg x 2 QD Formulation 3				
				All fasting and Tablets				

[1] Refer to Table of Investigational Formulations, Section 2.4 in the NDA
[2] Number of subjects who received at least one dose of the study drug
[3] M=Male, F=Female, C=Caucasian, B=Black, O=Other

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Table 2.B. Table of Studies Providing New Data by Study Design, Sponsored

Long-Term Epilepsy Studies

Abbott Study Number/Title/ Abbott Report Number	Investigator Name/ Location	Design, Blinding, Randomization	Start/ Stop Date	Treatment/ Dose Regimen/ Formulation [1]	Number Treated [2]	Age Range (Mean)	Gender [3] Race [3]	Treatment Duration
Study M91-578/ TIA-105: An Open-Label Extension Study of Tiagabine in the Treatment of Patients with Epilepsy R&D/95/649 [4]	Multi-center Study - See Study Summary (5 sites)	Open-label Non-comparative	10/16/91 Ongoing [5]	Tiagabine 4-80 mg QID Tablets	30	21-57 (35)	M (70%) F (30%) C (100%)	open
Study M92-877/ TIA-111: An Open-Label Extension Study of Tiagabine: Safety and Efficacy in Treatment of Patients with Partial Seizures R&D/95/650 [4]	Multi-center Study - See Study Summary (16 sites)	Open-label Non-comparative	08/07/92 Ongoing [5]	Tiagabine 2-80 mg Variable regimen Tablets	156	17-71 (35)	M (64%) F (36%) C (100%)	open
Study M91-047/ TIA-115: An Open-Label Study of the Safety and Efficacy of Long-Term Tiagabine Administration in Patients with Epilepsy R&D/95/656 [4]	Multi-center Study - See Study Summary (25 sites)	Open-label Non-comparative	03/17/93 Ongoing [5]	Tiagabine 2-92 mg Variable regimen Tablets	395	13-72 (35)	M (52%) F (48%) C (98%) O (2%)	open

[1] Refer to Table of Investigational Formulations, Section 2.4 in the NDA.
[2] Number of patients who received at least one dose of the study drug.
[3] M=Male, F=Female; C=Caucasian, B=Black, O=Other.
[4] Interim report based on patient visit cut-off of 02/01/95.
[5] Safety Update II includes data through 08/31/96.

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Table 2.B. Table of Studies Providing New Data by Study Design, Sponsored (continued)

Long-Term Epilepsy Studies (continued)

Abbott/ Study Number/Title/ Abbott Report Number	Investigator Name/ Location	Design, Blinding, Randomization	Start/ Stop Date	Treatment/ Dose Regimen/ Formulation [1]	Number Treated [2]	Age Range (Mean)	Gender [3] Race [3]	Treatment Duration
Study M93-065/ TIA-116: An Open-Label Study of the Safety and Efficacy of Long-Term Tiagabine Administration in Patients with Epilepsy Unsatisfactorily Controlled with Other Antiepileptic Medication R&D/95/657 [4]	Multi-center Study - See Study Summary (22 investigators enrolled patients at 21 sites)	Open-label Non-comparative	05/1993 Ongoing [5]	Tiagabine 2-72 mg Variable regimen Tablets	139	12-69 (33)	M (49%) F (51%) C (99%) O (1%)	open
Study M93-092/TIA-124: An Open-Label Extension Study of Safety and Efficacy of Tiagabine in Children with Epilepsy	Multi-center Study (3 Sites)	Open-label Non-comparative	1993 Ongoing [5]	Tiagabine 2-56 mg Variable regimen Tablets	23	2-16 (9)	M (57%) F (43%) C (100%)	open
Study M94-179/TIA-129: An Open-Label Extension Study of Safety and Efficacy of Tiagabine in Patients with Partial Seizures	Multi-center Study	Open-label Non-comparative continuation study of TIA-121	1993 Ongoing [5]	Tiagabine 5-10 mg BID 7.5-10 mg TID Tablets	11	14-70 (39)	M (64%) F (36%) C (100%)	open

[1] Refer to Table of Investigational Formulations, Section 2.4 in the NDA.
[2] Number of patients who received at least one dose of the study drug.
[3] M=Male, F=Female; C=Caucasian, B=Black, O=Other.
[4] Interim report based on patient visit cut-off of 02/01/95.
[5] Safety Update II includes data through 08/31/96.

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Table 2.B. Table of Studies Providing New Data by Study Design, Sponsored (continued)

All Epilepsy Studies

Abbott Study Number/Title/ Abbott Report Number	Investigator Name/ Location	Design, Blinding, Randomization	Start/ Stop Date	Treatment/ Dose Regimen/ Formulation [1]	Number Treated [2]	Age Range (Mean)	Gender [3] Race [3]	Treatment Duration
Study M91-578/ TIA-105: An Open-Label Extension Study of Tiagabine in the Treatment of Patients with Epilepsy R&D/95/649 [4]	Multi-center Study - See Study Summary (5 sites)	Open-label Non-comparative	10/1991 Ongoing [5]	Tiagabine 4-80 mg QID Tablets	30	21-57 (35)	M (70%) F (30%) C (100%)	open
Study M92-873/ TIA-111: An Open-Label Extension Study of Tiagabine: Safety and Efficacy in Treatment of Patients with Partial Seizures R&D/95/650 [4]	Multi-center Study - See Study Summary (16 sites)	Open-label Non-comparative	08/07/92 Ongoing [5]	Tiagabine 2-80 mg Variable regimen Tablets.	156	17-71 (35)	M (64%) F (36%) C (100%)	open
Study M93-043/ TIA-113: A Single-Blind Tolerability and Preliminary Efficacy Study of Tiagabine in Children with Epilepsy	Multi-center Study - See Study Summary (2 sites)	Single-blind Non-comparative	04/28/93 06/11/95	Tiagabine 0.25-1.5 mg/kg/day TID Tablets	49	2-17 (9)	M (53%) F (47%) C (98%) B (2%)	16 weeks

[1] Refer to Table of Investigational Formulations, Section 2.4 in the NDA.
[2] Number of patients who received at least one dose of the study drug.
[3] M=Male, F=Female; C=Caucasian, B=Black, O=Other.
[4] Interim report based on patient visit cut-off of 02/01/95.
[5] Safety Update II includes data through 08/31/96.

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Table 2.B. Table of Studies Providing New Data by Study Design, -Sponsored (continued)

All Epilepsy Studies (continued)

Abbott Study Number/Title/ Abbott Report Number	Investigator Name/ Location	Design, Blinding, Randomization	Start/ Stop Date	Treatment/ Dose Regimen/ Formulation [1]	Number Treated [2]	Age Range (Mean)	Gender [3] Race [3]	Treatment Duration
Study M93-047/ TIA-115: An Open-Label Study of the Safety and Efficacy of Long-Term Tiagabine Administration in Patients with Epilepsy R&D/95/656 [4]	Multi-center Study - See Study Summary (25 sites)	Open-label Non-comparative	03/17/93 Ongoing [5]	Tiagabine 2-92 mg Variable regimen Tablets	395	13-72 (35)	M (52%) F (48%) C (98%) O (2%)	open
Study M93-065/ TIA-116: An Open-Label Study of the Safety and Efficacy of Long-Term Tiagabine Administration in Patients with Epilepsy Unsatisfactorily Controlled with Other Antiepileptic Medication R&D/95/657 [4]	Multi-center Study - See Study Summary (22 investigators enrolled patients at 21 sites)	Open-label Non-comparative	05/1993 Ongoing [5]	Tiagabine 2-72 mg Variable regimen Tablets	139	12-69 (33)	M (49%) F (51%) C (99%) O (1%)	open
Study M93-092/TIA-124: An Open-Label Extension Study of Safety and Efficacy of Tiagabine in Children with Epilepsy	Multi-center Study (3 Sites)	Open-label Non-comparative	01/10/93 Ongoing [5]	Tiagabine 2-56 mg Variable regimen Tablets	23	2-16 (9)	M (57%) F (43%) C (100%)	open

[1] Refer to Table of Investigational Formulations, Section 2.4 in the NDA
[2] Number of patients who received at least one dose of the study drug
[3] M=Male, F=Female; C=Caucasian, B=Black, O=Other
[4] Interim report based on patient visit cut-off of 02/01/95
[5] Safety Update II includes data through 08/31/96

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Table 2.B. Table of Studies Providing New Data by Study Design, Sponsored (continued)

All Epilepsy Studies (continued)

Abbott/ Study Number/Title/ Abbott Report Number	Investigator Name/ Location	Design, Blinding, Randomization	Start/ Stop Date	Treatment/ Dose Regimen/ Formulation [1]	Number Treated [2]	Age Range (Mean)	Gender [3] Race [3]	Treatment Duration
Study M94-179/TIA-129: An Open-Label Extension Study of Safety and Efficacy of Tiagabine in Patients with Partial Seizures	Multi-center Study (21 sites)	Open-label Non-comparative continuation study of TIA-121	02/23/95 Ongoing [5]	Tiagabine 5-10 mg BID 7.5-10 mg TID	11	14-70 (39)	M (64%) F (36%) C (100%)	open
Clinical Pharmacology: Drug Interaction Studies								
Study M96-444/TIA-087: An Open-Label, Randomized, Two-Period Crossover Pharmacokinetic Trial Evaluating the Possibility of Interaction Between Tiagabine and Erythromycin During Multiple Dose Administration to Healthy Volunteers	J. H. G. Jonkman, MD The Netherlands (1 site)	Open-label Two-period Crossover Multiple-dose Randomized	05/05/96 06/13/96	One period only: Erythromycin Day -1, 500 mg QD Days 1-4, 500 mg BID Day 5, 500 mg QD Both periods: Tiagabine Days 1-3, 4 mg BID Day 4, 4 mg QD Tablets	14	19-28 (22)	M (50%) F (50%) C (100%)	15 days

[1] Refer to Table of Investigational Formulations, Section 2.4 in the NDA
[2] Number of patients/subjects who received at least one dose of the study drug
[3] M=Male, F=Female; C=Caucasian, B=Black, O=Other
[4] Interim report based on patient visit cut-off of 02/01/95
[5] Safety Update II includes data through 08/31/96

Appendix 2

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Table 3. Summary of Patient/Subject Accountability

Type of Study	Tiagabine Patients/Subjects [1]	Placebo Patients/Subjects	Cumulative Unique Tiagabine Patients/Subjects
Placebo-Controlled, Parallel-Group Add-On			
M91-603	206	91	
M91-605	211	107	
M92-775	77	77	
Total	494	275	494
Placebo-Controlled, Parallel-Group Monotherapy			
M90-511	7	4	501
Low-Dose Versus High-Dose, Parallel-Group Monotherapy			
M93-090	198	0	699
Placebo-Controlled, Crossover Add-On			
M90-481 [2]	94	45	
M91-565	88	38	
Total:	182	83	881
Short-Term, Single-Blind, Add-On			
M93-043	49	0	930
Short-Term, Open-Label, Monotherapy			
M92-855	31	0	961
Long-Term, Open-Label Add-On	**Safety Update II (Safety Update I)**		**Safety Update II (Safety Update I)**
M91-604 [3]	815 [280] (764 [229])	0	
M91-578	30 [0]	0	
M91-595	2 [0]	0	
M91-710	3	0	
M92-813	674 (673)	0	
M92-873 [4]	156 [68]	0	
M93-047	395	0	
M93-065	139	0	
M93-092	23 [0]	0	
M94-179	11	0	
Total.	2248 [1570] (2185 [1507])	0	2531 (2468)

[1] Number of unique tiagabine patients/subjects. if different, is indicated in brackets. Unique tiagabine patients/subjects are patients/subjects not tabulated as receiving tiagabine with another study listed in this table.
[2] This includes five patients from M89-398, a Clinical Pharmacology study.
[3] This includes 82 patients from M91-603 and 100 patients from M91-605 that received placebo in the short-term studies; 73 patients from M92-825 (an ongoing study), 37 of whom did not receive tiagabine in that study; and 25 patients from M94-244, a Clinical Pharmacology study.
[4] This includes 68 patients from M92-775 that received placebo in the short-term studies.

Table 3. Summary of Patient/Subject Accountability (continued)

Type of Study	Tiagabine Patients/Subjects [1]		Placebo Patients/Subjects	Cumulative Unique Tiagabine Patients/Subjects
Clinical Pharmacology [2]	**Safety Update II (Safety Update I)**			**Safety Update II (Safety Update I)**
Subject, Single Dose				
M89-319	19		11	
M90-463	19		0	
M90-496	19		0	
M90-518	5		0	
M91-560	30		0	
M92-809	18		0	
M92-810	18		0	
M93-045	12		0	
M93-066	24		0	
M93-087	12		12	
M94-188	13		0	
M93-081	16		0	
M93-083B [3]	20 [19]		0	
M94-155 [3]	18 [16]		0	
M94-157 [3]	24 [20]		0	
M96-448	22	(0)	0	
Total:	289 [282]	(267 [260])	23	2813 (2728)
Subject, Multiple Dose				
M90-425	30		30	
M90-426	12		6	
M91-607	24		0	
M91-712	10		0	
M92-792	14		0	
M92-793	25		0	
M93-044 [4]	24		0	
M93-079	12		0	
M93-080	13		13	
M93-088	20		19	
M96-444	14	(0)	0	
Total	198	(184)	68	3011 (2912)

[1] Number of unique tiagabine patients/subjects if different, as indicated in brackets. Unique tiagabine patients/subjects are patients/subjects not tabulated as receiving tiagabine with another study listed in this table.

[2] Patients in study M93-009 were enrolled at the same time in either M91-604 or M92-813. safety data is tabulated in either M91-604 or M92-813.

[3] There were four patients enrolled in both M94-156 and M94-170. three patients in both M94-156 and M94-171. three patients in both M93-083b and M94-157. one patient in all of M93-081. M93-083b. and M94-157. and three patients in both M93-080 and M94-155.

[4] Eight of the 24 were patients.

Table 3. Summary of Patient/Subject Accountability (continued)

Type of Study	Tiagabine Patients/Subjects[1]	Placebo Patients/Subjects	Cumulative Unique Tiagabine Patients/Subjects
Clinical Pharmacology[2] (continued)			
Patient, Single Dose			**Safety Update II (Safety Update I)**
M89-398	16 [11]	17	
M91-590	12	0	
M94-244	25 [0]	0	
Total	53 [23]	17	3034 (2935)
Patient, Multiple Dose			
M93-089	12	0	
M94-156	28	0	
M94-170[3]	12 [8]	0	
M94-171[3]	12 [9]	0	
Total	64 [57]	0	3091 (2992)

[1] Number of unique tiagabine patients/subjects if different, is indicated in brackets. Unique tiagabine patients/subjects are patients/subjects not tabulated as receiving tiagabine with a study listed earlier in this table.

[2] Patients in study M93-009 were enrolled at the same time in either M91-604 or M92-813; safety data is tabulated in either M91-604 or M92-813.

[3] There were four patients enrolled in both M94-156 and M94-170, three patients in both M94-156 and M94-171, three patients in both M93-083b and M94-157, one patient in all of M93-081, M93-083b, and M94-157, and three patients in both M93-080 and M94-155.

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Appendix 3

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Deaths Occurring in Patients Who Received Tiagabine in Tiagabine Clinical Trials

Study	Patient Number	Age/ Gender	Days Since First Dose of Tiagabine to Onset of Event [1]	Daily Dose (mg) at Onset of Event	Cause of Death	Alternative Etiology
M90-481/M91-578	4006/151	34/M	1148	32	@Grand Mal Convulsion	No data
			1148	32	@Sudden Death	No data
M90-481/M91-578	5010/102	43/F	847	16	@Respiratory Disorder	No data
M91-603/M91-604	11307/11305	18/M	159	40	@Arteriosclerosis	Arteriosclerosis
			159	40	@Heart Failure	Arteriosclerosis
			159	40	@Sudden Death	Arteriosclerosis
M91-605/M91-604	11113/51116	66/M	412 [199]	OFF	@Sepsis	Aspiration pneumonia
M91-603/M91-604	11601/31603	24/M	286 [218]	OFF	@Drowning (presumably during a seizure)	No data
M91-605/M91-604	10817/50817	40/F	247	40	@Temporal Astrocytoma	Recurrence of left temporal astrocytoma
M91-605	11807	27/F	1 [6]	PRE	Aplastic Anemia	Related to carbamazepine or phenytoin
M92-775/M92-871	19011/70902	49/M	198	12	@Myocardial Ischemia	No data
M92-813	1501	22/F	648	42	Sudden Death	Intractable seizures
M92-813	1901	57/F	133	52	Accidental Injury	Head trauma secondary to fall
			133	52	Subarachnoid Hemorrhage	Head trauma secondary to fall
M92-813	2309	14/M	55	6	Accidental Injury	Seizure

@ Documented in Extension Study, the second of the two studies listed

[1] Total days on tiagabine shown in brackets when the event(s) that led to death began while the patient was not on drug.

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Deaths Occurring in Patients Who Received Tiagabine in Tiagabine Clinical Trials (continued)

Study	Patient Number	Age/ Gender	Days Since First Dose of Tiagabine to Onset of Event [1]	Daily Dose (mg) at Onset of Event	Cause of Death	Alternative Etiology
M92-813	3621	42/M	379	40	Sudden Death	Underlying heart condition
M92-813C	6611	33/M	53 [43]	OFF	Sudden Death	Seizure disorder
M92-813C	6701	44/M	344	68	Sudden Death	Sudden unexpected death
M92-813C	6707	48/M	540	64	Respiratory Failure	Sudden unexpected death in epilepsy
M92-047	1222	53/F	276	12	Intestinal Perforation	No data
M93-047	1223	43/M	45	24	Skin Carcinoma	No data
M93-047	1515	48/M	90 [28]	OFF	Sudden Death	No data
M93-047	2105	29/F	286	36	Asphyxia	No data
M93-047	2306	35/M	168	48	Sudden Death	No data
M93-047	3108	28/M	399	32	Sudden Death	No data
M93-047	3619	49/M	-284 [9]	PRE	Carcinoma	No data
M93-065	1803	38/M	387	24	Asphyxia	No data
M93-090	10119	75/M	103 [77]	OFF	Apnea	Aspiration
M93-090	11331	32/M	21	6	Accidental Injury	Possibly seizure related

@ Documented in Extension Study, the second of the two studies listed.

[1] Total days on tiagabine shown in brackets when the event(s) that led to death began while the patient was not on drug.

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Deaths Occurring in Patients Who Received Tiagabine in Tiagabine Clinical Trials (continued)

Study	Patient Number	Age/ Gender	Days Since First Dose of Tiagabine to Onset of Event [1]		Daily Dose (mg) at Onset of Event	Cause of Death	Alternative Etiology
New Additions for Safety Update I							
M92-775/M92-873	30101	56/F	1143	[715]	OFF	@Subdural Hematoma	No data
M91-605/M91-604	12119/52115	18/F	757	[667]	OFF	@Drowning (secondary to a seizure)	Seizure while in bathtub
M93-000/M91-604	11319/91301	33/M	561		88	@CNS Neoplasia @Coma	Recurrence of astrocytoma
M91-605/M91-604	11508/51503	58/M	1110		80	@Sudden Death	Cardiovascular event, CVA, or pulmonary event
M92-813	2807	53/M	1011		64	CNS Neoplasia	Idiopathic astrocytoma
M92-813C	6705	34/F	805	[622]	OFF	Asphyxiation (secondary to seizure)	Seizure
New Additions for Safety Update II							
M91-605/M91-604	10807/50807	46/M	827		32	@Astrocytoma	History of neurofibromatosis
M91-605/M91-604	10403/50403	18/M	1486		80	@Intestinal Gangrene @Cardiac Arrest	Volvulus
M92-813C	6710	61/M	950 [3]	[845]	OFF	Pneumonia Sepsis	Aspiration versus bacterial infection Pneumonia
M92-813	1304	29/M	-1486 [4] 1302	[1146 [4]]	PRE OFF	Arteriovenous Malformation Coma	Congenital anomaly Secondary to surgery

@ Documented in Extension Study, the second of the two studies listed.
[1] Total days on tiagabine shown in brackets when the event(s) that led to death began while the patient was not on drug
[3] Days since first dose of tiagabine to death
[4] Estimated.

Appendix 4

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Appendix **Adverse Events for Which ≥1% of Tiagabine-Treated Patients Were Discontinued and for Which the Incidence Was at Least Twice the Incidence of Placebo-Treated Patients#**
Placebo-Controlled, Parallel-Group, Add-On Studies
Abbott + Results

Body System/ COSTART Term	Number (%) of Patients Discontinued with AE	
	Tiagabine (N=494)	Placebo (N=275)
Nervous System		
Ataxia	10 (2)	1 (<1)
Confusion	11 (2)	1 (<1)
Dizziness	19 (4)	2 (<1)
Headache	6 (1)	1 (<1)
Nervousness	5 (1)	1 (<1)
Somnolence	11 (2)	3 (1)
Speech Disorder	6 (1)	0
Tremor	5 (1)	1 (<1)

Multiple adverse events per patient may have been reported as resulting in premature discontinuation; however, a patient reporting more than one adverse event resulting in premature discontinuation for a particular COSTART is counted only once for that COSTART.

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Appendix 5

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Comment 2.a: ***Warnings Section: Withdrawal Seizures***

Before the 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 patents 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		
Rx type	Decrease	No change	Increase	Decrease	No change	Increase
GTC						
PS						
CPS						
Etc.						

Comment 2.b: ***Warnings Section: 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 a 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 Warning Statement.

The warning 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 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 possibly was assessed.

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Appendix 6

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Table 8 Withdrawal Seizures First Week

Distribution of Changes from Baseline in Four-week Seizure Rates During the Withdrawal Phase of Study M91-603

	Number of Patients (%)											
	Placebo Group			Tiagabine 16 mg/day Group			Tiagabine 32 mg/day Group			Tiagabine 56 mg/day Group		
Seizure Type	Decrease	No Change	Increase	Decrease	No Change	Increase	Decrease	No Change	Increase	Decrease	No Change	Increase
Atonic	4 (100)	0	0	0	0	0	2 (67)	0	1 (33)	1 (100)	0	0
Atypical Absence	1 (100)	0	0	0	0	0	1 (100)	0	0	0	0	0
Combined Partial	54 (64)	1 (1)	30 (35)	32 (55)	1 (2)	25 (43)	47 (59)	1 (1)	32 (40)	33 (69)	0	15 (31)
Complex Partial	57 (67)	1 (1)	27 (32)	33 (57)	1 (2)	24 (41)	51 (64)	1 (1)	28 (35)	34 (71)	0	14 (29)
Generalized Tonic-clonic	0	1 (100)	0	3 (75)	0	1 (25)	1 (33)	1 (33)	1 (33)	1 (50)	1 (50)	0
Myoclonic	0	0	0	0	0	0	0	0	0	0	0	1 (100)
Secondarily Generalized Tonic-clonic	22 (71)	1 (3)	8 (26)	12 (57)	2 (10)	7 (33)	18 (67)	2 (7)	7 (26)	17 (77)	1 (5)	4 (18)
Simple Partial	29 (60)	1 (2)	18 (38)	27 (75)	0	9 (25)	27 (60)	1 (2)	17 (38)	20 (71)	0	8 (29)
Tonic	0	0	1 (100)	0	0	1 (100)	0	0	0	1 (100)	0	0

Note: Patients are included in the tabulations of each seizure type for which they had at least one seizure during the baseline phase or the withdrawal phase (or both). However, only the seizure types which occurred in at least one patient during the withdrawal phase are summarized.

Cross Reference Appendix of Withdrawal Seizure Rates by Week

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Table 9. Withdrawal Seizures: Second Week

Distribution of Changes from Baseline in Four-week Seizure Rates During the Withdrawal Phase of Study M91-603

Number of Patients (%)

	Placebo Group			Tiagabine 16 mg/day Group			Tiagabine 32 mg/day Group			Tiagabine 56 mg/day Group		
Seizure Type	Decrease	No Change	Increase	Decrease	No Change	Increase	Decrease	No Change	Increase	Decrease	No Change	Increase
Atonic	4 (100)	0	0	0	0	0	3 (100)	0	0	0	0	1 (100)
Atypical Absence	1 (100)	0	0	0	0	0	1 (100)	0	0	0	0	0
Combined Partial	50 (59)	1 (1)	34 (40)	33 (59)	0	23 (41)	49 (62)	0	30 (38)	27 (59)	0	19 (41
Complex Partial	52 (61)	0	33 (39)	34 (61)	0	22 (39)	47 (59)	0	32 (41)	26 (57)	0	20 (43
Generalized Tonic-clonic	0	1 (100)	0	4 (100)	0	0	2 (67)	1 (33)	0	1 (50)	1 (50)	0
Myoclonic	0	0	0	0	0	0	0	0	0	0	1 (100)	0
Secondarily Generalized Tonic-clonic	21 (68)	1 (3)	9 (29)	12 (60)	3 (15)	5 (25)	19 (73)	1 (4)	6 (23)	14 (67)	2 (10)	5 (24
Simple Partial	31 (65)	2 (4)	15 (31)	25 (69)	0	11 (31)	33 (75)	0	11 (25)	15 (54)	0	13 (46
Tonic	0	0	1 (100)	0	0	1 (100)	0	0	0	1 (100)	0	0

Note: Patients are included in the tabulations of each seizure type for which they had at least one seizure during the baseline phase or the withdrawal phase (or both). However, only the seizure types which occurred in at least one patient during the withdrawal phase are summarized.

Cross Reference: Appendix of Withdrawal Seizure Rates by Week

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Table 10 Withdrawal Seizures: Third Week

Distribution of Changes from Baseline in Four-week Seizure Rates During the Withdrawal Phase of Study M91-603

	Number of Patients (%)											
	Placebo Group			Tiagabine 16 mg/day Group			Tiagabine 32 mg/day Group			Tiagabine 56 mg/day Group		
Seizure Type	Decrease	No Change	Increase	Decrease	No Change	Increase	Decrease	No Change	Increase	Decrease	No Change	Increase
Atonic	4 (100)	0	0	0	0	0	2 (67)	0	1 (33)	0	0	1 (100)
Atypical Absence	1 (100)	0	0	0	0	0	1 (100)	0	0	0	0	0
Combined Partial	60 (71)	1 (1)	23 (27)	29 (52)	1 (2)	26 (46)	47 (60)	1 (1)	30 (38)	29 (63)	0	17 (37)
Complex Partial	59 (70)	1 (1)	24 (29)	29 (52)	1 (2)	26 (46)	45 (58)	2 (3)	31 (40)	28 (61)	0	18 (39)
Generalized Tonic-clonic	0	0	1 (100)	2 (50)	0	2 (50)	1 (33)	0	2 (67)	1 (50)	1 (50)	0
Myoclonic	0	0	0	0	0	0	0	0	0	0	1 (100)	0
Secondarily Generalized Tonic-clonic	23 (77)	2 (7)	5 (17)	11 (55)	2 (10)	7 (35)	18 (72)	2 (8)	5 (20)	14 (67)	1 (5)	6 (29)
Simple Partial	35 (73)	2 (4)	11 (23)	23 (64)	0	13 (36)	29 (66)	1 (2)	14 (32)	18 (64)	0	10 (36)
Tonic	0	0	1 (100)	1 (100)	0	0	0	0	0	1 (100)	0	0

Note: Patients are included in the tabulations of each seizure type for which they had at least one seizure during the baseline phase or the withdrawal phase (or both). However, only the seizure types which occurred in at least one patient during the withdrawal phase are summarized.

Cross Reference: Appendix of Withdrawal Seizure Rates by Week

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Table 11 Withdrawal Seizures: Fourth Week

Distribution of Changes from Baseline in Four-week Seizure Rates During the Withdrawal Phase of Study M91-603

Number of Patients (%)

	Placebo Group			Tiagabine 16 mg/day Group			Tiagabine 32 mg/day Group			Tiagabine 56 mg/day Group		
Seizure Type	Decrease	No Change	Increase	Decrease	No Change	Increase	Decrease	No Change	Increase	Decrease	No Change	Increase
Atonic	3 (75)	0	1 (25)	0	0	0	1 (33)	0	2 (67)	1 (100)	0	0
Atypical Absence	0	0	1 (100)	0	0	0	1 (100)	0	0	0	0	0
Combined Partial	47 (56)	2 (2)	35 (42)	30 (55)	1 (2)	24 (44)	42 (54)	0	36 (46)	26 (60)	1 (2)	16 (37
Complex Partial	48 (57)	1 (1)	35 (42)	26 (47)	1 (2)	28 (51)	40 (51)	0	38 (49)	24 (56)	0	19 (44
Generalized Tonic-clonic	0	1 (100)	0	3 (75)	0	1 (25)	1 (33)	1 (33)	1 (33)	0	0	2 (100)
Myoclonic	0	0	0	0	0	0	0	0	0	0	1 (100)	0
Secondarily Generalized Tonic-clonic	22 (73)	1 (3)	7 (23)	12 (63)	2 (11)	5 (26)	14 (56)	0	11 (44)	10 (53)	2 (11)	7 (37
Simple Partial	28 (58)	2 (4)	18 (38)	22 (63)	0	13 (37)	26 (59)	1 (2)	17 (39)	17 (65)	0	9 (35
Tonic	0	0	1 (100)	1 (100)	0	0	0	0	0	1 (100)	0	0

Note: Patients are included in the tabulations of each seizure type for which they had at least on e seizure during the baseline phase or the withdrawal phase (or both) However, only the seizure types which occurred in at least one patient during the withdrawal phase are summarized

Cross Reference: Appendix of Withdrawal Seizure Rates by Week

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Table 12

Withdrawal Seizures: Full Four Weeks

Distribution of Changes from Baseline in Four-week Seizure Rates During the Withdrawal Phase of Study M91-603

Number of Patients (%)

	Placebo Group			Tiagabine 16 mg/day Group			Tiagabine 32 mg/day Group			Tiagabine 56 mg/day Group		
Seizure Type	Decrease	No Change	Increase	Decrease	No Change	Increase	Decrease	No Change	Increase	Decrease	No Change	Increase
Atonic	3 (75)	0	1 (25)	0	0	0	2 (67)	0	1 (33)	1 (100)	0	0
Atypical Absence	1 (100)	0	0	0	0	0	1 (100)	0	0	0	0	0
Combined Partial	59 (69)	0	26 (31)	28 (48)	1 (2)	29 (50)	45 (56)	0	35 (44)	29 (60)	0	19 (40)
Complex Partial	61 (72)	0	24 (28)	25 (43)	1 (2)	32 (55)	46 (58)	0	34 (43)	27 (56)	0	21 (44
Generalized Tonic-clonic	0	0	1 (100)	3 (75)	0	1 (25)	1 (33)	0	2 (67)	1 (50)	0	1 (50
Myoclonic	0	0	0 0	0	0	0	0	0	0	0	0	1 (100
Secondarily Generalized Tonic-clonic	19 (61)	1 (3)	11 (35)	11 (52)	0	10 (48)	15 (56)	0	12 (44)	10 (45)	0	12 (55
Simple Partial	32 (67)	0	16 (33)	23 (64)	0	13 (36)	27 (60)	0	18 (40)	16 (57)	0	12 (43
Tonic	0	0	1 (100)	0	0	1 (100)	0	0	0	1 (100)	0	0

Note: Patients are included in the tabulations of each seizure type for which they had at least one seizure during the baseline phase or the withdrawal phase (or both). However, only the seizure types which occurred in at least one patient during the withdrawal phase are summarized.

Cross Reference: Appendix of Withdrawal Seizures Rates Across 4 Weeks