Appendix 7

EEG: Patients with a history of spike/wave discharges on EEG have rarely been reported to have a possible exacerbation of the discharges coincident with CNS-related adverse events associated with Gabitril™ therapy. The CNS-related adverse events typically resolved with reductions of Gabitril™ dosage. (See Precautions, General).

Overview of Background/Methods: Analysis of Mental Status-Related Adverse Events (MRAEs)

At the request of the division, mental status-related adverse events (MRAEs) were evaluated to provide understanding and analysis for the "Warnings" section of the proposed Gabitril™ labeling. This request was answered by four specific analysis, each evaluating a particular aspect of MRAEs. For convenience, these analyses were designated as A, B, C, and D. Mental status is defined as the activities of higher associative cerebral cortical function including cognition, mood, behavior and level of consciousness. These functions are encompassed by the categories of level of consciousness, mood/behavior, thought content, and thought processes. In addition, dizziness was added as an additional category for those patients who did not specifically describe light-headedness. This was because dizziness could be a vague term for a reduced level of consciousness or even mild confusion. The MRAEs were identified by the Abbott Medical Director after reviewing the descriptions of all nervous system adverse events from the CRFs. These events all matched to medical and COSTART terms which were subsequently used in the following analyses. (See Appendix of Medical Terms and Descriptions of MRAEs Among All Nervous System Adverse Events).

Analysis A was performed to characterize the MRAEs as completely as possible. In most cases, the three double-blind, placebo-controlled (DBPC), parallel-group, add-on TGB studies were used so that a placebo group could be used for comparison. The analyses were performed as follows using the listed studies for further characterization of MRAEs:

• Incidence	- DBPC
• Demographics	- DBPC
• Severity	- DBPC
• Discontinuations	- DBPC
• Dose-Response	- M91-603 add-on dose-response study - M93-090 low-versus high-dose monotherapy
• Action Taken	- DBPC
• Dose-Frequency	- M91-603/M91-605 dose-response and dose-frequency (Abbott DBPC add-on studies, the 492-775 study used different initial doses and was excluded)
• Titration	- DBPC (M91-603/M91-605 studies only)
• Duration	- DBPC
• Neurological Examination	- DBPC
• Neuropsychological Tests	- M91-603
• Serious Adverse Events (SAEs)	- DBPC
• "Potential" Non-convulsive status epilepticus (NCSE)	- All epilepsy studies

In addition to these analyses, graphic representations of MRAEs for each patient in the three DBPC studies are included in the Appendix Table of Graphics of Mental Status Related Adverse Events. These graphics show the MRAEs over time and allow a visual presentation of the clustering of these events.

In the DBPC studies, the analyses were of one of two types: (1) those which compared the tiagabine and placebo groups separately for patients with and without MRAEs, and (2) the analysis which compared the tiagabine and placebo groups separately for each MRAE. Analyses of the second type were performed after grouping the MRAEs according to their medical terms.

Unless otherwise indicated, the tiagabine group included all tiagabine dose groups.

In these analyses, all MRAEs were used for incidence, demographics, outcomes, severity, neurological tests, and the neurological examination. A group of MRAE medical terms (12 in total) that had a higher incidence with TGB compared to placebo using specified criteria were used for the analyses of dose-response, dose-frequency, duration and incidence across time. The three DBPC, add-on studies were used to analyze incidence, demographics, discontinuations, severity, duration, neurological examination, and serious adverse events (SAEs). A special grouping of patients with specific mental and motor adverse events occurring concomitantly from all epilepsy trials was used for the "potential" non-convulsive status epilepticus (NCSE) group. Analyses of duration considered only the two Abbott studies for reasons described in the safety update.

The Group B analysis was performed to analyze the actions taken in response to non-convulsive status epilepticus (NCSE) and to determine if adjustments in TGB or other AED dosage was likely cause of the episodes.

Group C included 13 patients intensively studied for MRAEs and spike/wave discharges (SWDs) on EEG recordings. Two advisory meetings presented specific findings and recommendations concerning these patients.

The Group D analysis included the patients from the two US DBPC studies designated for the generation of descriptive narratives at the request of the Division. The patients were selected from the 11 investigators (top five in M91-603, top 6 in M91-605) randomizing the most patients in the two studies. This analysis was performed to obtain clinically understandable descriptions of MRAEs.

Summaries of the overall analysis plans and proposals presented to the Division are included in the Appendix. These analyses were integrated to

provide a statement for labeling, and as a result of the analyses we recommend that statement be used in the "Precautions" section.

GROUP A ANALYSIS: Characterization of Mental Status Related Adverse Events (MRAEs)

Group A Analysis - Background/Methods — Analysis of MRAEs

The NDA approvable letter expressed concern over mental status-related adverse events (MRAEs) with the use of tiagabine (Gabitril™). Abbott was asked to characterize these alterations in more detail to allow construction of a labeling statement to promote the safe use of Gabitril™. (See attached agenda to the 11/22/96 Abbott/FDA Teleconference in attached Appendix.

Two main strategies were adopted to review MRAEs. The first relied on the existing database from Safety Update II while the second was a sample of these events from 11 investigators in the two US, placebo-controlled parallel-group studies (M91-603 and M91-605). The adverse events were chosen from descriptions of all nervous-system adverse events from all epilepsy trials. Events were chosen from the list if there was a suggestion of alteration in:

- level of consciousness
- thought content
- thought processes
- behavior/personality
- dizziness (unless clearly designated as light-headedness)

This list of possible MRAEs was used to compare events in the three double-blind, placebo-controlled, parallel-group, add-on trials. All MRAEs were considered in the analysis of demographics, severity of the event, and discontinuation rates in the three DBPC trials. In other comparisons, a selected set of 12 MRAE medical terms that satisfied one of the following criteria were considered. MRAEs occurring <10% with placebo needed to be

at least 1.5 times greater with tiagabine. If the MRAEs were > 10% with placebo, then the tiagabine incidence needed to be at least 5% greater than placebo. The resulting MRAEs formed a list of 12 events used for analysis of action taken, duration, severity, incidence over time, dose response and dose frequency. Dose response included only the dose-response trial M91-603. Dose frequency only included the dose frequency study M91-605. This provides a detailed analysis of MRAEs that were more common with tiagabine than placebo.

To further assess the impact of mental status related adverse events (MRAEs) on the daily lives of patients, an additional analysis of the relationship of these events to neuropsychological testing was also performed. The original group of MRAEs as initially defined as any adverse event affecting level of consciousness, thought content, thought processes, behavior/personality, and dizziness (excluding light-headedness), were defined and the patients in tiagabine study M91-603 were divided between those who had an MRAE during the trial and those that did not have an MRAE. Study M91-603 was a double-blind, placebo-controlled, parallel-group, dose response trial of TGB 16 mg, 32, and 56 mg/day versus placebo. Neuropsychological testing was performed at baseline and during fixed-dose on 156 patients. These patients are included in the analysis. The patients with MRAEs and without MRAEs were compared between TGB and placebo in each group. In one analysis the TGB groups included all three TGB groups; in the second analysis, the TGB groups included only the 32 mg and 56 mg/day groups since these are the doses considered therapeutic. The groups were examined both for effect of the treatment and for any interaction effect of the MRAEs by a two way analysis of variance.

(2)

In addition to the analysis of MRAEs in the three placebo-controlled trials, a separate analysis to evaluate patients with possibly unrecognized non-convulsive status epilepticus (NCSE) was performed. In this analysis, symptoms most commonly associated with NCSE were derived from the medical literature by a consultant (James C. Sakellares, MD, Gainesville,

Florida). The most complete and largest descriptive clinical series found was reported by Tomson et. al. (Epilepsia, 1992, report attached). In this series of 32 consecutive patients, a combination of impaired level of consciousness with certain motor manifestations of NCSE were described and summarized as:

- Impaired level of consciousness or intellect
  - impairment of consciousness
  - unresponsiveness or reduced alertness
  - altered intellect
- Motor
  - gross movements, positioning, raising, flexation/extension, head deviations
  - rhythmic myoclonias of eyelids or extremities
  - irregular, discrete and infrequent twitches or tics of the extremities, perioral area, or eyelids

These descriptions of adverse events related to NCSE were matched to medical terms and a list of patients was generated from all clinical trials of epilepsy. Those patients from the DBPC trials and from all epilepsy trials exhibiting any impaired level of consciousness or intellect term along with any motor term for which the onsets were the same day or within one day of each other, as a "high risk" population for unrecognized or "potential" NCSE. In addition, an analysis of action taken was performed for all epilepsy studies which assessed TGB and other AED dosage adjustments, as well as whether IV drugs or benzodiazepine were taken within the 7 day period following the onset of the AE cluster. These analyses summarized whether TGB treatment was continuing 30 days after the onset of the AE cluster. A listing of the medical terms from each of the two categories are provided in the Appendix, Medical Terms For "Potential" NCSE Analysis Table.

Group D: Background/Methods — Analysis of Patient Narratives Requested by the Division

Background

It was noted in section 2.b of the October 31, 1996 approvable letter for the Gabitril™ (tiagabine) NDA that the COSTART medical terms used to describe adverse events suggestive of mental status changes were not clinically instructive or meaningful.

In order to generate useful labeling statements addressing possible mental status changes, the FDA's Division of Neuropharmacological Drug Products suggested that Abbott reassess the AEs from which the COSTART terms were derived. In compliance with this request, Abbott proposed a plan whereby Abbott would evaluate the appropriateness of the MRAE descriptions using data from selected investigator sites. In an agreement reached with FDA, the plan called for Abbott to confine its screening and evaluation of mental status-related descriptions (investigator verbatims) to the U.S. double-blind placebo-controlled studies (M91-603, M91-605). Additionally, Abbott would contact the 11 investigators (top 5 in M91-603, top 6 in M91-605) randomizing the most patients from the studies (comprising 248 patients out of 615) to confirm or clarify the originally recorded AE descriptions (investigator verbatims) used to report mental status changes for the patients they evaluated.

A summary of the overall plan's sequence of events is shown below:

Generate list of investigators (M91-603, M91-605)

↓

Generate list of mental status-related AEs

↓

Generate survey (questionnaire) form

↓

Confirm acceptability of questionnaire form / methodology with FDA

↓

Forward questionnaire to sites

↓

Collect data from sites

↓

Create questionnaire database

↓

Assign medical terms* and write patient narratives

↓

Return narratives with assigned medical terms to site

↓

Investigator review / approval (signature)

↓

Final changes to questionnaire database

↓

Produce summary tables

* assignment by Abbott Laboratories of medical terms from the COSTART dictionary to the verbatim descriptions provided by the investigator.

Methodology

Provided below is a detailed description of the methodology used to obtain data from the investigator sites for purposes of clarifying the MRAE descriptions.

An initial contact with the site's principal investigator was made by Kenneth W. Sommerville, M.D., Medical Director, Neurotherapeutics Venture, to provide background information on the objective, scope, and methodology agreed to by Abbott and the FDA for clarifying the verbatim description(s) of adverse event (AE) terms related to mental status changes.

After initial contact, an information package was sent by Abbott Laboratories to each site. Each package consisted of an explanatory cover letter (copy appended), investigator questionnaire (copy appended), and site-specific reference documents. A complete listing of the reference materials needed for completion of the survey (Abbott-supplied and site-supplied) was provided in the cover letter and is summarized below:

- Applicable mental status-related adverse event pages from the case report forms (CRF) (Abbott-supplied)
- Comment pages from the CRFs (Abbott-supplied)
- Neurologic exam data from the CRF (Abbott supplied)
- Patient-specific graphic presentations of mental-status adverse events over time (Abbott-supplied)
- Listing of CNS AEs identified as mental status-related (Abbott supplied). This listing included the originally recorded AE description, medical term and COSTART term for each event.
- Clinic notes/records or equivalent source documents (provided by site)

Upon review of the reference documents described above, the principal investigator at each site was instructed to complete the questionnaire and return it to Abbott Laboratories. A medical review team at Abbott reviewed the returned questionnaire and assessed the responses for any changes made by the investigator to the description of the AE or the assigned medical and COSTART terms.

Provided below is a description of the methodology / conventions used by Abbott for reporting the information received from the investigators from the returned questionnaires.

Description of the Adverse Event

Any change by the investigator to the originally recorded AE description was accepted without modification by Abbott as a new AE description. The new description was used to assign a medical term, if warranted. In instances where an investigator provided a single word AE description response only, the investigator was contacted by the Abbott Medical Director for further clarification. The method used for assigning all medical and COSTART terms was consistent with that used in the original study. An example of how AE descriptions are coded and the relationship to medical and COSTART terms is shown below:

Table 25. Examples of How Descriptions are Coded

Description of Adverse Event	*Medical Term*	*COSTART Term*
"aggression, rude, will hit"	aggressive reaction	hostility
"incoherent"	confusion	confusion
"difficulty with word finding"	dysphasia	speech disorder

In instances where the investigator provided additional (i.e., supplemental) descriptive information on a given AE for clarification purposes, but made no changes to the existing (original) AE description, the additional descriptive information was added to the existing AE description and no new medical term was assigned. A new medical term was accepted from an investigator, regardless of the change to the AE description, if the investigator felt that the more accurate medical term should be used. This new term was used for purposes of this response but was not changed in the original database.

In instances where a new (not previously reported) AE was added to the AE description section of the questionnaire by the investigator, then a new medical term was assigned based on the information provided.

Medical Terms

All medical terms assigned to the originally recorded AE descriptions remained unchanged if the AE description information received from the investigator represented supplemental (clarifying) descriptive information only and was consistent with the medical term already assigned.

In instances where the originally assigned medical term was not accurate, based either on the new descriptive information provided or the opinion of the investigator, a new medical term was assigned in agreement with the investigator.

COSTART Terms

All COSTART term assignments were made using the Adverse Event COSTART III Manual. No changes in COSTART terms were made unless there was a corresponding (linked) change in medical term per the COSTART dictionary. All AE description, medical term and COSTART term assignments were made in agreement with the investigator.

Narratives

Data from the questionnaires were integrated with additional study database information to produce brief, written patient narratives summarizing the adverse event(s) and medical terms assigned to reflect the event. The narratives were sent to the investigators for review, verification of accuracy, and signature/approval. In their review, the investigators were specifically asked to verify the accuracy of the AE description and the assigned medical and COSTART terms. A COSTART medical term dictionary was provided to each investigator as a reference for their review of the narratives and final assignment of medical terms. Provided below is a summary of the procedures for handling changes to the written patient narratives.

Any change by the investigator to any section of the written patient narrative was made directly on the narrative form by the investigator. The investigator was asked to sign and date all changes made to the narrative consistent with the procedure used for correcting/ revising case record forms. The narratives were then returned to Abbott for correction and/or revision. Revised narratives were then returned to the investigators for review, verification of accuracy and signature/approval. This iterative process occurred as often as necessary to achieve a final narrative.. The original and all subsequent revised narrative forms have been retained by Abbott as source documents.

If there was an inconsistency among the AE description, medical term, or COSTART term, the investigator was contacted by the Abbott Medical Director and review team for clarification and resolution.

If the investigator crossed-out a medical term and inserted an AE description for which no applicable medical term existed, the medical term remained and the additional descriptive information was added to the narrative.

In instances where the investigator felt that the COSTART term did not accurately reflect the AE, more than one medical term may have been assigned. For example, a patient with the COSTART of ASTHENIA might be coded for lack of energy and drowsiness.

No medical or COSTART terms were assigned to AEs that were not determined by the investigator to be mental status-related. However, descriptive information on the non mental status AE was included in the patient narrative.

The division requested that the sponsor produce narratives of patients experiencing mental status-related adverse events (MRAEs). By agreement, patients in the two US, double blind, placebo-controlled trials from the 11 highest-enrolling investigators were included. The MRAEs were from the same list as initially described in the "Group A" analysis. The terms used in the analysis are medical terms matched to the verbatim descriptions of adverse events in all tiagabine clinical trials. The terms were chosen by reviewing all the verbatim descriptions of adverse events from all clinical trials of epilepsy. The descriptions were matched to the medical term for any event compatible with dizziness not described as light-headedness, or that involved mood/behavior, thought content, thought processes, or levels of consciousness.

Among patients enrolled in the two clinical trials from the 11 investigators, those who had any of these adverse events were selected for evaluation. A questionnaire listing the event was sent to the investigator. The questionnaire listed each event and showed the verbatim description from the CRF. The investigator was asked if the description was accurate and complete and if any additional description could be given and whether these events were directly

or indirectly observed. The questionnaires were then evaluated and used to generate narratives subsequently sent for review and signature. The Abbott Medical Director interviewed each investigator about each patient and each adverse event in the sample series to be certain that as complete a clinical description was obtained as possible. Any further changes from the interview were sent to the investigator for review and signature. Their narratives were reviewed and new tables using both the new COSTART and matching medical terms for the possible MRAEs were generated.

The purpose of constructing patient narratives was to identify clinically meaningful descriptions of mental status-related adverse events (MRAEs). By agreement with the Division, a sample of the investigators from the two DBPC add-on studies done in the US was used. The five investigators with the largest number of patients from each study were selected. There were five investigators from M91-603 and six from M91-605 because there was a tie in the number of patients and an additional investigator was included. The listing of investigators with the corresponding number of patients for potential analysis is listed below.

Table 26. Investigators Selected for Patient Narrative Review

Study M91-603		Study M91-605	
Investigator	No. Patients	Investigator	No. Patients
Uthman	25	Sachdeo	39
Rowan	23	Leroy	23
Ahmann	20	Krauss	21
Schachter	20	Drake	19
Wannamaker	20	Green	19
		Leppik	19

Together, this group of investigators studied a total of 248 patients (TGB:168, PBO:80) or 248/615 (40%) of all patients treated in the two DBPC, add-on U.S. trials of tiagabine

Appendix 8

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APPENDIX GROUP A ANALYSIS.0

TREATMENT-EMERGENT MENTAL STATUS-RELATED ADVERSE EVENTS GROUPED BY CATEGORY
PLACEBO-CONTROLLED PARALLEL-GROUP ADD-ON EPILEPSY STUDIES

ABBOTT AND RESULTS &

	NUMBER (%) OF PATIENTS WITH AE								
	ABBOTT						TOTAL		
MENTAL STATUS CATEGORY /MEDICAL TERM #	PLACEBO (N=198)	TIAGABINE (N=417)	BTWN GRPS P-VALUE ●	PLACEBO (N= 77)	TIAGABINE (N= 77)	BTWN GRPS P-VALUE ●	PLACEBO (N=275)	TIAGABINE (N=494)	BTWN GRPS P-VALUE ●●
DIZZINESS $$	31 (16)	83 (20)	.223	4 (5)	19 (25)	.001*	35 (13)	102 (21)	.009*
DIZZINESS $$	31 (16)	83 (20)	.223	4 (5)	19 (25)	.001*	35 (13)	102 (21)	.009*
LEVEL OF CONSCIOUSNESS	52 (26)	134 (32)	.159	24 (31)	26 (34)	.863	76 (28)	160 (32)	.143
ASTHENIA	1 (<1)	4 (<1)	>.999	0	0	>.999	1 (<1)	4 (<1)	.558
DROWSINESS	9 (5)	31 (7)	.221	8 (10)	5 (6)	.564	17 (6)	36 (7)	.477
DRUGGEDNESS	3 (2)	3 (<1)	.393	0	0	>.999	3 (1)	3 (<1)	.349
DULLNESS	1 (<1)	0	.322	0	0	>.999	1 (<1)	0	.147
EXHAUSTION	0	2 (<1)	>.999	0	0	>.999	0	2 (<1)	.329
FATIGABILITY	0	1 (<1)	>.999	0	0	>.999	0	1 (<1)	.491
FATIGUE	9 (5)	36 (9)	.071	1 (1)	3 (4)	.620	10 (4)	39 (8)	.041*
FUZZY	0	1 (<1)	>.999	0	0	>.999	0	1 (<1)	.491
GROGGY	1 (<1)	1 (<1)	.541	0	0	>.999	1 (<1)	1 (<1)	.590
INITIATIVE LOSS OF	0	0	>.999	0	1 (1)	>.999	0	1 (<1)	.317
LETHARGY	4 (2)	16 (4)	.331	0	0	>.999	4 (1)	16 (3)	.236
SEDATION EXCESSIVE	1 (<1)	3 (<1)	>.999	2 (3)	2 (3)	>.999	3 (1)	5 (1)	.832
SLEEPINESS	13 (7)	16 (4)	.155	3 (4)	4 (5)	>.999	16 (6)	20 (4)	.255
SOMNOLENCE	1 (<1)	12 (3)	.071	0	1 (1)	>.999	1 (<1)	13 (3)	.034*
TIREDNESS	17 (9)	30 (7)	.626	10 (13)	13 (17)	.652	27 (10)	43 (9)	.923
MOOD/BEHAVIOR	18 (9)	89 (21)	<.001*	10 (13)	13 (17)	.652	28 (10)	102 (21)	<.001*
AGGRESSIVE REACTION	1 (<1)	3 (<1)	>.999	1 (1)	2 (3)	>.999	2 (<1)	5 (1)	.535
AGITATION	1 (<1)	4 (<1)	>.999	0	1 (1)	>.999	1 (<1)	5 (1)	.337
ALTERED MOOD	0	1 (<1)	>.999	0	0	>.999	0	1 (<1)	.491
ANXIETY	2 (1)	4 (<1)	>.999	2 (3)	1 (1)	>.999	4 (1)	5 (1)	.691
BEHAVIOR ABNORMAL	0	1 (<1)	>.999	0	0	>.999	0	1 (<1)	.491
CRYING UNCONTROLLABLE	0	1 (<1)	>.999	1 (1)	0	>.999	1 (<1)	1 (<1)	.795
DEPRESSED STATE	0	1 (<1)	>.999	0	0	>.999	0	1 (<1)	.491
DEPRESSION	1 (<1)	13 (3)	.045*	1 (1)	3 (4)	.620	2 (<1)	16 (3)	.024*
DEPRESSION SUICIDAL	0	1 (<1)	>.999	0	0	>.999	0	1 (<1)	.491
EMOTIONAL LABILITY	1 (<1)	9 (2)	.180	0	0	>.999	1 (<1)	9 (2)	.130
EUPHORIA	0	0	>.999	1 (1)	0	>.999	1 (<1)	0	.317

& ABBOTT STUDIES M91-603 AND M91-605 (INCLUDES TITRATION AND FIXED-DOSE BUT EXCLUDES TERMINATION);
STUDY M92-775 (INCLUDES TITRATION AND FIXED-DOSE BUT EXCLUDES TERMINATION).
● FROM FISHER'S EXACT TEST.
●● FROM COCHRAN-MANTEL-HAENSZEL TEST.
* INDICATES STATISTICAL SIGNIFICANCE OF THE TWO-TAILED TEST AT THE .05 LEVEL.
# A PATIENT REPORTING MORE THAN ONE ADVERSE EVENT FOR A PARTICULAR MEDICAL TERM (MENTAL STATUS CATEGORY) IS COUNTED ONLY ONCE FOR THAT MEDICAL TERM (MENTAL STATUS CATEGORY).
WHERE $ OR $$ IS SHOWN BESIDE A MEDICAL TERM IT INDICATES A P-VALUE LESS THAN OR EQUAL TO .10 OR .05, RESPECTIVELY, FOR THE TEST OF HOMOGENEITY OF THE TIAGABINE EFFECT RELATIVE TO PLACEBO BETWEEN ABBOTT AND

APPENDIX GROUP A ANALYSIS.0

TREATMENT-EMERGENT MENTAL STATUS RELATED ADVERSE EVENTS GROUPED BY CATEGORY
PLACEBO-CONTROLLED PARALLEL-GROUP ADD-ON EPILEPSY STUDIES

ABBOTT AND RESULTS &

MENTAL STATUS CATEGORY /MEDICAL TERM #	NUMBER (%) OF PATIENTS WITH AE								
	ABBOTT						TOTAL		
	PLACEBO (N=198)	TIAGABINE (N=417)	BTWN GRPS P-VALUE @	PLACEBO (N= 77)	TIAGABINE (N= 77)	BTWN GRPS P-VALUE @	PLACEBO (N=275)	TIAGABINE (N=494)	BTWN GRPS P-VALUE @@
MOOD/BEHAVIOR (cont.)									
FEELING FLOATING	0	1 (<1)	>.999	0	0	>.999	0	1 (<1)	.491
FEELING HIGH	0	2 (<1)	>.999	0	0	>.999	0	2 (<1)	.329
FEELING STRANGE	1 (<1)	2 (<1)	>.999	0	0	>.999	1 (<1)	2 (<1)	.966
FEELING TENSE	0	1 (<1)	>.999	0	0	>.999	0	1 (<1)	.491
HIGH FEELING	1 (<1)	0	.322	0	0	>.999	1 (<1)	0	.147
HOSTILITY	0	7 (2)	.103	0	0	>.999	0	7 (1)	.067
HYPERACTIVITY	0	2 (<1)	>.999	0	1 (1)	>.999	0	3 (<1)	.167
INSOMNIA	2 (1)	19 (5)	.030*	3 (4)	4 (5)	>.999	5 (2)	23 (5)	.033*
IRRITABILITY	3 (2)	25 (6)	.012*	1 (1)	1 (1)	>.999	4 (1)	26 (5)	.017*
LAUGHTER	0	1 (<1)	>.999	0	0	>.999	0	1 (<1)	.491
MOOD CHANGE	1 (<1)	2 (<1)	>.999	0	0	>.999	1 (<1)	2 (<1)	.966
MOOD SWINGS	1 (<1)	0	.322	0	0	>.999	1 (<1)	0	.147
NERVOUSNESS $$	0	9 (2)	.064	1 (1)	0	>.999	1 (<1)	9 (2)	.105
PANIC REACTION	0	1 (<1)	>.999	0	0	>.999	0	1 (<1)	.491
SLEEP DIFFICULT	1 (<1)	1 (<1)	.541	0	1 (1)	>.999	1 (<1)	2 (<1)	.862
SLEEP DISTURBED	2 (1)	0	.103	0	0	>.999	2 (<1)	0	.040*
SLEEP RHYTHM REVERSAL	0	1 (<1)	>.999	0	0	>.999	0	1 (<1)	.491
SLEEPLESSNESS	0	1 (<1)	>.999	0	0	>.999	0	1 (<1)	.491
TENSION NERVOUS	1 (<1)	1 (<1)	.541	0	0	>.999	1 (<1)	1 (<1)	.590
WEEPING	0	1 (<1)	>.999	0	1 (1)	>.999	0	2 (<1)	.230
THOUGHT CONTENT	3 (2)	5 (1)	.717	0	1 (1)	>.999	3 (1)	6 (1)	.957
DREAMS ABNORMAL	1 (<1)	1 (<1)	.541	0	0	>.999	1 (<1)	1 (<1)	.590
DREAMS BIZARRE UNUSUAL OR FRIG	1 (<1)	0	.322	0	0	>.999	1 (<1)	0	.147
HALLUCINATION	0	1 (<1)	>.999	0	0	>.999	0	1 (<1)	.491
HALLUCINATION VISUAL	0	2 (<1)	>.999	0	0	>.999	0	2 (<1)	.329
NIGHTMARES	1 (<1)	1 (<1)	.541	0	0	>.999	1 (<1)	1 (<1)	.590
PARANOIA	0	0	>.999	0	1 (1)	>.999	0	1 (<1)	.317
PHOBIA	0	1 (<1)	>.999	0	0	>.999	0	1 (<1)	.491

& ABBOTT STUDIES M91-603 AND M91-605 (INCLUDES TITRATION AND FIXED-DOSE BUT EXCLUDES TERMINATION);
STUDY M92-775 (INCLUDES TITRATION AND FIXED-DOSE BUT EXCLUDES TERMINATION).
@ FROM FISHER'S EXACT TEST.
@@ FROM COCHRAN-MANTEL-HAENSZEL TEST.
* INDICATES STATISTICAL SIGNIFICANCE OF THE TWO-TAILED TEST AT THE .05 LEVEL.
# A PATIENT REPORTING MORE THAN ONE ADVERSE EVENT FOR A PARTICULAR MEDICAL TERM (MENTAL STATUS CATEGORY) IS COUNTED ONLY ONCE FOR THAT MEDICAL TERM (MENTAL STATUS CATEGORY).
WHERE $ OR $$ IS SHOWN BESIDE A MEDICAL TERM IT INDICATES A P-VALUE LESS THAN OR EQUAL TO .10 OR .05, RESPECTIVELY, FOR THE TEST OF HOMOGENEITY OF THE TIAGABINE EFFECT RELATIVE TO PLACEBO BETWEEN ABBOTT AND

APPENDIX GROUP A ANALYSIS.0

TREATMENT-EMERGENT MENTAL STATUS-RELATED ADVERSE EVENTS GROUPED BY CATEGORY
PLACEBO-CONTROLLED PARALLEL-GROUP ADD-ON EPILEPSY STUDIES

ABBOTT AND RESULTS &

	NUMBER (%) OF PATIENTS WITH AE								
	ABBOTT						TOTAL		
MENTAL STATUS CATEGORY /MEDICAL TERM #	PLACEBO (N=198)	TIAGABINE (N=417)	BTWN GRPS P-VALUE ●	PLACEBO (N= 77)	TIAGABINE (N= 77)	BTWN GRPS P-VALUE ●	PLACEBO (N=275)	TIAGABINE (N=494)	BTWN GRPS P-VALUE ●●
THOUGHT PROCESSES	18 (9)	62 (15)	.054	2 (3)	7 (9)	.167	20 (7)	69 (14)	.014*
AMNESIA	0	3 (<1)	.555	0	0	>.999	0	3 (<1)	.232
APHASIA	0	5 (1)	.181	0	1 (1)	>.999	0	6 (1)	.068
COGNITIVE DISTURBANCE	0	0	>.999	1 (1)	0	>.999	1 (<1)	0	.317
CONCENTRATION IMPAIRED	3 (2)	18 (4)	.095	0	1 (1)	>.999	3 (1)	19 (4)	.049*
CONFUSION $$	7 (4)	13 (3)	.810	0	5 (6)	058	7 (3)	18 (4)	.406
DIFFICULTY THINKING	0	1 (<1)	>.999	0	0	>.999	0	1 (<1)	.491
DISORIENTATION	1 (<1)	5 (1)	.670	0	0	>.999	1 (<1)	5 (1)	.414
DYSPHASIA	0	1 (<1)	>.999	0	1 (1)	>.999	0	2 (<1)	.230
FORGETFULNESS	1 (<1)	4 (<1)	>.999	0	0	>.999	1 (<1)	4 (<1)	.558
MEMORY DISTURBANCE	0	0	>.999	1 (1)	0	>.999	1 (<1)	0	.317
MEMORY IMPAIRED	6 (3)	11 (3)	.795	0	0	>.999	6 (2)	11 (2)	.782
MEMORY LOSS OF	0	1 (<1)	>.999	0	0	>.999	0	1 (<1)	.491
MENTAL ACTIVITY DECREASED	0	1 (<1)	>.999	0	0	>.999	0	1 (<1)	.491
MENTAL DETERIORATION	0	2 (<1)	>.999	0	0	>.999	0	2 (<1)	.329
MENTAL DULLNESS	0	1 (<1)	>.999	0	0	>.999	0	1 (<1)	.491
SPEECH DISORDER	0	1 (<1)	>.999	0	1 (1)	>.999	0	2 (<1)	.230
THINKING ABNORMAL	1 (<1)	4 (<1)	>.999	0	0	>.999	1 (<1)	4 (<1)	.558
THINKING SLOW	1 (<1)	1 (<1)	.541	0	0	>.999	1 (<1)	1 (<1)	.590
THINKING SLUGGISH	0	1 (<1)	>.999	0	0	>.999	0	1 (<1)	.491

& ABBOTT STUDIES M91-603 AND M91-605 (INCLUDES TITRATION AND FIXED-DOSE BUT EXCLUDES TERMINATION);
STUDY M92-775 (INCLUDES TITRATION AND FIXED-DOSE BUT EXCLUDES TERMINATION).
● FROM FISHER'S EXACT TEST.
●● FROM COCHRAN-MANTEL-HAENSZEL TEST.
• INDICATES STATISTICAL SIGNIFICANCE OF THE TWO-TAILED TEST AT THE .05 LEVEL.
A PATIENT REPORTING MORE THAN ONE ADVERSE EVENT FOR A PARTICULAR MEDICAL TERM (MENTAL STATUS CATEGORY) IS COUNTED ONLY ONCE FOR THAT MEDICAL TERM (MENTAL STATUS CATEGORY).
WHERE $ OR $$ IS SHOWN BESIDE A MEDICAL TERM IT INDICATES A P-VALUE LESS THAN OR EQUAL TO .10 OR .05, RESPECTIVELY, FOR THE TEST OF HOMOGENEITY OF THE TIAGABINE EFFECT RELATIVE TO PLACEBO BETWEEN ABBOTT AND

APPENDIX GROUP A ANALYSIS.7

SEVERITY OF MENTAL STATUS-RELATED TREATMENT-EMERGENT ADVERSE EVENTS ●
PLACEBO-CONTROLLED PARALLEL-GROUP ADD-ON EPILEPSY STUDIES

ABBOTT AND RESULTS &

BODY SYSTEM /MEDICAL TERM #	NUMBER (%) OF PATIENTS WITH AE					
	PLACEBO (N=275)			TIAGABINE (N=494)		
	MILD	MODERATE	SEVERE	MILD	MODERATE	SEVERE
NERVOUS SYSTEM						
AGGRESSIVE REACTION	85 (31)	37 (13)	0	155 (31)	116 (23)	13 (3)
AGITATION	1 (<1)	1 (<1)	0	2 (<1)	2 (<1)	1 (<1)
ALTERED MOOD	0	1 (<1)	0	4 (<1)	1 (<1)	0
AMNESIA	0	0	0	1 (<1)	0	0
ANXIETY	0	0	0	2 (<1)	1 (<1)	0
APHASIA	3 (1)	1 (<1)	0	4 (<1)	1 (<1)	0
ASTHENIA	0	0	0	3 (<1)	3 (<1)	0
BEHAVIOR ABNORMAL	1 (<1)	0	0	3 (<1)	1 (<1)	0
COGNITIVE DISTURBANCE	0	0	0	0	1 (<1)	0
CONCENTRATION IMPAIRED	0	1 (<1)	0	0	0	0
CONFUSION	2 (<1)	1 (<1)	0	15 (3)	4 (<1)	0
CRYING UNCONTROLLABLE	6 (2)	1 (<1)	0	5 (1)	12 (2)	1 (<1)
DEPRESSED STATE	1 (<1)	0	0	1 (<1)	0	0
DEPRESSION	0	0	0	0	1 (<1)	0
DEPRESSION SUICIDAL	2 (<1)	0	0	10 (2)	6 (1)	0
DIFFICULTY THINKING	0	0	0	0	0	1 (<1)
DISORIENTATION	0	0	0	1 (<1)	0	0
DIZZINESS	1 (<1)	0	0	1 (<1)	4 (<1)	0
DREAMS ABNORMAL	31 (11)	4 (1)	0	61 (12)	41 (8)	0
DREAMS BIZARRE UNUSUAL OR FRIGHTENING	0	1 (<1)	0	1 (<1)	0	0
DRONSINESS	0	1 (<1)	0	0	0	0
DRUGGEDNESS	12 (4)	5 (2)	0	22 (4)	10 (2)	1 (<1)
DULLNESS	2 (<1)	1 (<1)	0	2 (<1)	1 (<1)	0
DYSPHASIA	1 (<1)	0	0	0	0	0
EMOTIONAL LABILITY	0	0	0	1 (<1)	1 (<1)	0
EUPHORIA	1 (<1)	0	0	5 (1)	4 (<1)	0
EXHAUSTION	0	1 (<1)	0	0	0	0
FATIGABILITY	0	0	0	0	2 (<1)	0
FATIGUE	0	0	0	1 (<1)	0	0
FEELING FLOATING	6 (2)	4 (1)	0	27 (5)	12 (2)	0
FEELING HIGH	0	0	0	0	1 (<1)	0
	0	0	0	1 (<1)	1 (<1)	0

& ABBOTT STUDIES M91-603 AND M91-605; STUDY M92-775.
● INCLUDES EVENTS WITH ONSET DURING TITRATION OR FIXED-DOSE (EXCLUDES EVENTS WITH ONSET DURING TERMINATION).
A PATIENT REPORTING MORE THAN ONE ADVERSE EVENT FOR A PARTICULAR MEDICAL TERM (BODY SYSTEM) IS COUNTED ONCE FOR THAT MEDICAL TERM (BODY SYSTEM), UNDER THE MOST SEVERE OCCURRENCE.

27JAN97 13:45 <ae aev.sas boodhoot>

APPENDIX GROUP A ANALYSIS.7

SEVERITY OF MENTAL STATUS-RELATED TREATMENT-EMERGENT ADVERSE EVENTS ●
PLACEBO-CONTROLLED PARALLEL-GROUP ADD-ON EPILEPSY STUDIES

ABBOTT AND . RESULTS &

BODY SYSTEM /MEDICAL TERM #	NUMBER (%) OF PATIENTS WITH AE					
	PLACEBO (N=275)			TIAGABINE (N=494)		
	MILD	MODERATE	SEVERE	MILD	MODERATE	SEVERE
NERVOUS SYSTEM (cont'd)						
FEELING STRANGE	1 (<1)	0	0	2 (<1)	0	0
FEELING TENSE	0	0	0	1 (<1)	0	0
FORGETFULNESS	1 (<1)	0	0	2 (<1)	2 (<1)	0
FUZZY	0	0	0	1 (<1)	0	0
GROGGY	1 (<1)	0	0	1 (<1)	0	0
HALLUCINATION	0	0	0	0	1 (<1)	0
HALLUCINATION VISUAL	0	0	0	0	2 (<1)	0
HIGH FEELING	0	1 (<1)	0	0	0	0
HOSTILITY	0	0	0	3 (<1)	4 (<1)	0
HYPERACTIVITY	0	0	0	2 (<1)	1 (<1)	0
INITIATIVE LOSS OF	0	0	0	0	1 (<1)	0
INSOMNIA	4 (1)	1 (<1)	0	17 (3)	6 (1)	0
IRRITABILITY	3 (1)	1 (<1)	0	23 (5)	3 (<1)	0
LAUGHTER	0	0	0	0	1 (<1)	0
LETHARGY	4 (1)	0	0	10 (2)	5 (1)	1 (<1)
MEMORY DISTURBANCE	0	1 (<1)	0	0	0	0
MEMORY IMPAIRED	4 (1)	2 (<1)	0	10 (2)	1 (<1)	0
MEMORY LOSS OF	0	0	0	1 (<1)	0	0
MENTAL ACTIVITY DECREASED	0	0	0	0	1 (<1)	0
MENTAL DETERIORATION	0	0	0	1 (<1)	1 (<1)	0
MENTAL DULLNESS	0	0	0	1 (<1)	0	0
MOOD CHANGE	1 (<1)	0	0	1 (<1)	1 (<1)	0
MOOD SWINGS	1 (<1)	0	0	0	0	0
NERVOUSNESS	1 (<1)	0	0	7 (1)	2 (<1)	0
NIGHTMARES	1 (<1)	0	0	0	1 (<1)	0
PANIC REACTION	0	0	0	0	1 (<1)	0
PARANOIA	0	0	0	0	1 (<1)	0
PHOBIA	0	0	0	0	1 (<1)	0
SEDATION EXCESSIVE	2 (<1)	1 (<1)	0	2 (<1)	2 (<1)	1 (<1)
SLEEP DIFFICULT	0	1 (<1)	0	1 (<1)	1 (<1)	0
SLEEP DISTURBED	2 (<1)	0	0	0	0	0

& ABBOTT STUDIES M91-603 AND M91-605; STUDY M92-775.
● INCLUDES EVENTS WITH ONSET DURING TITRATION OR FIXED-DOSE (EXCLUDES EVENTS WITH ONSET DURING TERMINATION).
A PATIENT REPORTING MORE THAN ONE ADVERSE EVENT FOR A PARTICULAR MEDICAL TERM (BODY SYSTEM) IS COUNTED ONCE FOR THAT MEDICAL TERM (BODY SYSTEM), UNDER THE MOST SEVERE OCCURRENCE.

APPENDIX GROUP A ANALYSIS.7

SEVERITY OF MENTAL STATUS-RELATED TREATMENT-EMERGENT ADVERSE EVENTS ●
PLACEBO-CONTROLLED PARALLEL-GROUP ADD-ON EPILEPSY STUDIES

ABBOTT AND RESULTS &

BODY SYSTEM /MEDICAL TERM #	NUMBER (%) OF PATIENTS WITH AE					
	PLACEBO (N=275)			TIAGABINE (N=494)		
	MILD	MODERATE	SEVERE	MILD	MODERATE	SEVERE
NERVOUS SYSTEM (cont'd)						
SLEEP RHYTHM REVERSAL	0	0	0	1 (<1)	0	0
SLEEPINESS	13 (5)	3 (1)	0	12 (2)	7 (1)	1 (<1)
SLEEPLESSNESS	0	0	0	1 (<1)	0	0
SOMNOLENCE	1 (<1)	0	0	8 (2)	4 (<1)	1 (<1)
SPEECH DISORDER	0	0	0	2 (<1)	0	0
TENSION NERVOUS	1 (<1)	0	0	1 (<1)	0	0
THINKING ABNORMAL	1 (<1)	0	0	4 (<1)	0	0
THINKING SLOW	1 (<1)	0	0	0	1 (<1)	0
THINKING SLUGGISH	0	0	0	0	1 (<1)	0
TIREDNESS	22 (8)	5 (2)	0	30 (6)	9 (2)	4 (<1)
WEEPING	0	0	0	1 (<1)	1 (<1)	0

& ABBOTT STUDIES M91-603 AND M91-605; STUDY M92-775.
● INCLUDES EVENTS WITH ONSET DURING TITRATION OR FIXED-DOSE (EXCLUDES EVENTS WITH ONSET DURING TERMINATION).
A PATIENT REPORTING MORE THAN ONE ADVERSE EVENT FOR A PARTICULAR MEDICAL TERM (BODY SYSTEM) IS COUNTED ONCE FOR THAT MEDICAL TERM (BODY SYSTEM), UNDER THE MOST SEVERE OCCURRENCE.

Appendix 9

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ON ORIGINAL

12FEB97 10:17 <pcaedc.sas hentzj>
ABBOTT-70569 (TIAGABINE HCL)

APPENDIX GROUP A ANALYSIS.&

ADVERSE EVENTS RELATED TO MENTAL STATUS CHANGES (MSC) IDENTIFIED AS THE PRIMARY REASON FOR PREMATURE DISCONTINUATION
PLACEBO-CONTROLLED PARALLEL-GROUP ADD-ON EPILEPSY STUDIES

ABBOTT ANL RESULTS &

COSTART TERM /MEDICAL TERM	NUMBER (%) OF PATIENTS WITH MSC AE #											
	ABBOTT								TOTAL			
	PLACEBO (N=198)		TIAGABINE (N=417)		PLACEBO (N= 77)		TIAGABINE (N= 77)		PLACEBO (N=275)		TIAGABINE (N=494)	
ANY MSC AE RESULTING IN D/C	4	(2)	22	(5)	1	(1)	9	(12)	5	(2)	31	(6)
AGITATION	1	(<1)	0		0		1	(1)	1	(<1)	1	(<1)
AGITATION	1	(<1)	0		0		0		1	(<1)	0	
PANIC REACTION	0		0		0		1	(1)	0		1	(<1)
ASTHENIA	0		2	(<1)	1	(1)	1	(1)	1	(<1)	3	(<1)
TIREDNESS	0		2	(<1)	1	(1)	1	(1)	1	(<1)	3	(<1)
CONFUSION	0		5	(1)	0		2	(3)	0		7	(1)
CONFUSION	0		4	(<1)	0		2	(3)	0		6	(1)
DISORIENTATION	0		1	(<1)	0		0		0		1	(<1)
DEPRESSION	0		2	(<1)	0		0		0		2	(<1)
DEPRESSION	0		2	(<1)	0		0		0		2	(<1)
DIZZINESS	1	(<1)	3	(<1)	0		1	(1)	1	(<1)	4	(<1)
DIZZINESS	1	(<1)	3	(<1)	0		1	(1)	1	(<1)	4	(<1)
HALLUCINATIONS	0		1	(<1)	0		0		0		1	(<1)
HALLUCINATION VISUAL	0		1	(<1)	0		0		0		1	(<1)
HOSTILITY	0		1	(<1)	0		2	(3)	0		3	(<1)
AGGRESSIVE REACTION	0		1	(<1)	0		2	(3)	0		3	(<1)
NERVOUSNESS	0		1	(<1)	0		0		0		1	(<1)
IRRITABILITY	0		1	(<1)	0		0		0		1	(<1)
PSYCHOTIC DEPRESSION	0		1	(<1)	0		0		0		1	(<1)
DEPRESSION SUICIDAL	0		1	(<1)	0		0		0		1	(<1)

& ABBOTT STUDIES M91-603 AND M91-605; STUDY M92-775.
# INCLUDES DISCONTINUATIONS DURING THE TITRATION, AND FIXED DOSE PERIODS.

APPENDIX GROUP A ANALYSIS.@

ADVERSE EVENTS RELATED TO MENTAL STATUS CHANGES (MSC) IDENTIFIED AS THE PRIMARY REASON FOR PREMATURE DISCONTINUATION
PLACEBO-CONTROLLED PARALLEL-GROUP ADD-ON EPILEPSY STUDIES

ABBOTT AND RESULTS &

COSTART TERM /MEDICAL TERM	NUMBER (%) OF PATIENTS WITH MSC AE @									
	ABBOTT						TOTAL			
	PLACEBO (N=198)		TIAGABINE (N=417)		PLACEBO (N= 77)	TIAGABINE (N= 77)		PLACEBO (N=275)		TIAGABINE (N=494)	
SOMNOLENCE	2	(1)	4	(<1)	0	2	(3)	2	(<1)	6	(1)
DROWSINESS	1	(<1)	1	(<1)	0	1	(1)	1	(<1)	2	(<1)
DULLNESS	1	(<1)	0		0	0		1	(<1)	0	
SEDATION EXCESSIVE	0		0		0	1	(1)	0		1	(<1)
SLEEPINESS	0		1	(<1)	0	0		0		1	(<1)
SOMNOLENCE	0		2	(<1)	0	0		0		2	(<1)
THINKING ABNORMAL	0		2	(<1)	0	0		0		2	(<1)
CONCENTRATION IMPAIRED	0		1	(<1)	0	0		0		1	(<1)
THINKING SLOW	0		1	(<1)	0	0		0		1	(<1)

& ABBOTT STUDIES M91-601 AND M91-605; STUDY M92-775.
@ INCLUDES DISCONTINUATIONS DURING THE TITRATION, AND FIXED DOSE PERIODS.

Actions Taken In Response To The First Occurrence Of Nonconvulsive Status Epilepticus

Epilepsy Studies

Abbott and Results [4]	Number (%) of Patients with Each Action
Actions within 1 Day *	Total [5] (N=77)
TGB Discontinued (No benzodiazepines or IV meds changed or added)	2 (2.6)
Con AED Dose Adjusted/Added Disc	1 (1.3)
Con AED Dose Unchanged	1 (1.3)
TGB Dose Decreased (No benzodiazepines changed or added)	11 (14)
Con AED Dose Adjusted/Added Disc	9 (12)
IV Drugs Added Disc	2 (2.6)
Benzodiazepines Added Disc	1 (1.3)
Con AED Dose Unchanged	2 (2.6)
TGB Dose Unchanged (No benzodiazepines changed or added)	57 (74)
Con AED Dose Adjusted/Added Disc	24 ~~(26)~~ ← (31)
IV Drug Added Discontinued	2 (2.6)
Con AED Dose Unchanged	33 ~~(43)~~ ← (43)
TGB Dose Increased (No benzodiazepines or IV meds changed or added)	7 (9.1)
Con AED Dose Adjusted/Added Disc	3 (3.9)
Con AED Dose Unchanged	4 (5.2)

& Abbott Studies M90-481, M90-511, M91-603, M91-604, M91-604, M91-605, M92-813, M92-855, M92-825, M93-090, Studies M91-565, M91-578, M91-595, M91-710, M92-775, M92-873, M93-043, M93-047, M93-065, M93-092, &M94-179.
# Indented categories are subsets other preceding level. Categories at the same level are mutually exclusive.
$ Total summarizes unique patients (i.e., patients who entered Abbott short-term studies and long-term studies are counted only once)
Cross Reference: Appendix Group B, Analysis 1A

Actions Taken In Response To The Last Occurrence Of Nonconvulsive Status Epilepticus For Patients With More Than One Status Episode

Epilepsy Studies

Abbott and Results [&]	Number (%) of Patients with Each Action
Actions within 1 Day [#]	Total [$] (N=36)
TGB Discontinued (No Benzodiazepines or IV meds changed or added)	1 (2.8)
Con AED Dose Adjusted/Added/Disc/	1 (2.8)
TGB Temporarily Suspended (Benzodiazepines and IV meds unchanged)	1 (2.8)
Con AED Dose Adjusted/ Added/Disc	1 (2.8)
TGB Dose Decreased (No Benzodiazepines or IV meds changed or added)	5 (14)
Con AED Dose Adjusted/Added/Disc/	3 (8.3)
Con AED Dose Unchanged/	2 (5.6)
TGB Dose Unchanged (No Benzodiazepines changed or added)	26 (72)
Con AED Dose Adjusted/Added/Disc/	5 (14)
IV Drug Added/Disc	1 (2.8)
Con AED Dose Unchanged	21 (58)
TGB Dose Increased (No Benzodiazepines changed or added)	3 (8.3)
Con AED Dose Adjusted/Added/Disc/	2 (2.8)
Con AED Dose Unchanged	1 (5.6)

& Abbott Studies M90-481, M90-511, M91-603, M91-604, M91-604, M91-605, M92-813, M92-855, M92-825, M93-090. Studies M91-565, M91-578, M91-595, M91-710, M92-775, M92-873, M93-043, M93-047, M93-065, M93-092, &M94-179.

Indented categories are subsets other preceding level. Categories at the same level are mutually exclusive.

$ Total summarizes unique patients (i.e., patients who entered Abbott short-term studies anc long-term studies are counted only once)

Cross Reference: Appendix Group B, Analysis .1B

Actions Within 7 Days Prior to First Event of Nonconvulsive Status Epilepticus (NCSE) For All Patients With At Least One Episode In All Epilepsy Studies

Abbott and Results Combined &

Actions During the 7-Day Period of Interest #	Number (%) of Patients with NCS Events (N=77)	Number (%) of Patients with No NCS Events (N=1247)
Tiagabine Dose Unchanged	55 (71)	937 (75)
Concomitant AED Dose Unchanged	44 (57)	852 (68)
Concomitant AED Dose Increased	5 (6.5)	37 (3.0)
Concomitant AED Dose Decreased	5 (6.5)	34 (2.7)
Concomitant AED Dose Increased and Decreased	1 (1.3)	14 (1.1)
Tiagabine Dose Increased	20 (26)	220 (18)
Concomitant AED Dose Unchanged	15 (19)	184 (15)
Concomitant AED Dose Increased	1 (1.3)	5 (0.4)
Concomitant AED Dose Decreased	3 (3.9)	28 (2.2)
Concomitant AED Dose Increased and Decreased	1 (1.3)	3 (0.2)
Tiagabine Dose Decreased	1 (1.3)	85 (6.8)
Concomitant AED Dose Unchanged	1 (1.3)	74 (5.9)
Concomitant AED Dose Increased	0 (0.0)	7 (0.6)
Concomitant AED Dose Decreased	0 (0.0)	2 (0.2)
Concomitant AED Dose Increased and Decreased	0 (0.0)	2 (0.2)
Tiagabine Dose Increased and Decreased	1 (1.3)	5 (0.4)
Concomitant AED Dose Unchanged Decreased	0 (0.0)	5 (0.4)
Concomitant AED Dose Increased and Decreased	1 (1.3)	0 (0.0)

& Abbott Studies M90-481, M90-511, M91-603, M91-604, M91-604, M91-605, M92-813, M92-855, M92-825, M93-090. Studies M91-565, M91-578, M91-595, M91-710, M92-775, M92-873, M93-043, M93-047, M93-065, M93-092, &M94-179.

Actions during the 7-day period prior to the first NCS event for patients with NCS events, and during the 7-day period prior to day 172 (median time to first NCS event) for patients with no NCS event.

Cross Reference: Appendix Group B, Analysis 2A

Actions Within 7 Days Prior to Last Event of Nonconvulsive Status Epilepticus (NCSE) For Patients With More Than One Episode In All Epilepsy Studies

Abbott ano Results Combined &

Actions During the 7-Day Period of Interest #	Number (%) of Patients with NCS Events (N=36)		Number (%) of Patients with No NCS Events (N=1168)	
Tiagabine Dose Unchanged	26	(72)	968	(83)
Concomitant AED Dose Unchanged	22	(61)	885	(76)
Concomitant AED Dose Increased	2	(5.6)	28	(2.4)
Concomitant AED Dose Decreased	1	(2.8)	36	(3.1)
Concomitant AED Dose Increased and Decreased	2	(2.8)	19	(1.6)
Tiagabine Dose Increased	7	(19)	110	(9.4)
Concomitant AED Dose Unchanged	3	(8.3)	94	(8.0)
Concomitant AED Dose Increased	3	(8.3)	0	(0.0)
Concomitant AED Dose Decreased	2	(2.8)	16	(1.4)
Tiagabine Dose Decreased	3	(8.3)	89	(7.6)
Concomitant AED Dose Unchanged	2	(5.6)	77	(6.6)
Concomitant AED Dose Increased	0	(0.0)	9	(0.8)
Concomitant AED Dose Decreased	1	(2.8)	1	(0.1)
Concomitant AED Dose Increased and Decreased	0	(0.0)	2	(0.2)
Tiagabine Dose Increased and Decreased	0	(0.0)	1	(0.1)
Concomitant AED Dose Increased and Decreased	0	(0.0)	1	(0.1)

& Abbott Studies M90-481, M90-511, M91-603, M91-604, M91-604, M91-605, M92-813, M92-855, M92-825, M93-090.
Studies M91-565, M91-578, M91-595, M91-710, M92-775, M92-873, M93-043, M93-047, M93-065, M93-092, &M94-179.

Actions during the 7-day period prior to the first NCS event for patients with NCS events, and during the 7-day period prior to day 172 (median time to first NCS event) for patients with not NCS event.

Cross Reference: Appendix Group B, Analysis 2B

APPENDIX Gk . ANALYSIS . 1A

ACTIONS TAKEN IN RESPONSE TO THE FIRST OCCURRENCE OF NONCONVULSIVE STATUS EPILEPTICUS
EPILEPSY STUDIES

ABBOTT AND . RESULTS &

ACTIONS WITHIN 1 DAY #	NUMBER (%) OF PATIENTS WITH EACH ACTION		
	ABBOTT (N=37)	(N=40)	TOTAL (N=77)
TGB DOSE INCREASED	4 (11)	3 (7.5)	7 (9.1)
CONC AED DOSE ADJUSTED/ADDED/DISC	2 (5.4)	1 (2.5)	3 (3.9)
IV DRUGS UNCHANGED	2 (5.4)	1 (2.5)	3 (3.9)
BENZODIAZEPINES UNCHANGED	2 (5.4)	1 (2.5)	3 (3.9)
CONC AED DOSE UNCHANGED	2 (5.4)	2 (5.0)	4 (5.2)
IV DRUGS UNCHANGED	2 (5.4)	2 (5.0)	4 (5.2)
BENZODIAZEPINES UNCHANGED	2 (5.4)	2 (5.0)	4 (5.2)
TGB DOSE UNCHANGED	25 (68)	32 (80)	57 (74)
CONC AED DOSE ADJUSTED/ADDED/DISC	17 (46)	7 (18)	24 (31)
IV DRUGS ADDED/DISC	2 (5.4)	0 (0.0)	2 (2.6)
BENZODIAZEPINES UNCHANGED	2 (5.4)	0 (0.0)	2 (2.6)
IV DRUGS UNCHANGED	15 (41)	7 (18)	22 (29)
BENZODIAZEPINES UNCHANGED	15 (41)	7 (18)	22 (29)
CONC AED DOSE UNCHANGED	8 (22)	25 (63)	33 (43)
IV DRUGS UNCHANGED	8 (22)	25 (63)	33 (43)
BENZODIAZEPINES UNCHANGED	8 (22)	25 (63)	33 (43)

& ABBOTT STUDIES M90-481,M90-511,M91-603,M91-604,M91-605,M92-813,M92-855,M92-825,AND M93-090.
STUDIES M91-565,M91-578,M91-595,M91-710,M92-775,M92-873,M93-043,M93-047,M93-065,M93-092,AND M94-179.
INDENTED CATEGORIES ARE SUBSETS OF THE PRECEDING LEVEL. CATEGORIES AT THE SAME LEVEL ARE MUTUALLY EXCLUSIVE.

APPENDIX GROUP B ANALYSIS . 1A

ACTIONS TAKEN IN RESPONSE TO THE FIRST OCCURRENCE OF NONCONVULSIVE STATUS EPILEPTICUS
EPILEPSY STUDIES

ABBOTT AND RESULTS &

ACTIONS WITHIN 1 DAY #	NUMBER (%) OF PATIENTS WITH EACH ACTION		
	ABBOTT (N=37)	(N=40)	TOTAL (N=77)
TGB DOSE DECREASED	7 (19)	4 (10)	11 (14)
CONC AED DOSE ADJUSTED/ADDED/DISC	6 (16)	3 (7.5)	9 (12)
IV DRUGS ADDED/DISC	2 (5.4)	0 (0.0)	2 (2.6)
BENZODIAZEPINES ADDED/DISC	1 (2.7)	0 (0.0)	1 (1.3)
BENZODIAZEPINES UNCHANGED	1 (2.7)	0 (0.0)	1 (1.3)
IV DRUGS UNCHANGED	4 (11)	3 (7.5)	7 (9.1)
BENZODIAZEPINES UNCHANGED	4 (11)	3 (7.5)	7 (9.1)
CONC AED DOSE UNCHANGED	1 (2.7)	1 (2.5)	2 (2.6)
IV DRUGS UNCHANGED	1 (2.7)	1 (2.5)	2 (2.6)
BENZODIAZEPINES UNCHANGED	1 (2.7)	1 (2.5)	2 (2.6)
TGB DISCONTINUED	1 (2.7)	1 (2.5)	2 (2.6)
CONC AED DOSE ADJUSTED/ADDED/DISC	1 (2.7)	0 (0.0)	1 (1.3)
IV DRUGS UNCHANGED	1 (2.7)	0 (0.0)	1 (1.3)
BENZODIAZEPINES UNCHANGED	1 (2.7)	0 (0.0)	1 (1.3)
CONC AED DOSE UNCHANGED	0 (0.0)	1 (2.5)	1 (1.3)
IV DRUGS UNCHANGED	0 (0.0)	1 (2.5)	1 (1.3)
BENZODIAZEPINES UNCHANGED	0 (0.0)	1 (2.5)	1 (1.3)

& ABBOTT STUDIES M90-481,M90-511,M91-603,M91-604,M91-605,M92-813,M92-855,M92-825,AND M93-090.
STUDIES M91-565,M91-578,M91-595,M91-710,M92-775,M92-873,M93-043,M93-047,M93-065,M93-092,AND M94-179.
INDENTED CATEGORIES ARE SUBSETS OF THE PRECEDING LEVEL. CATEGORIES AT THE SAME LEVEL ARE MUTUALLY EXCLUSIVE.

APPENDIX GROUP B ANALYSIS . 1B

ACTIONS TAKEN IN RESPONSE TO THE LAST OCCURRENCE OF NONCONVULSIVE STATUS EPILEPTICUS
FOR PATIENTS WITH MORE THAN ONE OCCURRENCE
EPILEPSY STUDIES

ABBOTT AND RESULTS &

ACTIONS WITHIN 1 DAY #	NUMBER (%) OF PATIENTS WITH EACH ACTION		
	ABBOTT (N=14)	(N=22)	TOTAL (N=36)
TGB DOSE INCREASED	2 (14)	1 (4.5)	3 (8.3)
CONC AED DOSE ADJUSTED/ADDED/DISC	0 (0.0)	1 (4.5)	1 (2.8)
IV DRUGS UNCHANGED	0 (0.0)	1 (4.5)	1 (2.8)
BENZODIAZEPINES UNCHANGED	0 (0.0)	1 (4.5)	1 (2.8)
CONC AED DOSE UNCHANGED	2 (14)	0 (0.0)	2 (5.6)
IV DRUGS UNCHANGED	2 (14)	0 (0.0)	2 (5.6)
BENZODIAZEPINES UNCHANGED	2 (14)	0 (0.0)	2 (5.6)
TGB DOSE UNCHANGED	7 (50)	19 (86)	26 (72)
CONC AED DOSE ADJUSTED/ADDED/DISC	2 (14)	3 (14)	5 (14)
IV DRUGS ADDED/DISC	1 (7.1)	0 (0.0)	1 (2.8)
BENZODIAZEPINES UNCHANGED	1 (7.1)	0 (0.0)	1 (2.8)
IV DRUGS UNCHANGED	1 (7.1)	3 (14)	4 (11)
BENZODIAZEPINES UNCHANGED	1 (7.1)	3 (14)	4 (11)
CONC AED DOSE UNCHANGED	5 (36)	16 (73)	21 (58)
IV DRUGS UNCHANGED	5 (36)	16 (73)	21 (58)
BENZODIAZEPINES UNCHANGED	5 (36)	16 (73)	21 (58)

& ABBOTT STUDIES M90-481,M90-511,M91-603,M91-604,M91-605,M92-813,M92-855,M92-825,AND M93-090.
STUDIES M91-565,M91-578,M91-595,M91-710,M92-775,M92-873,M93-043,M93-047,M93-065,M93-092,AND M94-179.
INDENTED CATEGORIES ARE SUBSETS OF THE PRECEDING LEVEL. CATEGORIES AT THE SAME LEVEL ARE MUTUALLY EXCLUSIVE.

APPENDIX GROUP B ANALYSIS . 1B

ACTIONS TAKEN IN RESPONSE TO THE LAST OCCURRENCE OF NONCONVULSIVE STATUS EPILEPTICUS
FOR PATIENTS WITH MORE THAN ONE OCCURRENCE
EPILEPSY STUDIES

ABBOTT AND RESULTS &

ACTIONS WITHIN 1 DAY #	NUMBER (%) OF PATIENTS WITH EACH ACTION		
	ABBOTT (N=14)	(N=22)	TOTAL (N=36)
TGB DOSE DECREASED	3 (21)	2 (9.1)	5 (14)
CONC AED DOSE ADJUSTED/ADDED/DISC	3 (21)	0 (0.0)	3 (8.3)
IV DRUGS UNCHANGED	3 (21)	0 (0.0)	3 (8.3)
BENZODIAZEPINES UNCHANGED	3 (21)	0 (0.0)	3 (8.3)
CONC AED DOSE UNCHANGED	0 (0.0)	2 (9.1)	2 (5.6)
IV DRUGS UNCHANGED	0 (0.0)	2 (9.1)	2 (5.6)
BENZODIAZEPINES UNCHANGED	0 (0.0)	2 (9.1)	2 (5.6)
TGB TEMPORARILY SUSPENDED	1 (7.1)	0 (0.0)	1 (2.8)
CONC AED DOSE ADJUSTED/ADDED/DISC	1 (7.1)	0 (0.0)	1 (2.8)
IV DRUGS UNCHANGED	1 (7.1)	0 (0.0)	1 (2.8)
BENZODIAZEPINES UNCHANGED	1 (7.1)	0 (0.0)	1 (2.8)
TGB DISCONTINUED	1 (7.1)	0 (0.0)	1 (2.8)
CONC AED DOSE ADJUSTED/ADDED/DISC	1 (7.1)	0 (0.0)	1 (2.8)
IV DRUGS UNCHANGED	1 (7.1)	0 (0.0)	1 (2.8)
BENZODIAZEPINES UNCHANGED	1 (7.1)	0 (0.0)	1 (2.8)

& ABBOTT STUDIES M90-481,M90-511,M91-603,M91-604,M91-605,M92-813,M92-855,M92-825,AND M93-090.
STUDIES M91-565,M91-578,M91-595,M91-710,M92-775,M92-873,M93-043,M93-047,M93-065,M93-092,AND M94-179.
INDENTED CATEGORIES ARE SUBSETS OF THE PRECEDING LEVEL. CATEGORIES AT THE SAME LEVEL ARE MUTUALLY EXCLUSIVE.

APPENDIX GROUP B ANALYSIS . 2A

ACTIONS WITHIN 7 DAYS PRIOR TO FIRST EVENT OF NONCONVULSIVE STATUS EPILEPTICUS (NCS)

EPILEPSY STUDIES

ABBOTT AND RESULTS COMBINED &

ACTIONS DURING THE 7-DAY PERIOD OF INTEREST #	NUMBER (%) OF PATIENTS WITH NCS EVENTS (N=77)		NUMBER (%) OF PATIENTS WITH NO NCS EVENTS (N=1247)	
TIAGABINE DOSE UNCHANGED				
CONCOMITANT AED DOSE UNCHANGED	55	(71)	937	(75)
CONCOMITANT AED DOSE INCREASED	44	(57)	852	(68)
CONCOMITANT AED DOSE DECREASED	5	(6.5)	37	(3.0)
CONCOMITANT AED DOSE INCREASED AND DECREASED	5	(6.5)	34	(2.7)
	1	(1.3)	14	(1.1)
TIAGABINE DOSE INCREASED				
CONCOMITANT AED DOSE UNCHANGED	20	(26)	220	(18)
CONCOMITANT AED DOSE INCREASED	15	(19)	184	(15)
CONCOMITANT AED DOSE DECREASED	1	(1.3)	5	(0.4)
CONCOMITANT AED DOSE INCREASED AND DECREASED	3	(3.9)	28	(2.2)
	1	(1.3)	3	(0.2)
TIAGABINE DOSE DECREASED				
CONCOMITANT AED DOSE UNCHANGED	1	(1.3)	85	(6.8)
CONCOMITANT AED DOSE INCREASED	1	(1.3)	74	(5.9)
CONCOMITANT AED DOSE DECREASED	0	(0.0)	7	(0.6)
CONCOMITANT AED DOSE INCREASED AND DECREASED	0	(0.0)	2	(0.2)
	0	(0.0)	2	(0.2)
TIAGABINE DOSE INCREASED AND DECREASED				
CONCOMITANT AED DOSE UNCHANGED	1	(1.3)	5	(0.4)
CONCOMITANT AED DOSE INCREASED AND DECREASED	0	(0.0)	5	(0.4)
	1	(1.3)	0	(0.0)

& ABBOTT STUDIES M90-481,M90-511,M91-603,M91-604,M91-605,M92-813,M92-855,M92-825,AND M93-050.
STUDIES M91-565,M91-578,M91-595,M91-710,M92-775,M92-873,M93-043,M93-047,M93-065,M93-092,AND M94-179.

ACTIONS DURING THE 7-DAY PERIOD PRIOR TO THE FIRST NCS EVENT FOR PATIENTS WITH NCS EVENTS, AND DURING THE 7-DAY PERIOD PRIOR TO DAY 172 (MEDIAN TIME TO FIRST NCS EVENT) FOR PATIENTS WITH NO NCS EVENT.

APPENDIX GROUP B ANALYSIS . 2B

ACTIONS WITHIN 7 DAYS PRIOR TO LAST EVENT OF NONCONVULSIVE STATUS EPILEPTICUS (NCS)

EPILEPSY STUDIES

ABBOTT AND RESULTS COMBINED &

ACTIONS DURING THE 7-DAY PERIOD OF INTEREST #	NUMBER (%) OF PATIENTS WITH NCS EVENTS (N=36)		NUMBER (%) OF PATIENTS WITH NO NCS EVENTS (N=1168)	
TIAGABINE DOSE UNCHANGED	26	(72)	968	(83)
CONCOMITANT AED DOSE UNCHANGED	22	(61)	886	(76)
CONCOMITANT AED DOSE INCREASED	2	(5.6)	30	(2.6)
CONCOMITANT AED DOSE DECREASED	1	(2.8)	34	(2.9)
CONCOMITANT AED DOSE INCREASED AND DECREASED	1	(2.8)	18	(1.5)
TIAGABINE DOSE INCREASED	7	(19)	110	(9.4)
CONCOMITANT AED DOSE UNCHANGED	3	(8.3)	94	(8.0)
CONCOMITANT AED DOSE INCREASED	3	(8.3)	0	(0.0)
CONCOMITANT AED DOSE DECREASED	1	(2.8)	16	(1.4)
TIAGABINE DOSE DECREASED	3	(8.3)	89	(7.6)
CONCOMITANT AED DOSE UNCHANGED	2	(5.6)	77	(6.6)
CONCOMITANT AED DOSE INCREASED	0	(0.0)	9	(0.8)
CONCOMITANT AED DOSE DECREASED	1	(2.8)	1	(0.1)
CONCOMITANT AED DOSE INCREASED AND DECREASED	0	(0.0)	2	(0.2)
TIAGABINE DOSE INCREASED AND DECREASED	0	(0.0)	1	(0.1)
CONCOMITANT AED DOSE INCREASED AND DECREASED	0	(0.0)	1	(0.1)

& ABBOTT STUDIES M90-481,M90-511,M91-603,M91-604,M91-605,M92-813,M92-855,M92-825,AND M93-090.
STUDIES M91-565,M91-578,M91-595,M91-710,M92-775,M92-873,M93-043,M93-047,M93-065,M93-092,AND M94-179.

ACTIONS DURING THE 7-DAY PERIOD PRIOR TO THE FIRST NCS EVENT FOR PATIENTS WITH NCS EVENTS, AND DURING THE 7-DAY PERIOD PRIOR TO DAY 172 (MEDIAN TIME TO FIRST NCS EVENT) FOR PATIENTS WITH NO NCS EVENT.

Appendix 10

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Summary of FDA Telephone Conference
NDA 20-646
(Tiagabine HCl Tablets)

Date: November 26, 1996

Purpose of Conference: Discuss and Obtain Clarification on Points from October 31, 1996 Approvable Letter for the Tiagabine NDA

Participants:

Food and Drug Administration, Division of Neuropharmacological Drug Products
Russell Katz, M.D., Deputy Director
Cynthia McCormick, M.D., Medical Review Officer
Gregory Burkhardt, M.D., Safety Team Leader
John Balian, M.D., Safety Reviewer
Michael Sevka, M.D., Safety Reviewer
Jackie Ware, Pharm. D., Regulatory Management Officer

Abbott Laboratories
Simon Arnold, Venture Head, Neurotherapeutics Venture
Roger Deaton, Statistician, Clinical Statistics
David Furlano, Ph.D., Associate Director, Regulatory Affairs
Linda Gustavson, Ph.D., Group Leader, Pharmacokinetics and Biopharmaceutics
Kenneth Kashkin, M.D., Director, Pharmaceutical Ventures
Janet Kolb, Operations Manager, Neurotherapeutics Venture
Gregory Lenz, Clinical Project Manager, Neurotherapeutics Venture
Vincent Shu, Ph.D., Section Manager, Clinical Statistics
Kenneth Sommerville, M.D., Associate Medical Director, Neurotherapeutics Venture
James Steck, Director, Regulatory Affairs

Following introductions, Abbott provided brief background information and stated our objective for the meeting, which was primarily to reach agreement with the Division on the acceptability of our plan for evaluating alterations in mental status, in order to respond to comment 2. b. from the October 31, 1996 approvable letter for the tiagabine NDA.

Dr. Katz then summarized the Agency's concerns and position on this matter. With regard to the mental status changes reported in patients receiving tiagabine, FDA does not believe we have made a coherent presentation of what is happening to patients' mental function and behavior in these cases. The terms used to describe these changes are devoid of content and are not considered to be useful in writing labeling. For example, aphasia is a focal neurological deficit and would not be a drug-induced state. Similarly, it would not be

immediately obvious to the presciber what the meaning is of terms such as thinking abnormal, delirium, and confusion, when used to describe these mental status changes. Labeling statements to describe this condition must be meaningful. Dr. Katz went on to say that one of the most important aspects of evaluating mental status changes is to obtain, on an individual patient basis, a "gestalt" of what is happening to patients who experienced mental status changes. The best way to do this in the Division's opinion is to go back to the reporting investigators and ask what was happening to patients who, for example, were said to have aphasia. The investigator may be able, by examining notes and records at the time, to say that the patient was actually groggy and somnolent. The investigator should then be asked to write a brief narrative summary describing what he believes was happening to the patient during the mental status change. This would then permit recoding ultimately to more appropriate COSTART terms and allow a real understanding of what these patients experienced.

Abbott representatives responded that COSTART terms were part of the problem. We agreed that terms like "thinking abnormal" are ambiguous and that, when we went back and looked at verbatim descriptions from the case report forms, we found these events were more aptly described as difficulty concentrating, slowed thinking, or mental lethargy. Abbott referred to our proposed plan for evaluating mental status changes that was faxed to FDA on November 15, 1996, which notes that verbatim descriptions will be reviewed to identify those potentially associated with, or possibly related to mental status changes and assigned more accurate and clinically meaningful COSTART terms.

Dr. Katz felt that if we (Abbott) go back and assign new COSTARTS based on review of verbatims, there is no way of knowing if the new terms are any more true than the original set. The Division feels that the investigator is the best person to carry out this evaluation, because he or she is in the best position to state what the problem was and give details of what was going on with the patient. If Abbott just retranslates the investigator verbatims, the second set of terms may not be any more accurate.

Abbott indicated that the verbatims are often the words used by the patients that are transcribed on to the case report forms. In using a dictionary like COSTART, something can be lost in the translation. With regard to querying investigators, Abbott expressed our concern that we would be asking them to look at events that may have occurred three or four years ago. He questioned whether their opinions today would be any more valid than when they recorded the information at the time.

Dr. Katz then stated that there is precedent for asking us to go back to investigators, and it is their belief that people think they can do this.

Dr. Sommerville noted that we cannot change the data that has already been obtained and that if an attempt is made to do this we may get a polyglot of information that will be impossible to summarize. He asked if it would be acceptable to the Division to restrict this activity to the double-blind, placebo controlled trials and to limit the querying of investigators to the top enrollers of patients into the studies. Furthermore, he proposed looking at just the two U.S. pivotal trials. He stated that this group would probably be the best source of information. Dr. Katz said he thought this would be a real possibility, but that the FDA participants would like to discuss this matter off line briefly. (At this point we had a brief recess in the conference while the FDA group discussed the matter among themselves).

When Dr. Katz and the FDA participants returned to the telephone, he stated that our proposal may be a practical way to get at the answer they are looking for. It would at least be a good start. He asked if we had gone back to the case report forms to see what the original verbatim terms were that indicated mental status changes. Dr. Sommerville replied that we had done this, as described in our proposal. We stated we used a very large net in identifying those verbatims that were possibly mental status changes. Dr. Katz asked if we cast the net just in placebo controlled studies. Abbott representatives said no, we looked at all epilepsy studies. We suggested to Dr. Katz that we could go ask investigators what they thought of particular medical terms assigned to verbatims and provide them with our old and new coding. Dr. Katz replied that this could be an important step in the process. We could confirm that what we have recoded, eg., somnolence instead of "thinking abnormal", is in agreement with the investigator's assessment of the event.

Getting back to the matter of restricting the investigator evaluation of mental status changes to placebo-controlled trials, Dr. Katz asked how many patients were included in these studies. Dr. Balian noted the total number of patients in these studies was 417. Abbott stated that possibly as many as 300 of them had some nervous system event that could have been related to a mental status change. Abbott said that if we look at the top five enrolling investigators in each study, this would probably yield about 100 patients.

Abbott pointed out that, in carrying out this activity, we will be looking to investigators to override what has been recorded on case report forms and questioned how this would be documented. Dr. Katz said that we need to document how we obtained the information from investigators. We need to be explicit in explaining how we questioned investigators; the Division wants to know in excruciating detail how we solicited comments from investigators on patients' mental status changes, and how the narrative paragraphs were prepared. He suggested we run a proposal by the Division on how we planned to query investigators and get their advance buy-in before we proceed.

Abbott noted that, considering that the data gathered from investigators in this activity may differ from what is recorded on the case report form, we could end up with an alternative database. Dr. Katz said the CRF database should remain unaltered, we do not need to submit new CRFs for the 100 patients. It is more a question of obtaining clarification from the investigator narratives that could lead to a more appropriate, clinically relevant recoding.

With respect to the patient narratives, we pointed to the practical difficulties in requiring investigators to actually write these summaries. Abbott asked if we could ask investigators what they think, assemble the information following the site interview, write the narratives for the investigators, and have them sign it to indicate their agreement. Dr. Katz felt that if the investigator signs to verify agreement, this would be acceptable.

Concerning Abbott's earlier comment of additionally casting a smaller net, ie, restricting the identification criteria to alterations of levels of consciousness, Dr. Katz asked what would be the purpose of truncating the net. Abbott replied that this may allow the selection of more clear and clinically relevant terms to describe mental status changes, which was the first concern of FDA. We said that this would also address the Division's second concern, as noted in the approvable letter, of differentiating mental status changes from non-convulsive status epilepticus.

Dr. Katz said that this second question was possibly only a small part of their concern. He believes that when we go back to investigators and primary documents, we should get a better idea of the patients who may have been in non-convulsive status epilepticus. Abbott noted that in our proposal, we are attempting to get at this question by examining both mental and motor symptoms which are likely to be associated with non-convulsive status epilepticus.

There followed a brief discussion of whether the evaluation of non-convulsive status epilepticus could be limited to just the subset of placebo-controlled studies. For the mental status change evaluation, it was agreed that this would be limited to U.S. placebo-controlled trials.

We then discussed the additional questions we had on the approvable letter, unrelated to the mental status change question, that were faxed to FDA on November 18, 1996. (We had earlier received a response to one of these, question #3. The Division agreed and confirmed that in our safety update, we can compare results back to the 4-month Safety Update, rather than to the original NDA Integrated Summary of Safety).

With regard to question #1 from the list faxed 11/18/96, this was answered by Dr. McCormick earlier in the telephone conference. The comments regarding possible incomplete

counting of partial seizures are those located in the case report tabulations, following the seizure count listings.

On question #2 from this list, there was considerable discussion on how the episodes of status epilepticus involving secondary generalization should be counted. Dr. McCormick stated that upon examination of the seizure comments, she believes a number of episodes of status epilepticus were not counted, and asked that we go back and verify that all these episodes were counted or add them into the database. Abbott then suggested that we examine these comments and, if some of the episodes of status were not included, we will add them into the database, using our 1 + maximum seizure count rule.

Dr. Katz stated that, if this question was related to FDA's request for an additional analysis of secondarily generalized seizures, we only need to count these status episodes as one episode of a secondary generalization following a partial seizure. This analysis is looking at the proportion of partial seizures that secondarily generalize, he said. To obtain the indication we are seeking, we must show tiagabine has an independent effect on preventing partial seizures from going on to secondarily generalized seizures.

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At this point, Dr. Arnold of Abbott summarized our agreement on the mental status change issue. He made the following points:

- The proposal that we faxed to the Division on November 15, 1996 was a useful starting point for responding to the approvable letter request.
- We will confine our screening and evaluation of altered mental status-related terms to U.S. double-blind placebo-controlled studies.
- We will examine the subset of patients who had conceivable mental status changes.
- Based on patient listings, we will go back to a sample of investigators from the U.S. placebo-controlled trials, and accurately transcribe any clarification and/or elaboration they can provide on the description of altered mental status reported for patients they studied

A few final issues were discussed before the telephone conference was concluded. Abbott raised our concern that there may be patients in which the investigators' retrospective opinions on what the patient experienced may be in disagreement with the information provided on the case report forms. This may also result in discrepancies between information in the new narrative information and what is recorded in source documents at the site, which could possibly raise issues in the event of a quality assurance audit. Dr. Katz did not see a major issue here, but noted that if this happens, we could cross this bridge when we come to it.

Abbott asked that if events are recoded for the specific sites selected for evaluation, what terms should be included in tabulations of adverse event incidence rates for the summary of the evaluations. Dr. Katz's response to this question was "COSTART terms." In addition, he indicated that this evaluation was only to help write labeling to better describe and characterize mental status changes seen in patients receiving tiagabine, to make them more understandable to prescribers. It should not impact the primary safety analyses already included in the NDA.

At this point, we thanked the FDA participants and concluded the telephone conference.

Appendix 11

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APPENDIX GROUP D ANALYSIS.0

TREATMENT-EMERGENT MENTAL STATUS-RELATED ADVERSE EVENTS FROM 11 SELECTED INVESTIGATORS
ABBOTT PLACEBO-CONTROLLED PARALLEL-GROUP ADD-ON EPILEPSY STUDIES &

BODY SYSTEM /MEDICAL TERM #	NUMBER (%) OF PATIENTS WITH AE: 11 SELECTED INVESTIGATORS TOTAL (N=248)	ALL OTHER INVESTIGATORS TOTAL (N=367)	P-VALUE ●
NERVOUS SYSTEM	135 (54)	189 (51)	.510
AGGRESSIVE REACTION	1 (<1)	3 (<1)	.652
AGITATION	1 (<1)	4 (1)	.653
ALTERED MOOD	1 (<1)	0	.403
AMNESIA	1 (<1)	2 (<1)	>.999
ANXIETY	3 (1)	3 (<1)	.689
APHASIA	2 (<1)	3 (<1)	>.999
ASTHENIA	3 (1)	2 (<1)	.397
BEHAVIOR ABNORMAL	0	1 (<1)	>.999
CONCENTRATION IMPAIRED	9 (4)	12 (3)	.824
CONFUSION	10 (4)	10 (3)	.367
CRYING UNCONTROLLABLE	0	1 (<1)	>.999
DEPRESSED STATE	0	1 (<1)	>.999
DEPRESSION	6 (2)	8 (2)	>.999
DEPRESSION SUICIDAL	1 (<1)	0	.403
DIFFICULTY THINKING	1 (<1)	0	.403
DISORIENTATION	2 (<1)	4 (1)	>.999
DIZZINESS	43 (17)	71 (19)	.597
DREAMS ABNORMAL	1 (<1)	1 (<1)	>.999
DREAMS BIZARRE UNUSUAL OR FRIG	0	1 (<1)	>.999
DROWSINESS	15 (6)	25 (7)	.742
DRUGGEDNESS	3 (1)	3 (<1)	.689
DULLNESS	0	1 (<1)	>.999
DYSPHASIA	0	1 (<1)	>.999
EMOTIONAL LABILITY	1 (<1)	9 (2)	.056
EXHAUSTION	0	2 (<1)	.518
FATIGABILITY	0	1 (<1)	>.999
FATIGUE	16 (6)	29 (8)	.532
FEELING FLOATING	0	1 (<1)	>.999
FEELING HIGH	1 (<1)	1 (<1)	>.999
FEELING STRANGE	2 (<1)	1 (<1)	.568
FEELING TENSE	1 (<1)	0	.403

& ABBOTT STUDIES M91-603 AND M91-605 (INCLUDES TITRATION AND FIXED-DOSE BUT EXCLUDES TERMINATION).
● FROM FISHER'S EXACT TEST.
* INDICATES STATISTICAL SIGNIFICANCE OF THE TWO-TAILED TEST AT THE .05 LEVEL.
# A PATIENT REPORTING MORE THAN ONE ADVERSE EVENT FOR A PARTICULAR MEDICAL TERM (BODY SYSTEM) IS COUNTED ONLY ONCE FOR THAT MEDICAL TERM (BODY SYSTEM).

APPENDIX GROUP D ANALYSIS.0

TREATMENT-EMERGENT MENTAL STATUS-RELATED ADVERSE EVENTS FROM 11 SELECTED INVESTIGATORS
ABBOTT PLACEBO-CONTROLLED PARALLEL-GROUP ADD-ON EPILEPSY STUDIES &

BODY SYSTEM /MEDICAL TERM #	NUMBER (%) OF PATIENTS WITH AE: 11 SELECTED INVESTIGATORS TOTAL (N=248)	ALL OTHER INVESTIGATORS TOTAL (N=367)	P-VALUE ●
NERVOUS SYSTEM (cont.)			
FORGETFULNESS	2 (<1)	3 (<1)	>.999
FUZZY	0	1 (<1)	>.999
GROGGY	2 (<1)	0	.162
HALLUCINATION	0	1 (<1)	>.999
HALLUCINATION VISUAL	0	2 (<1)	.518
HIGH FEELING	0	1 (<1)	>.999
HOSTILITY	2 (<1)	5 (1)	.707
HYPERACTIVITY	0	2 (<1)	.518
INSOMNIA	13 (5)	8 (2)	.068
IRRITABILITY	10 (4)	18 (5)	.696
LAUGHTER	0	1 (<1)	>.999
LETHARGY	10 (4)	10 (3)	.367
MEMORY IMPAIRED	7 (3)	10 (3)	>.999
MEMORY LOSS OF	1 (<1)	0	.403
MENTAL ACTIVITY DECREASED	0	1 (<1)	>.999
MENTAL DETERIORATION	1 (<1)	1 (<1)	>.999
MENTAL DULLNESS	0	1 (<1)	>.999
MOOD CHANGE	1 (<1)	2 (<1)	>.999
MOOD SWINGS	1 (<1)	0	.403
NERVOUSNESS	4 (2)	5 (1)	>.999
NIGHTMARES	1 (<1)	1 (<1)	>.999
PANIC REACTION	1 (<1)	0	.403
PHOBIA	0	1 (<1)	>.999
SEDATION EXCESSIVE	3 (1)	1 (<1)	.308
SLEEP DIFFICULT	0	2 (<1)	.518
SLEEP DISTURBED	1 (<1)	1 (<1)	>.999
SLEEP RHYTHM REVERSAL	0	1 (<1)	>.999
SLEEPINESS	10 (4)	19 (5)	.566
SLEEPLESSNESS	0	1 (<1)	>.999
SOMNOLENCE	3 (1)	10 (3)	.260
SPEECH DISORDER	1 (<1)	0	.403

& ABBOTT STUDIES M91-603 AND M91-605 (INCLUDES TITRATION AND FIXED-DOSE BUT EXCLUDES TERMINATION).
● FROM FISHER'S EXACT TEST.
* INDICATES STATISTICAL SIGNIFICANCE OF THE TWO-TAILED TEST AT THE .05 LEVEL.
# A PATIENT REPORTING MORE THAN ONE ADVERSE EVENT FOR A PARTICULAR MEDICAL TERM (BODY SYSTEM) IS COUNTED ONLY ONCE FOR THAT MEDICAL TERM (BODY SYSTEM).

APPENDIX GROUP D ANALYSIS.0

TREATMENT-EMERGENT MENTAL STATUS-RELATED ADVERSE EVENTS FROM 11 SELECTED INVESTIGATORS
ABBOTT PLACEBO-CONTROLLED PARALLEL-GROUP ADD-ON EPILEPSY STUDIES &

BODY SYSTEM /MEDICAL TERM #	NUMBER (%) OF PATIENTS WITH AE: 11 SELECTED INVESTIGATORS TOTAL (N=248)	ALL OTHER INVESTIGATORS TOTAL (N=367)	P-VALUE @
NERVOUS SYSTEM (cont.)			
TENSION NERVOUS	2 (<1)	0	.162
THINKING ABNORMAL	4 (2)	1 (<1)	.164
THINKING SLOW	0	2 (<1)	.518
THINKING SLUGGISH	0	1 (<1)	>.999
TIREDNESS	21 (8)	26 (7)	.539
WEEPING	0	1 (<1)	>.999

& ABBOTT STUDIES H91-603 AND H91-605 (INCLUDES TITRATION AND FIXED-DOSE BUT EXCLUDES TERMINATION).
@ FROM FISHER'S EXACT TEST.
* INDICATES STATISTICAL SIGNIFICANCE OF THE TWO-TAILED TEST AT THE .05 LEVEL.
# A PATIENT REPORTING MORE THAN ONE ADVERSE EVENT FOR A PARTICULAR MEDICAL TERM (BODY SYSTEM) IS COUNTED ONLY ONCE FOR THAT MEDICAL TERM (BODY SYSTEM).

SUMMARY OF TREATMENT-EMERGENT ADVERSE EVENTS (AEs) RELATED TO MENTAL STATUS CHANGES
ELEVEN TOP-ENROLLING INVESTIGATORS IN
PLACEBO-CONTROLLED, PARALLEL-GROUP, ADD-ON STUDIES M91-603 AND M91-605 ●

COSTART TERM /MEDICAL TERM #	NUMBER (%) OF PATIENTS WITH MENTAL STATUS CHANGE AE — PER ORIGINAL CASE REPORT FORM AE DESCRIPTION: PLACEBO (N= 80)	TIAGABINE (N=168)	PCB VS TGB P-VALUE &	RELATIVE RISK	PER QUESTIONNAIRE AE DESCRIPTION: PLACEBO (N= 80)	TIAGABINE (N=168)	PCB VS TGB P-VALUE &	RELATIVE RISK
ANY MENTAL STATUS CHANGE AE	40 (50)	95 (57)	.343	1.13 *	39 (49)	95 (57)	.277	1.16
ABNORMAL DREAMS	1 (1)	1 (<1)	.542	0.48	1 (1)	1 (<1)	.542	0.48
DREAMS ABNORMAL	0	1 (<1)	>.999		0	1 (<1)	>.999	
NIGHTMARES	1 (1)	0	.323		1 (1)	0	.323	
ABNORMAL GAIT	0	0						
GAIT UNSTEADY	0	0			0	1 (<1)	>.999	
					0	1 (<1)	>.999	
AGITATION	0	2 (1)	>.999					
AGITATION	0	1 (<1)	>.999		0	3 (2)	.553	
PANIC REACTION	0	1 (<1)	>.999		0	2 (1)	>.999	
					0	1 (<1)	>.999	
AMNESIA	3 (4)	8 (5)	>.999	1.27	2 (3)	5 (3)	>.999	1.19
AMNESIA	0	1 (<1)	>.999		0	0		
FORGETFULNESS	0	2 (1)	>.999		0	1 (<1)	>.999	
MEMORY IMPAIRED	3 (4)	4 (2)	.684	0.63	2 (3)	3 (2)	.659	0.71
MEMORY LOSS OF	0	1 (<1)	>.999		0	1 (<1)	>.999	
ANXIETY	0	4 (2)	.308					
ANXIETY	0	3 (2)	.553		0	5 (3)	.178	
FEELING TENSE	0	1 (<1)	>.999		0	4 (2)	.308	
					0	1 (<1)	>.999	
APHASIA	0	2 (1)	>.999					
APHASIA	0	2 (1)	>.999		0	2 (1)	>.999	
APHASIA MOTOR	0	0			0	1 (<1)	>.999	
					0	1 (<1)	>.999	
ASTHENIA	11 (14)	28 (17)	.709	1.21	10 (13)	27 (16)	.568	1.29
ASTHENIA	1 (1)	2 (1)	>.999	0.95	0	2 (1)	>.999	
FATIGUE	3 (4)	13 (8)	.281	2.06	4 (5)	11 (7)	.780	1.31
LASSITUDE	0	0			0	2 (1)	>.999	
TIREDNESS	8 (10)	13 (8)	.627	0.77	7 (9)	12 (7)	.621	0.82

● INCLUDES EVENTS WITH ONSET DURING TITRATION OR FIXED-DOSE (EXCLUDES EVENTS WITH ONSET DURING TERMINATION).
& FROM FISHER'S EXACT TEST.
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# A PATIENT REPORTING MORE THAN ONE ADVERSE EVENT FOR A PARTICULAR MEDICAL TERM (COSTART TERM) IS COUNTED ONLY ONCE FOR THAT MEDICAL TERM (COSTART TERM).

SUMMARY OF TREATMENT-EMERGENT ADVERSE EVENTS (AEs) RELATED TO MENTAL STATUS CHANGES
ELEVEN TOP-ENROLLING INVESTIGATORS IN
PLACEBO-CONTROLLED, PARALLEL-GROUP, ADD-ON STUDIES M91-603 AND M91-605 ●

COSTART TERM /MEDICAL TERM #	NUMBER (%) OF PATIENTS WITH MENTAL STATUS CHANGE AE — PER ORIGINAL CASE REPORT FORM AE DESCRIPTION				PER QUESTIONNAIRE AE DESCRIPTION			
	PLACEBO (N= 80)	TIAGABINE (N=168)	PCB VS TGB P-VALUE &	RELATIVE RISK	PLACEBO (N= 80)	TIAGABINE (N=168)	PCB VS TGB P-VALUE &	RELATIVE RISK
ATAXIA	0	0						
ATAXIA	0	0			0	3 (2)	.553	
BALANCE DIFFICULTY	0	0			0	2 (1)	>.999	
					0	1 (<1)	>.999	
CONFUSION	4 (5)	7 (4)	.750	0.83	2 (3)	6 (4)	>.999	1.43
CONFUSION	4 (5)	6 (4)	.731	0.71	2 (3)	5 (3)	>.999	1.19
DISORIENTATION	0	2 (1)	>.999		0	1 (<1)	>.999	
DEPERSONALIZATION	1 (1)	1 (<1)	.542	0.48	0	0		
FEELING STRANGE	1 (1)	1 (<1)	.542	0.48	0	0		
DEPRESSION	1 (1)	5 (3)	.667	2.38	1 (1)	6 (4)	.434	2.86
DEPRESSION	1 (1)	5 (3)	.667	2.38	1 (1)	5 (3)	.667	2.38
SUICIDAL TENDENCY	0	0			0	1 (<1)	>.999	
DIZZINESS	11 (14)	32 (19)	.371	1.39	11 (14)	30 (18)	.469	1.3
DIZZINESS	11 (14)	32 (19)	.371	1.39	11 (14)	29 (17)	.581	1.26
LIGHT-HEADED	0	0			0	2 (1)	>.999	
EMOTIONAL LABILITY	2 (3)	2 (1)	.596	0.48	2 (3)	1 (<1)	.244	0.24
ALTERED MOOD	0	1 (<1)	>.999		0	1 (<1)	>.999	
EMOTIONAL LABILITY	0	1 (<1)	>.999		0	0		
MOOD CHANGE	1 (1)	0	.323		1 (1)	0	.323	
MOOD SWINGS	1 (1)	0	.323		1 (1)	0	.323	
EUPHORIA	0	1 (<1)	>.999					
FEELING HIGH	0	1 (<1)	>.999		0	0		
					0	0		
HOSTILITY	0	3 (2)	.553					
AGGRESSIVE REACTION	0	1 (<1)	>.999		0	2 (1)	>.999	
HOSTILITY	0	2 (1)	>.999		0	0		
					0	2 (1)	>.999	

● INCLUDES EVENTS WITH ONSET DURING TITRATION OR FIXED-DOSE (EXCLUDES EVENTS WITH ONSET DURING TERMINATION).
& FROM FISHER'S EXACT TEST.
* INDICATES STATISTICAL SIGNIFICANCE OF THE TWO-TAILED TEST AT THE 0.05 LEVEL.
# A PATIENT REPORTING MORE THAN ONE ADVERSE EVENT FOR A PARTICULAR MEDICAL TERM (COSTART TERM) IS COUNTED ONLY ONCE FOR THAT MEDICAL TERM (COSTART TERM).

SUMMARY OF TREATMENT-EMERGENT ADVERSE EVENTS (AEs) RELATED TO MENTAL STATUS CHANGES
ELEVEN TOP-ENROLLING INVESTIGATORS IN
PLACEBO-CONTROLLED, PARALLEL-GROUP, ADD-ON STUDIES M91-603 AND M91-605 ●

COSTART TERM /MEDICAL TERM #	NUMBER (%) OF PATIENTS WITH MENTAL STATUS CHANGE AE — PER ORIGINAL CASE REPORT FORM AE DESCRIPTION				PER QUESTIONNAIRE AE DESCRIPTION			
	PLACEBO (N= 80)	TIAGABINE (N=168)	PCB VS TGB P-VALUE &	RELATIVE RISK	PLACEBO (N= 80)	TIAGABINE (N=168)	PCB VS TGB P-VALUE &	RELATIVE RISK
INSOMNIA	2 (3)	12 (7)	.237	2.86	1 (1)	13 (8)	.041*	6.19
INSOMNIA	1 (1)	12 (7)	.067	5.71	1 (1)	13 (8)	.041*	6.19
SLEEP DISTURBED	1 (1)	0	.323		0	0		
NERVOUSNESS	3 (4)	12 (7)	.398	1.9	3 (4)	11 (7)	.558	1.75
IRRITABILITY	2 (3)	8 (5)	.508	1.9	2 (3)	8 (5)	.508	1.9
NERVOUSNESS	0	4 (2)	.308		0	3 (2)	.553	
TENSION NERVOUS	1 (1)	1 (<1)	.542	0.48	1 (1)	1 (<1)	.542	0.48
PSYCHOTIC DEPRESSION	0	1 (<1)	>.999		0	0		
DEPRESSION SUICIDAL	0	1 (<1)	>.999		0	0		
SLEEP DISORDER	0	0			1 (1)	0	.323	
SLEEP DISORDER	0	0			1 (1)	0	.323	
SOMNOLENCE	13 (16)	29 (17)	>.999	1.06	15 (19)	32 (19)	>.999	1.02
DROWSINESS	3 (4)	12 (7)	.398	1.9	3 (4)	12 (7)	.398	1.9
DRUGGEDNESS	2 (3)	1 (<1)	.244	0.24	2 (3)	1 (<1)	.244	0.24
GROGGY	1 (1)	1 (<1)	.542	0.48	1 (1)	1 (<1)	.542	0.48
LETHARGY	2 (3)	8 (5)	.508	1.9	2 (3)	5 (3)	>.999	1.19
SEDATION EXCESSIVE	1 (1)	2 (1)	>.999	0.95	1 (1)	2 (1)	>.999	0.95
SLEEPINESS	6 (8)	4 (2)	.081	0.32	8 (10)	7 (4)	.089	0.42
SOMNOLENCE	0	3 (2)	.553		0	6 (4)	.181	
SPEECH DISORDER	0	1 (<1)	>.999		0	1 (<1)	>.999	
SPEECH DISORDER	0	1 (<1)	>.999		0	1 (<1)	>.999	
THINKING ABNORMAL	1 (1)	14 (8)	.042*	6.67	5 (6)	17 (10)	.474	1.62
CONCENTRATION (MENTAL) ABNORMAL	0	0			1 (1)	0	.323	
CONCENTRATION IMPAIRED	0	9 (5)	.061		1 (1)	8 (5)	.279	3.81
DIFFICULTY THINKING	0	1 (<1)	>.999		0	0		
MENTAL CONCENTRATION DIFFICULTY	0	0			0	1 (<1)	>.999	
MENTAL DETERIORATION	0	1 (<1)	>.999		0	0		

● INCLUDES EVENTS WITH ONSET DURING TITRATION OR FIXED-DOSE (EXCLUDES EVENTS WITH ONSET DURING TERMINATION).
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SUMMARY OF TREATMENT-EMERGENT ADVERSE EVENTS (AEs) RELATED TO MENTAL STATUS CHANGES
ELEVEN TOP-ENROLLING INVESTIGATORS IN
PLACEBO-CONTROLLED, PARALLEL-GROUP, ADD-ON STUDIES M91-603 AND M91-605 @

COSTART TERM /MEDICAL TERM #	NUMBER (%) OF PATIENTS WITH MENTAL STATUS CHANGE AE — PER ORIGINAL CASE REPORT FORM AE DESCRIPTION: PLACEBO (N= 80)	TIAGABINE (N=168)	PCB VS TGB P-VALUE &	RELATIVE RISK	PER QUESTIONNAIRE AE DESCRIPTION: PLACEBO (N= 80)	TIAGABINE (N=168)	PCB VS TGB P-VALUE &	RELATIVE RISK
THINKING ABNORMAL (cont.)								
MENTAL DULLNESS	0	0			0	1 (<1)	>.999	
THINKING ABNORMAL	1 (1)	3 (2)	>.999	1.43	3 (4)	5 (3)	.715	0.79
THINKING SLUGGISH	0	0			0	1 (<1)	>.999	
THOUGHT BLOCK	0	0			0	2 (1)	>.999	
TREMOR								
TREMOR	0	0			0	1 (<1)	>.999	
	0	0			0	1 (<1)	>.999	

@ INCLUDES EVENTS WITH ONSET DURING TITRATION OR FIXED-DOSE (EXCLUDES EVENTS WITH ONSET DURING TERMINATION).
& FROM FISHER'S EXACT TEST.
* INDICATES STATISTICAL SIGNIFICANCE OF THE TWO-TAILED TEST AT THE 0.05 LEVEL.
# A PATIENT REPORTING MORE THAN ONE ADVERSE EVENT FOR A PARTICULAR MEDICAL TERM (COSTART TERM) IS COUNTED ONLY ONCE FOR THAT MEDICAL TERM (COSTART TERM).

Appendix 12

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Data from the 20-mg tablet bioavailability study M96-546 is not included in safety update II by the sponsor since results were not available prior to the cutoff date. However, the report for the study including safety information is included in this submission (volumes 7-8) in response to the approvable letter. The study design was that of a randomized, single-dose, fasting, open-label, two-period, crossover study to compare the bioavailability of 20 mg of tiagabine in epilepsy patients taking one or two hepatic enzyme-inducing AED's. Sixty patients participated in study (58 completed both dosing periods). Review of the safety data failed to reveal any new safety issues.

Two patients discontinued prematurely (patient nos. 11 and 18). Patient 11, 32-year -old female (167 cm/70kg; 1.79 m^2) with a history of occasional headache, discontinued study participation due to moderate dizziness experienced after the Period I dose (five 4 mg tablets tiagabine 0.29mg/kg b.w.); the onset of the event was 25 minutes post dose and the duration of the event was five hours. Moderate intermittent nausea occurred concurrent with the dizziness; treatment consisted of a cold rag applied to the neck. Two other events which began approximately one hour post dose included a swollen numb lip (COSTART terms edema and circumoral paresthesia) and tongue numbness and tingling (COSTART term paresthesia) which were both characterized as mild in severity. These two events resolved approximately 5.5 hours after dosing. Both were considered to possibly be related to tiagabine. The stress of the study was given as an alternative etiology. She decided to discontinue participation in the study. The headache resolved after two hours. The patient was taking one concomitant AED (carbamazepine, 200 mg TID) and hormone replacement medication daily. An assay for plasma tiagabine levels revealed a maximum concentration of 667 ng/ml (average of 2 assay results) at the time of event onset.

Patient 18, a 33-year-old female (162 cm/78 kg; 1.85m^2) with a history of migraine, experienced moderate headache beginning approximately 26 hours prior to her Period I dose of tiagabine (20 mg tablet; 0.26 mg/kg b.w.) and evolving into a severe headache late the following day (Day 1); she experienced dizziness and nausea beginning one hour and 45 minutes after administration of the tiagabine dose in Period 1; these symptoms ranged from mild to moderate in severity. Mild intermittent vomiting began nine hours post dose. The dizziness resolved by the day after dosing. Complete resolution of the headache and nausea occurred two days after dosing. Promethazine and acetaminophen with hydrocodone were provided for treatment of nausea and headache, and the patient was directed to rest in a cool, dark environment. All post-dose events for the patient were considered to probably be related to tiagabine though migraine secondary to menstruation was reported as an alternative etiology. The patient elected to withdraw from the study due to headache and did not enter into period 2. This patient had a medical history of migraine from age 13-29 years, and headache associated with birth control use from age 17 to 27 years. The patient's antiepilepsy treatment consisted of 400 mg phenytoin QHS. Plasma assay for tiagabine concentration revealed a peak level obtained at 1.0 to 1:15 (hrs:minutes) after dosing (188-190 ng/ml). At the time of the event (1:45) the plasma level was 107 ng/ml.

In this submission serious adverse events were not discussed. However, there were 27 adverse events characterized as <u>severe</u> which occurred among 13 patients. The most frequently reported <u>severe</u> events were: somnolence (n=10), dizziness (n=5), thinking abnormal (n=2), headache (n=2), and amnesia (n=2). Other severe event terms with an occurrence in one patient were: abdominal pain, aphasia, confusion, diarrhea, hypokinesia, and nausea. Severe adverse event terms suggestive of cognitive dysfunction (thinking

abnormal, confusion, memory loss, amnesia) were not examined by the sponsor in the context of whether or not there was any correlation with the occurrence of these events and plasma levels of tiagabine. However, plasma levels were reported. Therefore, all cases characterized by decreased cognitive function (medical term cognitive disturbance) were assessed with respect to relationship between the adverse event and plasma levels of tiagabine (plasma levels from Sponsor's Appendix table B.21.A). Patient number 60 reported the event difficulty thinking as severe in period 1 and period 2. This case is summarized.

Patient 60, a 21-year-old female (163 cm/46 kg; 1.46m^2) experienced severe adverse events following both tiagabine regimens. Beginning 25 minutes after the Period 1 dose (five 4 mg tiagabine tablets; 0.43 mg/kg b.w.), the patient began to experience severe amnesia (described as total amnesia of event) and moderate dizziness. Within 45 minutes, the patient displayed moderate encephalopathy and severe inability to communicate (assigned the medical term aphasia, COSTART term aphasia), difficulty thinking (COSTART term thinking abnormal), and loss of voluntary motor movement (assigned the medical term motor activity retarded, COSTART term hypokinesia); as a result of these adverse events, the patient was unable to remain in a sitting position for the required three hours after dosing. All events resolved within approximately six hours of dosing. Mild right hemiparesis had been reported at all physical and neurological examinations performed during the study, including screening. Beginning 55 minutes after the Period 2 dose (tiagabine 20 mg tablet), the patient experienced moderate dizziness that lasted for four hours. She experienced moderate somnolence and difficulty thinking (COSTART term thinking abnormal) beginning 1.3 hours after dosing; 45 minutes later, the somnolence was considered severe. Both of these events resolved within five hours post

dosing. The adverse events following both tiagabine doses were considered to probably be related to tiagabine, and the patient's medical history was not significant with respect to any of these events. The patient's antiepilepsy medication consisted of carbamazepine, 400 mg/200 mg/400 mg. The patient's symptoms of thinking abnormal, aphasia and encephalopathy occurred at a time (45 min) when assay results revealed plasma tiagabine levels to be significantly greater than other times of measurement (672 ng/ml), dropping to 45 ng/ml at 6 hrs. after tiagabine exposure at a time when symptoms were reported to have resolved. The symptoms of dizziness and somnolence reported during period 1 and period 2, respectively occurred at a time of rising tiagabine plasma levels (394 ng/ml and 320 ng/ml, respectively). Three other patients (nos. 43, 50, and 58) reported thinking abnormal as an adverse event, but mild to moderate in severity. Plasma levels of tiagabine ranged from 265 to 729 ng/ml. Time to onset of the adverse event relative to the dose was 25 to 30 minutes (PK data indicates Tmax is about 48 minutes in the fasting state). In each of these 3 patients as well as patient number 60 thinking abnormal occurred at approximately the same time as the report of the adverse event dizziness. Three of the 4 patients (nos. 50, 58, and 60) were taking carbamazepine as a concomitant antiepileptic, and the forth patient (no. 43) was taking phenytoin.

Reports of cognitive dysfunction occurred in patients in whom the plasma concentrations of tiagabine were significantly greater than in the majority of those patients who did not report severe cognitive dysfunction such as difficulty thinking. Whether or not mean plasma tiagabine concentrations as well as the Tmax have predictive value for such adverse events as abnormal thinking, confusion, amnesia requires further documentation.

Appendix 13

This section summarizes the information available as of safety update II on the incidence of rash in tiagabine-treated patients, as well as information on clinical study patients referenced in the IND Annual Report (June 30, 1997).

Discontinuations Due to Rash

In the placebo-controlled parallel-group add-on studies <1% (1/494) of tiagabine-treated patients discontinued because of the AE rash. There was no placebo-treated patient who discontinued prematurely because of rash. These data are unchanged from the report in safety update I.

There are actually no new cases of rash (as COSTART term rash) leading to premature discontinuation in Safety Update II compared to Safety Update I when the rash was either a secondary or primary reason for discontinuation. The apparent increase of three patients as the primary AE leading to discontinuation in Safety Update II is a result of the fact that the primary AE leading to discontinuation for patients was not identified until Safety Update II. The 3 patients are a subset of the 4 patients in "AE Potentially Associated with Premature Discontinuation category", as the total 7 "primary AE" patients are a subset of the 12 with rash "potentially associated" with discontinuation.

In Safety Update II the sponsor has supplied line listings with applicable narrative summaries for those patients unique to safety update II (contained in volume 16 as appendix D.3.2). There were 2 unique patients with rash which resulted in patient discontinuation (numbers 2223 and 3205), both of whom are discussed in this review of safety update II. Similarity, the line listing for serious adverse events since the last update was provided (sponsor's appendix table D.5, volume 16).

Serious Adverse Event

There were no reports of rash as a serious AE in the placebo-controlled add-on studies.

In all epilepsy studies, rash was identified as a serious AE in <1% (3/2531; 2 in Abbott, 1 in studies) of tiagabine-treated persons, unchanged since safety update I. Vesiculobulous rash was identified in one patient (patient number 3205) and STevens-Johnson was identified in one patient (patient number 2102) as a serious AE. Information obtained from sponsor's appendix table C.1.7.29, volume 15.

In the long-term epilepsy studies, <1% (3/2248) of tiagabine-treated patients had a rash reported as a serious adverse event, (2 in Abbott and one in studies). Information was obtained from sponsor's appendix table C.1.9.28, volume 15.

Treatment-emergent adverse event, rash

In placebo-controlled parallel-group add-on epilepsy studies there was no statistically significant difference between reports of rash as a treatment-emergent event in tiagabine (5%; 24/494) and placebo (4%; 10/275) treated patients. Information was obtained from sponsor's appendix table C.1.7.2, volume 15.

In all epilepsy studies the following COSTART terms were used to describe rash as a treatment-emergent adverse event (AE). There were a total of 27 additional patients with COSTART rash in safety update II compared with I (278-251 = 27).

COSTART Term	Number (%) of patients with AE N = (2531)
Maculopapular	24 (<1)
petechial	1 (<1)
pustular	2 (<1)
rash	278 (11)
vesiculobullous	13 (<1)

From Sponsor's Appendix Table C.1.7.5, volume 15.

There are four additional treatment emergent events in safety-update II with other relevant COSTART terms, one each for maculopapular,vesticulobullous, urticaria and Stevens-Johnson Syndrome.

In the long-term epilepsy studies the following COSTART terms described rash as a treatment-emergent adverse event (AE)

COSTART Term	Number (%) of patients with AE (N = 2248)
maculopapular	20 (<1)
petechial	19 (<1)
pustular	2 (<1)
rash	264 (12)
vesiculobullous	12 (<1)

From Sponsor's Appendix Table C.1.7.4, Volume 15.
A patient reporting more than one AE for a particular COSTART is counted only once for that COSTART.

Annual Report for IND for Tiagabine

The Annual Report for this IND which covers the reporting period May 1, 1996 through April 30, 1997 was examined for reports of premature discontinuations and serious adverse events due to rashes. From Tables 3.A and 3.B in the Annual Report, 2 patients prematurely discontinued because of rash. The case summaries follow.

Patient No. 1507 ( ) is a 54 year old Caucasian female participating in Study M96-825. She had a screening history of hypersensitivity (rash) to lamotrigine and several other drugs. The patient was taking carbamazepine as her baseline antiepileptic drug. She initiated treatment with tiagabine (double-blind portion of the study) on September 3, 1996. On October 7, 1996 she returned for her next study visit and informed the study staff that on September 6, 1996 she experienced rash and shortness of breath, both rated as moderate in severity. The patient stated that she telephoned her daughter's physician who advised her to discontinue the study drug. The patient stopped taking the study drug that same day (September 6, 1996). The shortness of breath and rash were resolved two days following onset and discontinuation of study drug. The patient was prescribed nine different drugs including carbamazepine and rapinirole. Possible drug interactions increase dramatically with polypharmacy.

This patient had a history of hypersensitivity to numerous drugs therefore the possibility of an adverse reaction to tiagabine certainly would not be unfeasible. With the report of transient dyspnea and rash by the patient, could she have had an anaphylactoid type reaction (Type 1)? Without further information about this case it is not possible to answer the question or to determine the significance of the case.

Patient No. 11402 ( ) is a 7 year old white/Hispanic male who started in the M96-421 study on July 23, 1996 has an ongoing medical history of cerebral palsy, occasional otitis media, bronchitis, small ventricular septal defect, lymph telangiectasia (gastrointestinal), abdominal ascites, and intermittent diarrhea. The patient has a hypersensitivity (head/facial/abdominal edema; rash) to carbamazepine. The patient started blinded drug (tiagabine or placebo) on September 17, 1996 and the blind is being maintained. The patient's concurrent medications were phenobarbital 120 mg/day and calamine lotion topically (September 20, 1996 - September 21, 1996 for insect bites). On October 13, 1996 the patient experienced an adverse event of edema & epidermolysis bullosa - like ankle ulceration both ankles. The patient was medicated with hydrogen peroxide topically and PRN from October 16, 1996 through November 5, 1996. The investigator thought the severity was moderate and probably related to study drug., The adverse event stopped on November 2, 1996. Blinded drug was stopped October 14, 1996. The investigator and a dermatologist now thinks the above event was related to insect bites.

The patient as rechallenged in the open label M96-460 study on November 5, 1996 and no lesion of this type has reappeared. The patient is now on a lower dose of phenobarbital at 60 mg/day. The patient is presently on tiagabine 10 mg/day.

Neither of these cases have an impact upon the adverse event profile of tiagabine. Additional follow-up information on patient No. 1509 (, may be prudent.

REVIEW AND EVALUATION OF CLINICAL DATA: SAFETY

Application Information

NDA # 20-646

Sponsor: Abbott Laboratories

Clock Date November 6, 1995

Drug Name

Generic Name: Tiagabine

Proposed Trade Name: Tibex®

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 milligram strengths available.

Reviewer Information

Safety Reviewer: John Dikran Balian, M.D.

Review Completion Date: 7/25/96

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TABLE OF CONTENTS

1. Introduction

a. Background

Gamma-aminobutyric acid (GABA) is an inhibitory neurotransmitter with an important role in the regulation of seizure activity. Enhancement of the GABA-mediated inhibition is expected to have an anticonvulsant effect. Nipecotic acid is a well established compound that inhibits the GABA uptake into the glial cells and thus possesses anticonvulsant properties. Tiagabine is formed by the linking of an aliphatic chain to nipecotic acid and developed by the sponsor as an anti-epileptic drug (AED). Tiagabine was demonstrated to have anticonvulsant activity in rodents.

b. Animal Toxicity

In animal safety data, the no-toxic effect dose for tiagabine was reported to be 30 mg/kg/day for rats and 0.5 mg/kg/day for dogs. The median oral lethal dosage in mice was 500-1000 mg/Kg. Tiagabine was reported to cross the rat placenta and excreted in the milk of lactating rats. The maternal and development no-effect level (rats and rabbits) was reported to be 20 mg/kg/day. There was no evidence of mutagenicity. Long-term (2 year) carcinogenicity studies in rats revealed increased incidence of hepatocellular adenomas and/or carcinomas and benign Leydig cell tumors in the highest dose groups (200 mg/kg/day). The sponsor claims that the liver adenomas and/or carcinomas are most likely secondary to the effects of enzyme induction of the cytochrome P450 system. The induction of this drug metabolizing enzyme is known to be associated with increases in liver neoplasms in rodents, but not in humans.

Dogs receiving up to 15 mg/kg/day for a period of 3 months survived but experienced CNS dysfunction (recumbent behavior, sedation, irregular gait, tremors, lethargy, hyperactivity, vocalization, lack of awareness and visual impairment). Laboratory, opthalmologic, and microscopic exams of brain and spinal cord were not revealing. Depression of the spontaneous respiration rate was noted in dogs anesthetized with isoflurane and receiving tiagabine at doses of 10 and 30 mg/kg. A review of the human data revealed 50 patients receiving anesthetics concomitantly with tiagabine but no respiratory depression was noted.

Repeated-dosing studies in rats while receiving 100 or 400 mg/kg/day exhibited generalized gaseous distention of the alimentary tract, gastric ulceration, lymphoid depletion, hepatocytic hypertrophy and enlarged livers. In both single- and repeated-dose tiagabine studies produced signs of central nervous system (CNS) suppression and/or stimulation: reduced motor activity, ataxia, body weight loss or gain, retardation and excitatory responses (including convulsions and tremors) that

often preceded depressant actions and decreased body temperature.

c. Sponsor Labeling

In the annotated labeling, tiagabine is described as a compound that enhances the activity of GABA by binding to recognition sites for uptake of GABA. The sponsor claims that, in several of the models they studied, tiagabine was a more potent anticonvulsant than the commonly used antiepileptic drugs (AEDs). Tiagabine is indicated as adjunctive therapy in adults and children 12 years and older in the treatment of partial seizures with and without secondary generalization. The recommended dosing in patients 12-18 years of age is at an initial dose of 4 mg, which maybe increased at 4 mg weekly to a total of 32 mg/day in divided doses (2-4 times daily), while in adults at an initial dose of 8-12 mg daily which maybe increased at 8-12 mg weekly, up to a total of 32-56 mg/day in divided doses (2-4 times daily).

Tiagabine is rapidly absorbed with an approximate bioavailibilty of 90%. The elimination half-life is 7-9 hours in healthy volunteers. It is primarily eliminated by hepatic mechanisms (primarily via the CYP 450 3A enzyme system) and is highly protein bound. The sponsor claims that the parent drug is the active ingredient.

In the warning section of the labeling, the sponsor mentions the incidence of sudden deaths observed in their trials and compares it to the historical incidence in this population and does not find an increased risk. Also, specifically mentioned by the sponsor in the precautions section are the adverse events (AEs) of generalized weakness (limiting ambulation) and a non-diagnostic generalized spike-wave changes on EEG. In the AEs section of the labeling, there is special mention of dizziness, asthenia and nervousness as the most common AEs noted in the clinical trials.

d. Development

Tiagabine was developed by the (Novo), was licensed to Abbott Laboratories (Abbott) and jointly developed as an anticonvulsant. There were 18 phase 2-3 clinical trials, 8 were conducted and/or sponsored by Abbott and involved 1649 unique tiagabine-treated patients and the other 10 were conducted and/or sponsored by and involved an additional 819 unique tiagabine-treated patients. Key studies in the clinical program include 3 parallel-group, placebo-controlled, add-on studies involving more than 700 patients (Abbott studies # M91-603 and M91-603 and study # M92-775). There were 9 open-label, long-term studies involving more than 2100 patients. There were 32 phase 1 studies involving more than 500 patients.

At the time of this review, tiagabine had not been marketed in

any country.

2. Methods and Sources for the Review

The tiagabine NDA integrated safety summary (ISS), the Four-Month Safety-Update, the data listings, Case Report Forms (CRFs), Patient Narratives (PNs), reports of deaths, premature terminations, common and serious AEs, overdose reports and reports of treatment emergent changes in vital signs, clinical laboratory values, and ECGs were the sources used to review the safety aspects of this drug. The cut-off dates for the data reviewed are on or before November 30, 1995, for Abbott studies and on or before August 31, 1995, for the studies.

For the safety review the entire database was evaluated for all AEs, dropouts, uncommon and serious AEs, suicides and deaths. Where appropriate, the overall data is mentioned in the review, but most tables presented in the review reflect data obtained from the placebo-controlled trials. Data from uncontrolled trials would not be useful to draw any comparisons with placebo.

During the review process, the sponsor was frequently contacted for clarification, resubmission of data and explanation and occasionally reanalysis of certain data. The sponsor was always helpful and forthcoming. For methods of review of specific areas please see below.

3. Findings

a. Quality and Completeness of Submission

Overall, the submission meets the criteria noted in the 45 day refuse to file report of the DNDP for filing and review of the NDA. The index is orderly, but not very clear and comprehensive. There are two NDA volume numbering systems with appendices listed without description and frequently two or three steps are needed to locate a desired volume or a specific PN and CRF. The Integrated Safety Summary (ISS) and the individual study reports are complete and adequate.

The tables generally requested by the agency, such as 1% AEs table, premature terminations table, exposure, dosing and demographics tables were properly presented by the sponsor. Line Listings of patients of special interest are listed, but not indexed properly for cross referencing. PN summaries of premature terminations, deaths and serious AEs are provided.

70 PNs were randomly reviewed and found to be sketchy and sometimes not reflecting contents of the CRFs. Most of the PNs had less information than recorded in the CRFs, but occasionally

more information regarding the past medical history of the patient. There were no AEs noted in the PNs that were not in the CRF and the primary database. The PNs were not indexed properly for cross referencing to locate the same individual in the data listings.

The CRFs of deaths, dropouts and serious AEs are also provided. CRFs of all death cases and 50 other CRFs were randomly selected for review and were found to be sketchy and sometimes not reflecting contents of the PNs. These were also not indexed to locate data listings. The most useful aspect of the CRFs were the listing of reported AEs, however, it was not possible to formulate a history. The reported AEs in the CRFs are not indexed properly, but it is possible to locate and verify the transferred information in the data listings and this exercise did not reveal any irregularities or omissions.

In the original ISS, there was a discrepancy in the numbers regarding deaths. The numbers mentioned did not match with actual cases. This error has been corrected in the safety update.

b. Quality of AEs Surveillance in the Development Program

A review of the CRFs revealed a rather thorough surveillance of the spontaneous reporting of the AEs at every visit. Despite the difficulties encountered, due to the inadequacies (reported above) of cross-referencing and indexing, it was possible to certify the transfer of these reports to the data listings and verify their coding. A major weakness of the submission (this is common to almost all NDAs) is the lack of clinical descriptions of the AEs in the CRFs. Issues of co-morbidity, previous history, workup, follow-up, clinical characterization of a symptom, special testing, special treatment and start and stop dates of a symptom are usually not addressed in the CRFs. Occasionally, PNs may shed some light on these issues, but most PNs are scanty and when not reflective of the contents of the CRF a reviewer can not determine their reliability.

c. Quality of Coding

Investigator and patient descriptions for AEs were categorized by the sponsor using the COSTART II dictionary. Events were listed by body system and COSTART terms for patients participating in ABBOTT and clinical trials. All treatment emergent AEs were listed, regardless of the investigator's opinion concerning the relationship of the AE to the study drug. Seizure occurrences and hospitalizations resulting from them were not considered as AEs.

Data listings were examined to assess whether or not AEs subsumed under COSTART terms were too narrow or too broad. There were infrequent instances where AE terms were subsumed incorrectly, e.g., the term anemia under COSTART Abdominal Pain. Occasionally,

in the data listings of these coded terms, a series of unrelated AEs were listed on one line. This could be a problem if groupings were not done correctly, or if it lead to under- or overcounting of AEs. It was not possible to verify the grouping of these AEs, but the occurrences were infrequent enough, where a major problem is not expected even if not correctly grouped.

In the Abbott trials premature withdrawals from an AE were listed properly. These primary events were tabulated by body system and COSTART term. The tabulations are not as reliable. The studies did not identify one AE as the principal event for a withdrawal, therefore the sponsor tabulated AEs that potentially are associated with premature terminations.

Overall, the sponsor's coding approach was neither too conservative nor too inclusive.

d. Review of Specific Definitions

Treatment emergent AEs were interpreted properly by the sponsor. All AEs, whether or not considered drug related or not were reported. Patients freely reported AEs without solicitation, additionally, the investigators would solicit AEs from patients by using a checklist of AEs listed in the CRFs.

The most commonly reported AEs (occurrence of >5% and 2 times placebo) noted in the placebo-controlled trials were reviewed specifically and age and gender analyses performed. Special safety analyses were performed for several AEs related to central nervous system (CNS) toxicity, as well. these are mentioned in the review of systems (section 16).

Due to either the common occurrence of certain AEs or the seriousness of the AE, it is worthwhile to mention and report the investigator terms that were grouped under the COSTART terms that defined the AE. (i) The COSTART term accidental injury is a commonly occurring AE and a commonly reported serious AE. Investigator terms placed under this category were all inclusive of any trauma (serious or otherwise) secondary to falls or other injuries (mostly seizure induced) such as fractures, lacerations, pain, etc. (ii) Aphasia: investigator terms placed under this category included aphasia, anomia, loss of speech, disoriented, expressive aphasia, unable to talk, word substitution, language more impaired, etc. (iii) Asthenia: feeling tired, drugged feeling, run down, weak, muscle weakness, decreased energy, etc. (iv) Confusion: confused, abnormal thinking, dazed, altered mental status, disoriented, etc. (v) Encephalopathy: recurrent encephalopathy, mental slowing, decreased memory, etc. (vi) Psychosis: bizarre behavior, cloudiness of thought, psychosis, uncontrolled behavior, etc. (vii) Thinking abnormal: mentality slowed, cloudy thinking, altered thinking, concentration impaired, decreased cognition, etc. (viii) Tremor: shaky feeling

in hands, trembling, tremor, jittery, etc.

e. Findings From the Audit

An audit of CRFs and PNs was performed, as mentioned above. 50 cases were randomly selected from the patient AE data listings and the CRFs were reviewed for the completeness of the AE reporting system. Aside from few infrequent cases of incorrect classification, overall, there was a close match of records in CRFs and the data listings. A random sample of mortality CRFs and PNs was reviewed for content and there were no contradictions or misrepresentation found.

4. Review of Study Design Adherence

The investigators and sponsor seem to have adhered to the protocol designs of all trials, and there is no evidence to the contrary.

The protocols for the key studies (the placebo-controlled studies of Abbott # M91-603 and M91-603 and # M92-775) and the other clinical studies are very thorough and well designed. There were well devised plans in place to capture adverse events and to follow patients post termination with follow-up visits. In the Abbott studies, patients who withdrew prematurely from any trial due to adverse experiences were characterized as those who either gave adverse experiences as their principal reason for withdrawal or who had data from the CRF indicating an adverse experience at the time of the withdrawal. Due to the lack of attribution of specific causes for the terminations at time of occurrence, the withdrawal data is retrospective analysis.

Early phase II-III studies revealed no significant laboratory abnormalities, hence the investigators decided to perform laboratory testing at three to six week intervals. A special attempt was made of capturing neurological adverse events due to the frequency of those reports.

5. Study Population and Demographics

There are three adequate and well-controlled trials (M91-603-Abbott, M91-605-Abbott and M92-775-) in this submission that are similarly designed and will serve as the focus of the presentation of comparisons with placebo. These multicenter, parallel-group, placebo-controlled studies were conducted to determine the efficacy and safety of tiagabine as add-on therapy for the treatment of partial seizures in doses ranging from 16-64 mg daily administered as TID or QID dosing regimens. The patient selection criteria were similar in these 3 studies.

Study M91-603 is a placebo-controlled, parallel-group, randomized, double-blind 20 week study of three dose levels (4 mg QID--n=61, 8 mg QID--n=88, 14 mg QID--n=57 and placebo QID--n=91) of tiagabine as adjunctive treatment for complex partial seizures. Study M91-605 is a placebo-controlled, parallel-group, randomized, double-blind 16 week study of two dose levels (8 mg QID--n=105, 16 mg QID--n=106 and placebo QID--n=107) of tiagabine as adjunctive treatment for partial seizures. Study M92-775 is a placebo-controlled, parallel-group, randomized, double-blind 22 week study of a single dose (10 mg TID--n=77 and placebo TID--n=77) of tiagabine as adjunctive treatment for partial seizures.

In studies M91-603 and M91-605, patients 12-75 years of age (mean age 34) and for study M92-775 patients 17-71 years of age (mean age 37), who met the protocol criteria of partial seizures were enrolled. All patients were maintained on one to three AEDs (at least one of which had to be an inducer of hepatic enzymes).

Two other multicenter studies (M90-481 and M91-565) that used a randomized, double-blind, placebo-controlled, crossover design and a double-blind, non-placebo-controlled high-dose versus low-dose study (M93-090) that explored the dose response of tiagabine, will supplement the controlled safety data of the above three pivotal studies. This review will concentrate on the pivotal studies, without disregarding the other studies and the NDA safety summary.

a. Extent of Exposure

The number of unique normal subjects and patients receiving tiagabine worldwide is presented in table 5.a.1

Table 5.a.1 Patient Accountability				
		Number of Patients		
		Abbott	.	Total
Phase I (Clinical Pharmacology)				
	Tiagabine	403	151	554+
	Placebo	77	31	108
Phase II/III (Epilepsy Studies)				
	Tiagabine	1649	851*	2468
	Placebo	202	77	279
+ 30 Phase I tiagabine-treated patients entered Phase II/III studies.				
* 32 patients from Abbott short-term studies enrolled in extension studies.				

The total clinical program (excluding the clinical pharmacology trials) consists of 18 clinical trials (8 Abbott and 10 ' in which a total of 2468 unique patients have been exposed for a total of 3231 patient years. This includes 494 patients in three double-blind, placebo-controlled, parallel-group studies.

The sponsor evaluated tiagabine exposure (in 30-day months), average daily dose, maximum daily dose, and modal daily dose for each patient. A total of 1236 patients (50%) have been treated with tiagabine for more than one year, and 698 patients (28%) have been treated for more than two years. The modal daily dose was defined as the most frequently used daily dose. Table 5.a.2 displays patient exposure in patient years:

Table 5.a.2 Duration of Patient Exposure in Patient Years Phase II/III (Epilepsy Studies) Abbott + Results			
Type of Trial		Tiagabine	Placebo
Placebo-Controlled	N	494	275
Parallel-Group, Add-On	Patient Years	143.2	89.7
Other Epilepsy Studies	N	2406	4
	Patient Years	3221.2@	<0.1
Total	N	2468	279
	Patient Years	3231,5	89.7
@For patients from the extension studies, this also includes any tiagabine exposure in the parallel-group, placebo-controlled, add-on studies.			

b. Extent of Exposure by Dose

Appendices 5.b.1 and 5.b.2 show the number of patients exposed to Tiagabine by modal and maximum doses, respectively. Of the patients treated with tiagabine for more than one year, 28% (349/1236) had a most frequent daily dose of greater than 60 mg. Of the patients treated with tiagabine for more than two years, 35% (242/698) had a most frequent daily dose of greater than 60 mg.

Almost all the studies were dose escalation studies. In the pivotal studies (double-blind and placebo-controlled) patients were randomized to one of five fixed total daily doses: 16 mg (4 mg QID), 30 mg (10 mg TID), 32 mg (8 mg QID), 32 mg (16 mg BID) and 56 mg (14 mg QID). There was a 5-6 week titration period followed by an 8-12 week fixed-dose period and a 4-week termination period.

c. Demographics

Appendix 5.c.1 shows the demographics of all the studies and 5.c.2 the controlled trials only. In the controlled trials, there were no statistically significant differences between the tiagabine and placebo groups with respect to age, sex or race. The ages ranged from 12-77, with an average of around 34 years, the overwhelming majority (90%) were caucasian and 57% were male.

In the controlled trials, the highest proportion of patients were between 18-39 years old (60%), followed by 40-64 years old (31%). The median duration of epilepsy was 23 years with patients having received an average of 8 anti-epileptic drugs as treatment prior to enrollment to the study and had a mean of 1.6 anti-epileptic drugs given concomitantly during the study. There were no statistically significant differences between the tiagabine and placebo groups with respect to patient disease characteristics at baseline.

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6. Review of Deaths

The sponsor reports a total of 34 patient deaths in the tiagabine NDA: 31 from the tiagabine-treated patients, 1 patient (#11014 study M91-603) from the placebo patients, and 2 patients died during the baseline period before randomization. A review of the PNs and CRFs revealed 4 deaths among the tiagabine-treated patients occurred while the patients had been off tiagabine for a period of 1-14 months. If a death occurred more than 1 month after discontinuation and the event started more than 1 month after discontinuation, the case was removed from the list of deaths and incidence rates by this reviewer.

The revised numbers are 27 patient deaths in the tiagabine-treated arm of which 13 are considered sudden and unexplained deaths (SUD) by this reviewer. The Abbott/ criteria for sudden and unexplained deaths (SUDs) were unwitnessed death and no other likely explanation of death either by history or autopsy. The sponsor reports 10 such deaths, one of the deaths occurred 2 months after discontinuation of the drug. When the criteria of only unwitnessed death (including unwitnessed drowning) is used with no clear explanation as to causality, then the number of SUDs rises to 13 (the number used in the table above). These 27 deaths are summarized in Appendix 6.1. Some cases representing the different diagnoses (SUD, CNS neoplasia, aplasstic anemia, drowning, etc.) listed in appendix 6.1 are presented below:

Patient 31305 (study # M91-604), an 18 year old male was found dead in bed 159 days after initiation of tiagabine therapy. For seven months prior to the demise the patient had complained of chest pains responsive to antacid treatment. The investigator attributed the death to arteriosclerosis and heart failure despite the absence of a postmortem. This reviewer considers this a case of SUD.

Patient 50817 (study # M91-604), a 40 year old female with history of astrocytoma was diagnosed with a recurrence of the malignant neoplasm 247 days after initiation of tiagabine therapy. Her demise is attributable to the CNS neoplasia.

Patient 51116 (study # M91-604), a 66 year old male with history of peripheral vascular disease (PVD), hypertension (HTN), hyperlipidemia and tobacco abuse was hospitalized at day 227 of treatment for unstable angina, day 252 for bronchitis, day 334 for confusion, day 336 agitation, day 343 for a myocardial infarction (MI) and day 412 for aspiration pneumonia and sepsis. The patient expired from complications of the sepsis.

Patient 11807 (study # M91-605), a 27 year old female, on chronic carbamazepine and mesantoin therapy was hospitalized with a diagnosis of aplastic anemia one day after initiation of

tiagabine therapy. She died of complications of the aplastic anemia.

Patient 1501 (study # M92-813), a 22 year old female was found dead in the bathroom 648 days after initiation of tiagabine therapy. No post mortem was performed. This is one case that is listed as SUD.

Patient 1901 (study # M92-813), a 57 year old female with a history of headaches and craniotomy, was hospitalized following an accidental injury and subarachnoid hemorrhage 133 days after initiation of tiagabine therapy. For 2 weeks prior to the fall patient was complaining of dizziness and difficulty in talking. Tiagabine was discontinued and patient expired 5 days later. The Neurosurgeon thought that the subarachnoid hemorrhage occurred prior to the fall.

Patient 102 (study # M91-578), a 43 year old female had a seizure fell in a pool and suffered respiratory failure from the near drowning 17 months after initiation of tiagabine therapy. She died two months later in the ICU.

Patient 2807 (study # M92-813), a 51 year old male was diagnosed with astrocytoma 868 days after initiation of tiagabine therapy. After a craniotomy and several episodes of hospitalizations patient expired 1034 days after initiation of tiagabine therapy.

Overall mortality was determined and table 6.1 displays the cumulative risk of mortality and the mortality rate:

Table 6.1 Mortality

Sponsor	Drug	# Patients	Patient Years of Exposure	Deaths	Cumulative Risk	Mortality Rate**
Abbott	Tiagabine	1649	2242.7	15@	0.009	0.67
	Placebo	202	57.0	1	0.0050	1.75
	Tiagabine	851*	1003.0	12@	0.0141	1.20
	Placebo	77	32.8	0	0	0
Total	Tiagabine	2468	3231.5	27@	0.011	0.84
	Placebo	279	89.7	1	0.0036	1.11

@ No deaths occurred among the patients in the placebo-controlled, parallel-group, add-on studies.

* 32 patients from Abbott short-term studies enrolled in extension studies.

** per100 Patient Years

The cumulative risk of sudden death and the sudden death rates are displayed in table 6.2:

Table 6.2 SUDS

Sponsor	Drug	# Patients	Patient Years of Exposure	SUDs*	Cumulative Risk	SUD Rate***
Abbott	Tiagabine	1649	2242.7	9	0.0055	0.4
	Placebo	202	57.0	0	0	0
.	Tiagabine	851**	1003.0	4	0.0047	0.40
	Placebo	77	32.8	0	0	0
Total	Tiagabine	2468	3231.5	13	0.005	0.4
	Placebo	279	89.7	0	0	0

* No SUDS occurred among the patients in the placebo-controlled, parallel-group, add-on studies.
** 32 patients from Abbott short-term studies enrolled in extension studies.
*** per 100 Patient Years

The sponsor cites leterature references that mention an incidence rate for sudden death in the general epilepsy population of 0.0005, 0.003 for a clinical trial population, and 0.005 in patients with refractory epilepsy (Sudzak et al, 1995; and Nielsen et al, 1988). Patients in the tiagabine trials, in most cases are similar to patients with refractory epilepsy since they have been refractory to multiple AEDs. The topiramate NDA indicates an SUD rate of 5/1,000 patient years for topiramate, tiagabine has a rate of 4/1,000 patient years.

The patient narratives (PNs)and the CRFs on these patients are not very revealing, but in this reviewer's opinion no causal relationship of the deaths to the study medication can be identified.

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7. Review of Serious Events

The Code of Federal Regulations (CFR) defines serious adverse events as "...any experience that is fatal or life-threatening, is permanently disabling, requires inpatient hospitalization, or is a congenital anomaly, cancer, or overdose" (21 CFR § 312.32).

The cumulative incidence (CI) of serious AEs was 19% (469/2468) with tiagabine. Of these 469, 193 were neurologic, the most common being confusion (31/2468=1.3%) and depression (26/2468=1.1%). In the controlled trials the CI was reported to be 10.5% (52/494) in the tiagabine group and 11.3% (31/275) in the placebo group (of these 10 cases in the tiagabine arm and 2 in the placebo arm were CNS related). The slightly higher incidence rates of serious AEs noted in the placebo arm of the controlled trials suggests that there is no sufficient evidence to relate causality of events to the drug on a statistical basis. However, the predominance of neurological events with tiagabine may be a signal regarding further consideration.

Additionally, incidence rates of serious events (as defined by the CFR) are reported under specific headings (review of systems, etc.). It should be noted, once again that most information (CRFs and PNs) is very sketchy, when available. To draw conclusions as to whether an event is drug related or not is very difficult. Nonetheless, an attempt was made to classify the events as drug related or not and lists prepared (if a case falls under the related category, it simply means that in this reviewer's clinical judgement from reading the sketchy PNs, there is no strong evidence to rule out that it was not associated to the drug). Appendix 7.1 displays a listing of serious AEs for tiagabine that in this reviewer's opinion are not attributed to treatment. Please note that fatalities have already been included in Appendix 6.1 and are not repeated in Appendix 7.1. Appendix 7.2 displays a listing of serious AEs that may possibly be drug related. These appendices closely resemble the information and tables provided by the sponsor. In the text (under specific headings, such as deaths, review of systems, etc.), some cases of interest that may either indicate a causal relationship to treatment or exonerate tiagabine are discussed.

Appendix 7.3 displays the cumulative rates of serious AEs for the phase II-III studies and the placebo controlled trials.

8. Review of Dropouts

a Overall Pattern of Dropouts

Over the entire phase 2-3 database, a total of 1641 (1641/2468=66%) patients terminated prematurely; higher proportions were discontinued due to lack of efficacy (31%), followed by AEs (20%). As a comparison, the last 4 AED NDAs reviewed by this division report the following AE related premature discontinuation rates: Gabapentine at 17%, felbamate 12%, lamotrigine 9% and topiramate 25%.

In the Abbott randomized controlled trials (RCTs), a total of 73 (73/417=17.5%) patients terminated prematurely in the tiagabine arm and 21 (21/198=10.6%) patients terminated prematurely in the placebo arm. Table 8.a.1 summarizes the reasons for patients's premature terminations in the database for the RCTs conducted by Abbott (US studies):

Table 8.a.1 Distribution of Patients Who Prematurely Terminated Treatment Placebo-Controlled, Parallel-Group, Add-On Studies Abbott Results

	M91-603		M91-605		Total	
Primary Reason Discontinued	Tiagabine (N=206)	Placebo (N=91)	Tiagabine (N=211)	Placebo (N=107)	Tiagabine (N=417)	Placebo (N=198)
Lack of Efficacy	8 (3.9)	6 (6.6)	2 (1.0)	1 (0.9)	10 (2.4)	7 (3.5)
Adverse Events	24 (11.7)	5 (5.5)	21 (10.0)	7 (6.5)	45 (10.8)	12 (6.1)
Intercurrent Medical Events	0	0	2 (1.0)	0	2 (0.5)	0
Administrative	7 (3.4)	0	9 (4.3)	2 (1.9)	16 (3.8)	2 (1.0)
Noncompliance	1 (0.5)	0	2 (1.0)	0	3 (0.7)	0
Personal Reasons	2 (1.0)	0	2 (1.0)	0	4 (1.0)	0
Lost to Follow-Up	1	0	0	0	1 (0.2)	0
Did Not Meet Baseline Criteria	0	0	4 (2.0)	2 (1.9)	4 (1.0)	2 (1.0)
Other	3 (1.5)	0	1 (0.5)	0	4 (1.0)	0
Total	39 (18.9)	11 (12.1)	34 (16.1)	10 (9.4)	73 (17.5)	21 (10.6)

When the above discontinuations were evaluated by study period, discontinuations for AEs in the drug treated group were highest (8%) in the titration period. These numbers dropped to 3% in the fixed dose period and 1% in the termination period. Placebo rates remained constant at 3% for all three periods. This finding is reflected for the overall database as well.

Table 8.a.2 summarizes the reasons for patients's premature terminations in the database for the controlled trials conducted

by studies did not identify a primary reason for premature terminations, the following table was generated retrospectively by the sponsor):

Table 8.a.2 Distribution of Patients Who Prematurely Terminated Treatment
Placebo-Controlled, Parallel-Group, Add-On Studies
Novo Results

Primary Reason Discontinued	Tiagabine (N=77)	Placebo (N=77)
Lack of Efficacy	2 (2.6)	1 (1.3)
Adverse Events	17 (22.1)	2 (2.6)
Administrative	2 (2.6)	5 (6.5)
Noncompliance	1 (1.3)	0
Personal Reasons	0	1 (1.3)
Lost to Follow-Up	0	1 (1.3)
Other	1 (1.3)	3 (3.9)
Total	21 (27.3)	8 (10.4)

In the controlled studies, a statistically significant number of patients discontinued from the tiagabine treatment groups when compared to placebo ($p \leq 0.001$) with a significantly higher proportion of tiagabine patients discontinuing for AEs ($p \leq 0.001$).

A low-dose versus high-dose monotherapy study was conducted by Abbott, where fixed doses of 6 mg (N = 102) or 36 mg (N = 96) were used following a titration period. The proportion of patients discontinuing for lack of efficacy in the low-dose group (41%) was higher than, but not statistically significantly different from the high-dose group (29%). The proportion of patients discontinued for AEs in the high-dose group (43%) was statistically significantly higher than the low-dose group (18%).

b. Dropout Secondary to Adverse Events

In all Abbott epilepsy studies 19% (310/1649) of tiagabine treated patients had an AE identified as the primary reason for premature termination. Within the Abbott placebo controlled add-on epilepsy studies 10.8% (45/417) of the tiagabine patients and 6.1% (12/198) of placebo patients prematurely terminated due to AEs.

Appendix 8.b.1 displays AEs for which two or more tiagabine

treated patients dropped out in the placebo-controlled studies. Appendix 8.b.2 displays AEs for which ≥ 1% of tiagabine treated patients dropped out and for which the incidence was at least twice the placebo-treated patients in the placebo-controlled studies. All items listed in appendix 8.b.2 are CNS events: ataxia, confusion, dizziness, headaches, nervousness, somnolence, speech disorder and tremor.

In the low-dose vs high-dose monotherapy study (M93-090), more patients in the high-dose group (41/96=43%) prematurely terminated due to AEs than in the low-dose group (23/102=23%).

The pattern in the long-term epilepsy studies was no different from the data presented above. CNS AEs were the most frequent reason that led to premature terminations in all studies.

9. Laboratory Findings, ECG and Vital Signs

a. Laboratory Findings

In the presentation of the laboratory findings, the sponsor has used the criteria recommended by this division.

In the overall database the incidence rate for serious AEs related to laboratory findings was <1% (16/2468), of which 8 were chemistry and 8 were hematology related. In the placebo controlled trials serious AEs related to laboratory findings were reported at <1% (3/494, 2 chemistry and 1 hematology related) in the tiagabine arm and <1% (1/275, 1 chemistry case) in the placebo arm.

a.1 Serum Chemistry

Appendix 9.a.1.1 lists the criteria and incidence of clinically significant chemistry laboratory abnormalities. As this table indicates, there are no areas of concern regarding chemistry abnormalities in the available data.

There were a total of 8 (N=2468) discontinuations due to chemistry abnormalities. 3 premature discontinuations were from the placebo-controlled trials: Patient 10721 (study M91-603), with a history of hyponatremia was discontinued due to hyponatremia. Patient 10321 (study M91-605), with a history of diabetes mellitus (DM) on hypoglycemic agents, was discontinued on day 16 due to hyperglycemia (glucose was 333 mg/dL). Two weeks after discontinuation the glucose was 379 mg/dL. Patient 18010 (study M92-775), with a history of DM on phenytoin and carbamazepine, was discontinued due to hypoglycemia.

There was 1 premature discontinuation from the low vs high dose trial (study M93-090) due to elevated liver enzymes. Patient 10904 had mildly elevated liver enzymes at baseline attributed to phenytoin therapy. After initiation of tiagabine (6 mg daily) the levels of SGOT went from 56 to 201 u/L, SGPT from 63 to 332 u/L, and GGT from 322 to 332 u/L. The patient was diagnosed with hepatitis C. Concurrent medications included phenytoin and carbamazepine. Approximately 5 months after discontinuation the levels were back down to the baseline elevated levels.

There were 4 premature discontinuations from the long-term trials due to elevated liver enzyme values. From study M91-604: Patient 30706 presented with SGOT of 1365 IU/L, SGPT of 2320 IU/L, and alkaline phosphatase (AP) of 221 IU/L. The patient tested positive for hepatitis A and C, and a biopsy confirming the hepatitis. 4 months after discontinuation the enzymes were back to normal levels; patient 80309 had values of SGOT=57 IU/L and SGPT=116 IU/L and tested positive for EBV. 1 month after discontinuation the enzymes were back to normal levels; and

patient 31302 presented with jaundice and SGOT of 1454 IU/L, SGPT of 781 IU/L, and AP of 262 IU/L. The patient tested positive for hepatitis B. From study M92-813, patient 6201 with possible alcohol abuse and elevated carbamazepine levels had liver enzyme values as high as SGOT of 117 IU/L and SGPT of 50 IU/L both on and after discontinuation of tiagabine.

In all phase II-III trials, the proportion of patients meeting the DNDP criteria (for criteria see appendix) of very low or very high values of chemistry abnormalities and occurring in >1% of the patients are the following: Very low shifts--glucose 44/2093=2%, chloride 54/1894=3% and calcium 153/2293=7%. Very high shifts--glucose 40/2093=2% and potassium 61/2301=3% (the denominator is the number of patients with a normal baseline value for that variable). In most instances these very low or very high values were sporadic occurrences.

A causal relationship of treatment-emergent chemistry abnormalities and tiagabine is unlikely.

a.2 Hematology

Appendix 9.a.2.1 lists the criteria and incidence of clinically significant hematology laboratory abnormalities. As this table indicates, there are no areas of concern regarding hematology abnormalities in the available data.

There were a total of 7 (N=2468) discontinuations due to hematology abnormalities. 2 premature discontinuations were from the placebo-controlled trials: Patient 11121 (study M91-605), a 46 year old male with baseline platelet levels of 112-114,000 on day 14 presented with platelet levels of 89,000 while on 8 mg QID of tiagabine. He was discontinued on day 18. On day 42 platelet levels were 101,000. Concomitant medications included valproate. Patient 11807 (study M91-605), a 27 year old female presented with aplastic anemia at baseline.

There were 4 premature discontinuations from the long-term trials: From study M92-813, patient 605 for leukopenia (WBC fell to 3200 from 4,000, concomitant medication was carbamazepine); patient 2708 for thrombocytopenia (platelets were assessed at 87,000; concomitant medication was valproate); and patient 2711 for pancytopenia (patient had pyelonephritis with a decrease of hematocrit to 10.7 and WBC to 4,800). From study M93-047, patient 2113 for acute lymphoblastic leukemia (patient had lymphoproliferative changes at baseline). Additionally, patient 6021 from study M90-481 discontinued for leukopenia after 8 days of treatment, concomitant medications were carbamazepine and vigabatrin.

In all phase II-III trials, the proportion of patients meeting the DNDP criteria (for criteria see appendix) of very low or very

high values of hematology abnormalities and occurring in >1% of the patients are the following: Very low shifts--hematocrit 84/2095=4% and WBC 50/1875=3%. Very high shifts--monocytes 193/2264=9%, eosinophils 94/2259=4%, prothrombin time (PT) 63/828=8%, and partial thromboplastin time (PTT) 140/963=15% (the denominator is the number of patients with a normal baseline value for that variable). In most instances these very low or very high values were sporadic occurrences.

A causal relationship of treatment-emergent hematology abnormalities especially regarding PT and PTT elevations are possible. The clinical significance of these AEs is difficult to assess, though the abnormalities seem to be transient and reversible even with the continuation of the medication.

a.3 Urine Analysis

There were no reports of serious adverse experiences or premature terminations due to abnormalities in urinalysis parameters. For this section, no individual cases were reviewed. From the available data it is apparent that no particular urine analysis abnormality can be attributed to Tiagabine. There were no premature discontinuations.

b. ECG Findings

ECGs, at baseline and termination were performed in the Abbott controlled and long-term trials (n=1336). 0.9% (11/1336) of these had a clinically signigficant abnormality. No overall increase of adverse events were noted when compared to placebo. A review of the ECG abnormalities reported, revealed no particular tendencies. A discussion of this is presented in section 16 in the review of systems.

although no quantitive analyses were performed, tiagabine does not appear to induce heart rate, PR, QRS, or QTc interval abnormalities.

c. Vital Signs

Appendix 9.c.1 lists the criteria and incidence of clinically significant Vital Signs abnormalities. In the controlled trials, evaluation of postbaseline shifts for vital signs disclosed no differences between the tiagabine and the placebo groups.