10. Other Safety Findings

a. ADR Incidence Table And AE Lists

Appendices 10.a.1, 10.a.2 and 10.a.3 display the incidence of adverse events in the placebo-controlled studies of Abbott, and the pooled incidence, respectively.

The spontaneous reports of adverse events were classified by body system using Coding Symbols for Thesaurus of Adverse Reaction Terms II (COSTART).

b. Common and Drug Related AEs (the 5% Table)

Table 10.b displays adverse events in the placebo-controlled studies (Abbott anc combined), having an incidence of ≥ 5% and at least twice the incidence of placebo. Because of potential relevance, all treatment-emergent adverse events for which the incidence was statistically significantly higher for tiagabine than placebo are also included in the table.

Table 10.b Treatment-Emergent AEs Reported by ≥5% of Tiagabine-Treated Patients with at Least Twice the Incidence of the Placebo-Treated Patients@ Placebo-Controlled, Parallel-Group, Add-On Studies Abbott + Results

Body System	COSTART Term	Number (%) of Patients	
		Tiagabine (N=494)	Placebo (N=275)
Body as a Whole	Abdominal Pain	35(7)*	8(3)
Digestive System	Diarrhea	33(7)	8(3)
Nervous System	Aphasia	8(2)*	0(0)
	Asthenia	98(20)*	39(14)
	Depression	17(3)*	2(<1)
	Dizziness	131(27)***	40(15)
	Nervousness	50(10)***	8(3)
	Thinking Abnormal	30(6)*	6(2)
	Tremor	46(9)*	10(4)

@ All treatment-emergent adverse events for which incidence was statistically significantly higher for tiagabine than placebo also included.
*, *** Statistically significantly higher than placebo at $p \leq 0.05$ and 0.001, respectively.

It is apparent that the AEs listed reflect the commonly experienced problems with the CNS. As an indication of the clinical significance of these common AEs, the dropout rates and serious AEs reported under these COSTART terms were reviewed. For premature terminations, when considering the Abbott controlled

studies only (tiagabine n=417 and placebo n=198, reliable data for premature terminations does not exist for in the tiagabine arm there were 3 cases for dizziness; 2 for abdominal pain, depression, dizziness, nervousness and thinking abnormal; 1 for tremor; and none for diarrhea and aphasia, while in the placebo arm there was only 1 case for dizziness. For serious AEs and Abbott controlled trials combined, tiagabine n=494 and placebo n=275), there were 2 cases for diarrhea and depression, 1 case for abdominal pain and tremor in the tiagabine arm and 1 case for abdominal pain and dizziness in the placebo arm. There will be more thorough discussion of these AEs under section 10.a in the review of systems.

c. Dose Response For Common Adverse Events

The sponsor evaluated dose-response, concentration-response and frequency-response of treatment-emergent AEs in studies M91-603, M91-605 and M90-090. In study M91-603, a subset of AEs (asthenia, dizziness, nervousness, thinking abnormal and tremor) with an incidence of ≥ 5% in the tiagabine patients were analyzed for dose-response. In study M91-605, which had three treatment groups, 16 mg BID, 8 mg QID and placebo, the sponsor evaluated the comparison of BID and QID dosing regimens. And in the monotherapy study M93-090, done at two dose levels (16 and 32 mg daily) the sponsor evaluated a comparison of the AEs associated with dose levels.

Based upon the analyses of the above studies the sponsor concluded the following: (i)the frequency of common AEs correlated better with total tiagabine dose than dose frequency or tiagabine concentration; (ii)during the titration period of the studies, statistically significant dose-response relations across placebo and three tiagabine dose groups (16, 32 and 56 mg daily) were found for the 5 AEs mentioned above; (iii)during the experiment (maintenance dose) period of the studies, statistically significant dose-response relations across placebo and three tiagabine dose groups (16, 32 and 56 mg daily) were found for dizziness, thinking abnormal and tremor only; and (iv)a statistically significantly higher proportion of high-dose than low-dose patients in study M93-090 reported AEs related to the nervous system (dizziness, nervousness, somnolence, speech disorder, thinking abnormal and tremor). Additionally, amblyopia (COSTART term for temporary blurring of vision), within the special senses system, was the other AE reported by statistically significantly higher proportion of high-dose than low-dose patients.

In general the association between higher plasma concentration and increased incidence of AEs was not as clear as seen in the dose-response analysis. Depression and tremor were the 2 AEs that showed a significant concentration-response between placebo and three concentration groups (<50 ng/mL, 50-100 ng/mL and >100

ng/mL).

d. Adverse Event Incidence Over Entire Phase 2-3 Integrated Primary Database

Appendix 10.d.1 includes all other adverse events reported from the clinical trials that are not reported in the incidence ≥ 1% table (Appendices 10.a.1, 10.a.2 and 10.a.3).

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11. Effect of Age and Gender on Adverse Event Incidence

Appendices 11.1 and 11.2 reveal the age and gender based analysis performed. AEs for which tiagabine incidence rate is >1% and twice or more than the placebo incidence in the placebo-controlled trials were analyzed. There were no statistically significant differences in the occurrence of the AEs for either gender or age.

12. Human Reproductive Data

Pregnancy was an exclusion criterion for enrollment. There were 31 cases of pregnancies in the clinical trials. Three of the pregnancies occurred pre-randomization and never received tiagabine. Two others were randomized to other arms and also never received tiagabine. Nine patients carried to term with eight normal deliveries and one C-section for breech presentation leading to hip dysplasia in the baby. Six electively terminated the pregnancies. Four had miscarriages, one underwent D + C with suction for a fertilized blighted ovum, while another underwent laparotomy with salpingectomy for an ectopic pregnancy. One Patient drowned in the bathtub secondary to a seizure during her fifth month of pregnancy, she was off tiagabine for three months preceding the event. By the time of this submission the final outcome on the remaining four patients was not available.

13. Overdose Experience

During the worldwide development of tiagabine there were 8 instances of overdoses with tiagabine reported as serious AEs. There were three additional cases of overdose where tiagabine was not among the drugs taken for the overdose purpose.

Most common symptoms from the 8 tiagabine overdose patients were reports of confusion, somnolence, agitation, hostility, speech difficulty, weakness, impaired consciousness and myoclonus. All patients recovered fully. A brief summary of the cases follows:

Patient # 409 (study M92-813), a 22 year old female attempted suicide by tiagabine overdose (724 mg). She became somnolent, agitated, combative and confused. Treatment involved hospitalization for one day and the administration of IV fluids, naloxone, gastric lavage and charcoal.

Patient # 1307 (study M93-605), a 71 year old male attempted suicide by tiagabine overdose (800 mg). He became agitated and confused. Treatment involved sedation, intubation, IV fluids, gastric lavage and charcoal. He had full recovery after few days.

Patient # 1206 (study M93-047), a 30 year old male attempted suicide by tiagabine overdose (320 mg). He became unconscious, but when he awoke he was agitated and confused. He was sedated

and was discharged the following day.

Patient # 70903 (study M92-873), a 35 year old male accidentally ingested a double-dose of tiagabine (72 mg) and was briefly hospitalized with somnolence.

Patient # 30102 (study M91-604), a 45 year old male after taking his usual morning dose of tiagabine (18 mg) and carbamazepine (200 mg) had an unwitnessed seizure. His wife gave him another dose of tiagabine (18 mg) and carbamazepine (200 mg) within 30 minutes of his morning doses. For about 4 hours following that the patient was confused, combative and had aphasia with amnesia. He was hospitalized overnight for observation.

Patient # 5108 (study M92-813), a 43 year old female took an extra dose of tiagabine (16 mg) to treat increased seizures. She became agitated and confused complaining of numbness and tingling and inability to control her legs for few hours.

Patient # 70806 (study M92-873), an 18 year old male accidentally ingested a double-dose of tiagabine (12 mg) and was briefly hospitalized complaining of eye flickering and somnolence.

Patient # 80302 (study M91-604), a 26 year old male may have accidentally ingested an extra dose of tiagabine (4 mg) while in a post-ictal state. He was initially confused, somnolent and experienced myoclonic jerks. He was admitted with the suspicion of status epilepticus was given phenytoin and diazepam which caused respiratory depression requiring intubation.

Additionally, 10 more individuals, not enrolled in the trials were listed among serious AEs for taking tiagabine from a study patient:

A 94 year old female ingested 20 mg of tiagabine and she became sleepy, ataxic and confused. She later had a tonic-clonic seizure. Her concomitant medications were fluoxetine and famotidine. The tiagabine concentration 16 hours post ingestion was 64 mg/ml with an estimated C_{max} of 800 ng/nl. (With regular dosing even at highest daily doses (80 mg/day), an estimated C_{max} of < 400 ng/nl is expected).

A 2 year old female and 4 year old male child shared 12 mg of tiagabine but were asymptomatic..

A 19 month old infant ingested 8 mg of tiagabine and he experienced lethargy, agitation and myoclonus, but recovered the next day. The tiagabine concentration was 278 ng/ml.

A 3.5 year old child ingested 12 mg of tiagabine and had altered consciousness, agitation and speech impairment.

A 3 year old child ingested 12 mg of tiagabine but was asymptomatic.

There were four other cases, one adult and three toddlers with accidental exposure to low doses of tiagabine. All were asymptomatic.

14. Withdrawal Phenomenon/Abuse Potential

The sponsor assessed withdrawal related adverse events at the end of the placebo-controlled trial M91-603 as well as on or after taper and abrupt withdrawal of tiagabine in the Abbott long-term studies. No clinical trends were noted in these assessments. A comparison was made between gradual taper and abrupt withdrawal and no differences in withdrawal emergent adverse events were noted. Additionally there were no trends apparent to suggest withdrawal seizures.

The sponsor does not report any studies to evaluate instances of tiagabine abuse or dependence. There was absence of voluntary and persistent dose escalation by patients. Overall, there seemed to be no evidence of withdrawal phenomenon or abuse potential for this drug.

15. Summary of Drug Interactions

a. Drug-Demographic Interactions

Demographic subgroups were defined with respect to age (>12, 12-17, 18-39, 40-64 and >65), race, gender, and weight. There were no clinically meaningful differences noted in drug-demographic interactions in the various subgroups. (Refer to section 12 for more details).

The sponsor conducted a study to explore the pharmacokinetics of tiagabine in elderly healthy volunteers (n=8) and in elderly epilepsy patients (n=8) in treatment with one hepatic enzyme inducing AED as compared to healthy young volunteers (n=8). M93-044 was an open-label, single (8 mg) and multiple-dose (3 mg TID for 4 days and a single dose on day 5) study in 3 matched groups. Elderly subjects with epilepsy had markedly reduced C_{max}, AUC and $t_{1/2}$. The hepatic enzyme inducing AED significantly reduced the bioavailability and elimination $t_{1/2}$ of tiagabine in elderly epilepsy patients.

b. Drug-Disease Interactions

Disease subgroups were defined in terms of years with epilepsy, number of AEDs, and history of depression, psychiatric disorder, and secondarily-generalized tonic-clonic seizures. There were no clinically meaningful differences noted in drug-disease interactions in the various subgroups.

The sponsor conducted two studies to explore drug-disease interactions:

Study # M92-792 was an open-label, multiple-dose (4 mg BID for 5 days and a single dose on the sixth day) study designed to assess the influence of hepatic impairment on the pharmacokinetics and safety of tiagabine in 4 volunteers with mild hepatic disease, 4 volunteers with moderate hepatic disease and 6 control subjects, with ages ranging from 38 to 63 years. Subjects with mild to moderate hepatic disease had higher and more prolonged plasma concentrations of both total and unbound tiagabine than the control subjects. The side effects reported were the commonly reported NS AEs, but with a higher frequency when compared to the control group, reflecting the elevated levels of tiagabine in the hepatic impaired groups. It will be prudent to decrease dosing of hepatically impaired patients to avoid accumulation of the drug.

Study # M92-793 was an open-label, multiple-dose (4 mg BID for 5 days and a single dose on the sixth day) study designed to assess the effects of different stages of renal impairment on the pharmacokinetic safety of tiagabine in 25 volunteers divided into four groups of non-dialysis volunteers differentiated on the basis of the severity of their renal impairment (healthy and mild, moderate, and severe renal impairment) and a fifth group of dialysis patients that received a single dose of 4 mg predialysis on two occasions 8 days apart. There were no pharmacokinetic differences noted between groups. There was no evidence that subjects with advanced renal impairment tolerated tiagabine less well than those with normal renal function.

c. Drug-Drug Interactions

The sponsor performed several phase I studies to explore interactions of tiagabine with other drugs:

Study # M89-398 was a double-blind, placebo-controlled, 2 period cross-over interaction study of a single dose (8 mg) of tiagabine in epileptic patients who were on chronic treatment on valproate alone (group 1), carbamazepine and phenytoin (group 2), carbamazepine and primidone (group 3) and carbamazepine and vigabatrin (group 4). Each group had an n of 4. The study was designed to detect pharmacokinetic effects of the concomitant drugs on tiagabine. There was evidence of enzyme induction and hence a decrease in the AUC and $t_{1/2}$ of tiagabine. This once again suggests that tiagabine is a substrate for the hepatic cytochrome P450 enzyme system.

Study # M93-089 was performed to evaluate pharmacokinetic effects of tiagabine on carbamazepine. 12 adults with seizure history on fixed regimen of carbamazepine therapy, were given tiagabine 2 mg QID for days 2-5, 4 mg QID for days 6-9, 8 mg QID for days 10-13 and 12 mg QID for days 14-18. On day 18 the pharmacokinetic

evaluation was performed. 11 of the 12 patients reported AEs mostly CNS related, and 4 patients had dose reductions. The pharmacokinetic parameters of carbamazepine revealed no statistically significant differences upon the addition of tiagabine. This may suggest that tiagabine does not interfere with carbamazepine metabolism.

Study # M94-171 was performed to evaluate pharmacokinetic effects of tiagabine on phenytoin. 12 adults with seizure history on fixed regimen of phenytoin therapy, were given tiagabine 2 mg QID for days 2-5, 4 mg QID for days 6-9, 8 mg QID for days 10-13 and 12 mg QID for days 14-18. On day 18 the pharmacokinetic evaluation was performed. 11 of the 12 patients reported AEs mostly CNS related, and 3 patients had dose reductions. The pharmacokinetic parameters of phenytoin revealed no statistically significant differences upon the addition of tiagabine. This may suggest that tiagabine does not interfere with phenytoin metabolism.

Study # M93-081 was a double-blind, placebo-controlled, 2 period cross-over interaction study to evaluate pharmacokinetic effects of tiagabine on theophylline. 16 healthy adult males were administered 200 mg of theophylline every 6 hours for 17 consecutive doses. On day five the subjects received tiagabine 10 mg with their theophylline dose. On day 5 the pharmacokinetic evaluation was performed. The pharmacokinetic parameters of theophylline revealed no statistically significant differences upon the addition of single dose of tiagabine.

Study # M93-080 was a double-blind, placebo-controlled, 2 period cross-over study to evaluate the drug-drug interaction of tiagabine on the anticoagulant effects of warfarin. 28 healthy adult males were administered 10 mg of warfarin QD for 17 days, titrated individually to attain a PT of 14-18 seconds. On day 15, the subjects were randomized into two groups and given either placebo or tiagabine 4 mg every 8 hours for 15 consecutive doses. The pharmacokinetic parameters of warfarin revealed no statistically significant differences upon the addition of tiagabine with no significant changes in the PT.

Study # M93-087 was a double-blind, placebo-controlled, single-dose, 4 period cross-over study to evaluate whether tiagabine potentiates the effects of benzodiazepines on sedation and cognitive function. 12 healthy adult males were administered tiagabine 10 mg and triazolam 0.125, tiagabine 10 mg and placebo, placebo and triazolam 0.125, or placebo alone. There were no changes in the pharmacokinetic parameters of either tiagabine or triazolam when co-administered, but the pharmacodynamic effects seen individually appeared to be more pronounced and the effects lasting longer when co-administered.

Study # M93-079 was performed to evaluate pharmacokinetic effects

of tiagabine on cimetidine. The pharmacokinetic parameters of cimetidine revealed no statistically significant differences upon the addition of tiagabine.

Study # M93-088 was a double-blind, placebo-controlled, multiple-dose, cross-over study to evaluate whether tiagabine potentiates the effects of alcohol on cognitive function. 10 healthy males and 10 healthy females were enrolled. There were no changes in the pharmacokinetic parameters of tiagabine and alcohol when co-administered and there were no additive pharmacodynamic effects noted.

Study # M94-188 was performed to evaluate pharmacokinetic effects of tiagabine on digoxin. The pharmacokinetic parameters of digoxin revealed no statistically significant differences upon the addition of tiagabine.

Study # M91-712 was performed to evaluate the effects of tiagabine on oral contraceptives. In the 10 healthy females studied, there were no significant differences noted in hormone levels and there were no pregnancies upon the addition of tiagabine.

The deficiency in these drug-drug interaction studies is the fact that, the sponsor has concentrated on the effects of tiagabine on the other drugs but not the other way around. Nonetheless, from these studies and from the safety review, there seem to be no indication to recommend the avoidance of concomitant use of tiagabine with the AEDs, with the possible exception of caution while prescribing a benzodiazepine, because of the additive pharmacodynamic effects of the two. However, great caution is advised whenever an enzyme inducing medication is added or removed from therapy while a patient is on tiagabine. Doses of tiagabine may need to change as there is strong evidence of increased clearance of tiagabine in the presence of enzyme inducing medications.

16. Review of Safety by Organ Systems

This section concentrates, system by system, on commonly reported and serious AEs. Incidence rates of all serious AEs are given under each system. Appendix 7.1 displays serious AEs considered unlikely related to tiagabine intake and appendix 7.2 displays serious AEs that in this reviewer's opinion are possibly related to tiagabine intake. As mentioned in section 4, 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 not available.

Aside from the various efficacy outcome measures, the sponsor's safety analysis included looking at relapse episodes, hospitalizations, and clinically significant effects on vital signs, ECG or laboratory abnormalities. In the placebo controlled trials, physical examinations (PEs), complete neurological evaluations and laboratory evaluations were performed at baseline and at 3 subsequent visits as outlined by the sponsor's study protocols. Similarly for the other trials, there were designated visits for complete PEs and neurological evaluations. Reporting and recording of AEs happened at every visit.

17 AEs (abdominal pain, diarrhea, increased appetite, myasthenia, agitation, aphasia, asthenia, depression, dizziness, emotional lability, hostility, nervousness, paresthesia, speech disorder, thinking abnormal, tremor and pruritus) with tiagabine incidence rates of > 1% and twice the placebo rate were selected for specific subgroup (age and gender) analysis (see appendix 11.1 and 11.2).

a.1 Neurology--Treatment-emergent AEs associated with the CNS were the most frequently reported in the phase II-III trials (n=2468). Of these, the most common were dizziness (41% CI), somnolence (31%) and asthenia (31%). Appendix 9.a.3 displays the rates in the placebo controlled trials. In the placebo-controlled studies dizziness, asthenia, nervousness, tremor, thinking abnormal (generally representing difficulty in concentration or mental lethargy), depression and aphasia (representing a very wide range of investigator terms, including aphasia, expressive aphasia, speech loss, unable to communicate, word finding difficulty, word substitution, nonsensical speech, etc.) were reported by a statistically significantly greater percentage of tiagabine patients than placebo patients.

In the overall database the incidence rate for serious AEs related to the CNS was 8% (193/2468); the most common of these were confusion 31 cases (1%), depression 26 (1%), somnolence 24 (1%), dizziness 20, hostility 19, psychosis 15, ataxia 12, agitation 11, encephalopathy 10, tremor 10, thinking abnormal 8, anxiety 8, asthenia 6, aphasia 5, nervousness 5 and several others at 5 or lower. This represents a large number of CNS

related hospitalizations. A review of PNs of these cases is not revealing except for statements of hospitalizations at a certain time secondary to some of the AEs listed above. In the placebo controlled trials serious AEs related to the CNS were reported at 2% (10/494) for the tiagabine arm and <1% (2/275) for the placebo arm. A random review of PNs dealing with neurologic serious AEs and the statistical evidence for all AEs, noted above, leaves no doubt for a strong relationship of tiagabine with the neurologic AEs noted.

As noted in earlier sections, the most frequent adverse events associated with premature terminations were also those associated with the nervous system.

The sponsor conducted a separate analysis of psychosis, weakness, confusional states and status epilepticus to review possible association of tiagabine with these AEs using a simple comparison of drug vs placebo exposed patients in the placebo-controlled trials. A review of PNs and CRFs were not revealing of the clinical characteristics of this AEs. The sponsor investigated the possible association of tiagabine with psychosis, because "psychosis is prevalent in the epileptic population and multiple AEDs have been reported to be associated with psychosis". The COSTART terms catatonic reaction, delusion, hallucination, paranoid reaction, psychosis and schizophrenic reaction appearing in the data listings were subsumed under the COSTART term psychosis. In the placebo-controlled trials, 0.8% (4/494) in the tiagabine arm and 0.4% (1/275) in the placebo arm reported psychosis. 4% (91/2468) of the total number of people exposed to tiagabine reported psychosis as defined above. 34% (31/91) of these patients discontinued secondary to psychosis and another 19% (17/91) had dose reductions.

Myasthenia, asthenia, or hypotonia (excluding weakness related to post-ictal states) were subsumed under the COSTART term weakness. 1.5% (37/2468) of the total number of people exposed to tiagabine reported serious (mobility impairing) cases of weakness as defined above. No serious cases were reported in the controlled trials. In all cases the weakness resolved either spontaneously or after discontinuation of treatment.

Catatonia, coma, confusion, stupor and encephalopathy were subsumed under the COSTART term confusional state. In the placebo-controlled trials, 4% (22/494) of the tiagabine patients and 3% (8/275) of the placebo patients experienced confusional state. 18% (442/2468) of the total number of people exposed to tiagabine reported confusional state as defined above of which 14% (60/442) discontinued and another 36% (169/442) had dose reduction.

Status epilepticus occurred in 4/494 (0.8%) of the patients on tiagabine in controlled studies compared to 2/275 (0.7%) on

placebo. 5% (113/2468) of the total number of people exposed to tiagabine reported status epilepticus. The sponsor states that literature reports of incidence of status epilepticus in this population vary from 1.3-16%.

Nine patients in the Abbott studies experienced symptoms suggestive of non-convulsive seizures at tiagabine dose ranges of 24-58 and in 3 of them it was given as monotherapy. 4 of the nine were discontinued, but all recovered within a day. The EEGs performed on these patients were consistent with absence seizures, complex partial, status epilepticus or early encephalopathy.

In this reviewer's opinion, there is causal relationship between tiagabine exposure and the CNS AEs reported. The higher the dose the more likely the occurrence of these events.

a.2 Opthalmology--No specific focus in AE surveillance or conduct of specific testing.

a.3 Psychiatry--Special analyses of psychosis and confusional states are described above under neurology.

There were three reported suicides in this NDA, they are discussed in section 13.

a.4 Pulmonary--No specific focus in AE surveillance or conduct of specific testing. In the overall database the incidence rate for serious AEs related to the respiratory system was 2% (45/2468), 19 of which were pneumonia cases. In the placebo controlled trials serious AEs related to the respiratory system were reported at <1% (3/494) in the tiagabine arm and <1% (2/275) in the placebo arm.

a.5 Cardiovascular--In the overall database the incidence rate for serious AEs related to the cardiovascular system was 1% (29/2468), none of which were related to ECG changes. In the placebo controlled trials serious AEs related to the cardiovascular system were reported at <1% (1/494) in the tiagabine arm and <1% (2/275) in the placebo arm.

In the controlled trials, 0.5% (2/388) of tiagabine patients (none for placebo) experienced a treatment emergent deterioration of ECGs: Patient 10323 (study M91-605), a 51 year old male with history of smoking, hypercholesterolemia and exertional dyspnea presented with a baseline ECG of first degree AV block and interventricular conduction defect. At the end of study the ECG revealed T-wave inversion. The patient was enrolled into the long-term study M91-604 and after 8 months of treatment, he suffered an MI with ECG changes. Following the MI the patient was hospitalized on several occasions for angina, but the patient was not discontinued from tiagabine treatment. Patient 11815 (study

M91-603), a 40 year old female with baseline ECG of left atrial enlargement and non-specific ST-T wave changes, at final visit had a prolonged QT interval. The patient was enrolled into the long-term study M91-604, where a subsequent ECG was back to baseline.

In the low vs high dose trial (study M93-090) two patients with clinically significant deteriorations were noted: Patient 12001, a 13 year old female with normal baseline ECG where a repeat ECG revealed a prolonged QT interval and inferior Q waves. The patient was enrolled into the long-term study M91-604 and subsequent ECGs did not revert to baseline. Patient 10309, a 54 year old female with borderline abnormal baseline ECG with repeat ECGs deteriorating post treatment with poor R wave progression, non-specific ST-T wave changes and inverted T waves. The patient was enrolled into the long-term study, but was discontinued for neurologic reasons.

In the overall database, 7 more patients experienced deteriorations of their ECG from baseline: Patient 509 (study M92-813), a 55 year old male with history of hypertension and positive stress test had non-specific ST-T wave changes on day 372 of treatment. Patient 605 (study M92-813), a 22 year old male with history of heart murmur and tachycardia had baseline ECG of sinus bradycardia, sinus arrhythmia and left posterior fascicular block. Repeat ECGs on two occasions had minor changes from baseline. Patient 917 (study M92-813), a 26 year old male with normal baseline ECG, presented on day 365 with an R-S-R' pattern in the ECG. He remained in the study. Patient 51116 (study M91-604), a 67 year old male with history of smoking, angina, peripheral vascular disease, hypercholesterolemia, hypertension and abnormal baseline ECG indicative of inferior MI, four months into treatment was hospitalized for angina, first degree AV block and interventricular conduction defect. Four months following that he was hospitalized again this time with an MI. He was continued on tiagabine therapy for another two months, at which time he was discontinued for multiple medical reasons. Patient 50316 (study M91-604), a 42 year old female with hypertension but a normal baseline ECG presented on day 232 with repeat ECG deterioration showing inferior Q waves and non-specific ST-T wave changes. One month later she complained of chest pain, an ECG was normal and a cardiology evaluation ruled out cardiac etiology for the pain. The patient was not discontinued. Patient 90903 (study M91-604), a 56 year old female with hypercholesterolemia and baseline ECG showing occasional PVCs and non-specific ST-T wave changes. On study day 168 the patient was discontinued with an ECG showing a sinus tachycardia and frequent PVCs. Patient 1501 (study M92-825), a 28 year old female had a normal baseline ECG. On study day 112, an ECG showed a possible lateral infarct. The patient was not discontinued and was later enrolled into the long term study M91-604.

A causal relationship of treatment-emergent ECG deteriorations is unlikely.

a.6 Renal--No specific focus in AE surveillance or conduct of specific testing. In the overall database the incidence rate for serious AEs related to the urogenital system was 1% (37/2468), 6 of which were abortion cases. In the placebo controlled trials serious AEs related to the urogenital system were reported at <1% (4/494) in the tiagabine arm and <1% (1/275) in the placebo arm.

a.7 Gastrointestinal--No specific focus in AE surveillance or conduct of specific testing. In the overall database the incidence rate for serious AEs related to the gastrointestinal (GI) system was 2% (55/2468), of which there were 13 vomiting, 8 nausea, 8 gastroenteritis and 4 diarrhea cases. In the placebo controlled trials serious AEs related to the GI system were reported at 1% (5/494) in the tiagabine arm and 1% (4/275) in the placebo arm.

a.8 Musculoskeletal--No specific focus in AE surveillance or conduct of specific testing. In the overall database the incidence rate for serious AEs related to the musculoskeletal system was <1% (14/2468), of which there were 4 myasthenia cases. There were no serious AE cases in the placebo controlled trials.

a.9 Skin--No specific focus in AE surveillance or conduct of specific testing. In the overall database the incidence rate for serious AEs related to skin and appendages was <1% (14/2468). In the placebo controlled trials serious AEs related to this system were reported at <1% (1/494) in the tiagabine arm and <1% (1/275) in the placebo arm.

a.10 Endocrine/Metabolic--No specific focus in AE surveillance or conduct of specific testing. In the overall database the incidence rate for serious AEs related to metabolic, nutritional and endocrine system was <1% (17/2468), of which 6 were dehydration and 3 were hyponatremia cases. In the placebo controlled trials serious AEs related to this system were reported at <1% (2/494) in the tiagabine arm and 0% (0/275) in the placebo arm.

a.11 Hematologic/Oncologic--In the overall database the incidence rate for serious AEs related to this system was <1% (9/2468), of which 6 were dehydration and 3 were hyponatremia cases. In the placebo controlled trials serious AEs related to this system were reported at <1% (2/494) in the tiagabine arm and 0% (0/275) in the placebo arm. There were 28 reports of various cancers occurring in tiagabine clinical trials. The sponsor claims that of these 14 were treatment emergent. Three of the cases are noted below:

Patient 31111 in Study M91-604, a 73 year old male was diagnosed

with Hodgkin's Lymphoma after being on tiagabine for 2 years. Patient 50807 in Study M91-604, a 46 year old male with history of neurofibromatosis was diagnosed with astrocytoma after being on tiagabine for 26 months. Patient 3001 in Study M93-091, a 67 year old male was diagnosed with multiple myeloma after being on tiagabine for 10 months; tiagabine had been discontinued 2 months prior to diagnosis.

17. Conclusions

Tiagabine is presented by the sponsor to inhibit the GABA uptake into the glial cells and thus possessing anticonvulsant properties. The compound was demonstrated to have anticonvulsant activity in rodents. The efficacy of tiagabine in clinical trials is reviewed by Dr. McCormick as a separate review. The safety aspects of the drug reveal a series of treatment emergent AEs. As usual, it is difficult to attribute the etiology of the AEs to a specific treatment, but there is strong indication both statistically and this reviewer's clinical judgement that the commonly occurring CNS related AEs are causally related to the drug. The neurotoxicity of the drug is not disputed by the sponsor.

20. Recommendations

In this reviewer's opinion, the New Drug Application for tiagabine is approvable from a safety standpoint if the efficacy review finds the drug to be efficacious. However to further support the safe and effective use of tiagabine, it is recommended that the following issues be explored by the sponsor:

(i) In view of the significant pharmacokinetic interactions noted in the drug-drug interaction studies, it is imperative that the sponsor perform more complete clinical trials to study the potential drug-drug interactions of tiagabine and other AEDs;

(ii) in view of the clinically significant dose-response relationship noted between higher doses of tiagabine and several neurological AEs, it is imperative that the sponsor conduct further dose response and dose-ranging studies to find the lowest possible dose that is optimally effective; and

(iii) A study to better characterize and understand the potential hematologic effects of the drug, in particular the effects and consequences of elevated PTT levels.

A brief discussion of the annotated labeling is in section 1 of this review. Recommendations for the labeling include:

-In this reviewer's opinion the labeling should highlight (more than the sponsor's current proposed labeling) the common neurological AEs;

-The special mention of the incidence of the sudden deaths is appropriate;
-A clearer recommendation of dosing modifications with concomitant use of enzyme inducing agents is needed under the heading of drug-drug interactions;
-A more descriptive presentation of the in vitro metabolic studies will be helpful; and
-Although this is not an efficacy review, but in this reviewer's opinion, the labeling claim made by the sponsor that tiagabine is a more potent anticonvulsant than the commonly used AEDs may be misleading.

John Dikran Balian, MD 9/9/96

John Dikran Balian, M.D. Date
Clinical Reviewer Safety Group,
Div. of Neuropharmacologic Drug Products

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APPENDICES

Appendix 5.b.1 Duration of Exposure by Modal Dose
Phase II/III (Epilepsy Studies)
Abbott + Results

Modal Daily Dose (mg)	Number (%) of Patients							
	Duration of Tiagabine Exposure (30-Day Months)							
	>0-6	>6-12	>12-18	>18-24	>24-30	>30-36	>36	Total
>0-12	245 (10)	52 (2)	18 (<1)	5 (<1)	1 (<1)	14 (<1)	2 (<1)	337 (14)
>12-24	188 (8)	87 (4)	52 (2)	24 (<1)	25 (1)	31 (1)	20 (<1)	427 (17)
>24-36	130 (5)	188 (8)	82 (3)	71 (3)	40 (2)	60 (2)	22 (<1)	593 (24)
>36-48	64 (3)	114 (5)	61 (2)	69 (3)	63 (3)	70 (3)	30 (1)	471 (19)
>48-60	32 (1)	42 (2)	21 (<1)	28 (1)	22 (<1)	36 (1)	20 (<1)	201 (8)
>60-72	25 (1)	42 (2)	34 (1)	33 (1)	44 (2)	54 (2)	37 (1)	269 (11)
>72-84	6 (<1)	16 (<1)	22 (<1)	17 (<1)	27 (1)	49 (2)	30 (1)	167 (7)
>84-96	0	0	0	1 (<1)	0	1 (<1)	0	2 (<1)
>96-108	0	0	0	0	0	0	0	0
>108	1 (<1)	0	0	0	0	0	0	1 (<1)
Total	691 (28)	541 (22)	290 (12)	248 (10)	222 (9)	315 (13)	161 (7)	2468

Appendix 5.b.2 Duration of Exposure by Maximum Dose
Phase II/III (Epilepsy Studies)
Abbott + Results

Maximum Daily Dose (mg)	Number (%) of Patients							
	Duration of Tiagabine Exposure (30-Day Months)							
	>0-6	>6-12	>12-18	>18-24	>24-30	>30-36	>36	Total
>0-12	124 (5)	24 (<1)	6 (<1)	1 (<1)	0	0	0	155 (6)
>12-24	144 (6)	21 (<1)	17 (<1)	8 (<1)	5 (<1)	16 (<1)	3 (<1)	214 (9)
>24-36	198 (8)	109 (4)	41 (2)	36 (1)	32 (1)	41 (2)	11 (<1)	468 (19)
>36-48	98 (4)	132 (5)	70 (3)	76 (3)	57 (2)	73 (3)	18 (<1)	524 (21)
>48-60	61 (2)	89 (4)	37 (1)	44 (2)	27 (1)	37 (1)	30 (1)	325 (13)
>60-72	46 (2)	104 (4)	63 (3)	48 (2)	53 (2)	62 (3)	43 (2)	419 (17)
>72-84	19 (<1)	61 (2)	56 (2)	32 (1)	44 (2)	65 (3)	42 (2)	319 (13)
>84-96	0	1 (<1)	0	1 (<1)	2 (<1)	10 (<1)	7 (<1)	21 (<1)
>96-108	0	0	0	1 (<1)	0	6 (<1)	3 (<1)	10 (<1)
>108	1 (<1)	0	0	1 (<1)	2 (<1)	5 (<1)	4 (<1)	13 (<1)
Total	691 (28)	541 (22)	290 (12)	248 (10)	222 (9)	315 (13)	161 (7)	2468

Appendix 5.c.1 Demographics
Phase II/III (Epilepsy Studies)
Abbott + Results

Characteristic	Tiagabine	Placebo
Age (years)	N=2468	N=279
Mean ± SD	33.3 ± 12.90	34.9 ± 12.79
Range	2-77	12-77
Weight (kg)	N=2443	N=275
Mean ± SD	72.5 ± 19.71	74.4 ± 17.23
Range	13.0-162.4	40.8-137.0
Sex		
Male N (%)	1149 (47)	163 (58)
Female N (%)	1319 (53)	116 (42)
Race		
Caucasian N (%)	2281 (92)	251 (90)
Black N (%)	101 (4)	14 (5)
Other N (%)	86 (3)	14 (5)

Appendix 5.c.2 Demographics
Placebo-Controlled, Parallel-Group, Add-On Studies
Abbott + Results

Characteristic	Tiagabine	Placebo
Age (years)	N=494	N=275
Mean ± SD	33.8 ± 11.78	35.1 ± 12.79
Range	12-72	12-77
Weight (kg)	N=494	N=275
Mean ± SD	75.3 ± 19.13	74.4 ± 17.23
Range	33.4-161.9	40.8-137.0
Sex		
Male N (%)	281 (57)	160 (58)
Female N (%)	213 (43)	115 (42)
Race		
Caucasian N (%)	442 (89)	248 (90)
Black N (%)	30 (6)	13 (5)
Other N (%)	22 (4)	14 (5)

Appendix 6.1 Summary of Patient Deaths

Study	Patient Number	Age/Gender	Days in Study	Highest Dose mg	Cause of Death
M90-481/M91-578	4006/353	34/M	231	32	Sudden Death
M90-481/M91-578	5010/102	43/F	244	36	Respiratory failure from near Drowning
M91-603/M91-604	11307/31305	18/M	158	40	Sudden Death
M91-605/M91-604	11113/51116	66/M	399	76	Sepsis
M91-605/M91-604	10817/50817	40/F	505	44	Temporal Astrocytoma
M91-605	11807	27/F	6	8	Aplastic Anemia
M92-775/M92-873	19013/70902	49/M	197	12	Sudden Death
M92-813	1501	22/F	648	44	Sudden Death
M92-813	1901	57/F	133	80	Accidental Injury
M92-813	2309	14/M	55	12	Subarachnoid Hemorrhage Drowning
M92-813	3621	42/M	379	40	Sudden Death
M92-813C	6611	33/M	52	48	Sudden Death
M92-813C	6701	44/M	344	68	Sudden Death
M92-813C	6707	48/M	539	64	Sudden Death
M93-047	1222	53/F	280	12	Intestinal Perforation
M93-047	1515	48/M	29	12	Sudden Death
M93-047	2105	29/F	285	36	Sudden Death
M93-047	2306	35/M	168	48	Sudden Death
M93-047	3108	28/M	398	32	Sudden Death
M93-047	3619	49/M	9	12	Carcinoma(liver)
M93-065	1803	38/M	386	24	Asphyxia (Following a Seizure)
M93-090	10119	75/M	77	36	Apnea
M93-090	11331	32/M	21	6	Drowning
M92-755/M92-873	30101	56/F	716	32	Subdural Hematoma
M93-090/M91-604	11319/91301	33/M	561	88	CNS Neoplasia
M91-605/M91-604	11508/51503	58/M	1110	80	Sudden Death
M92-813	2807	53/M	1034	76	CNS Neoplasia

Appendix 7.1 Serious Adverse Experiences Considered Unlikely to be Related to Study Drug

Body System	Study Number	Patient Number	Age	Dose mg/day	Time from 1st Dose to AE On-set (days)	Adverse Event
BODY AS A WHOLE	M91-604	30713	30	56	1073	ABDOMINAL PAIN
BODY AS A WHOLE	M91-604	51502	38	80	453	ABDOMINAL PAIN
BODY AS A WHOLE	M91-604	52207	26	60	833	ABDOMINAL PAIN
BODY AS A WHOLE	M92-873	70319	42	_	-142	ABDOMINAL PAIN
BODY AS A WHOLE	M92-813	1406	46	8	624	ABDOMINAL PAIN
BODY AS A WHOLE	M93-092	2101	13	32	686	ABDOMINAL PAIN
BODY AS A WHOLE	M93-047	1422	20	34	718	ABDOMINAL PAIN
BODY AS A WHOLE	M93-065	2002	20	26	505	ABDOMINAL PAIN
BODY AS A WHOLE	M93-065	2803	18	64	380	ABDOMINAL PAIN
BODY AS A WHOLE	M91-604	90412	17	36	355	ABDOMINAL PAIN
BODY AS A WHOLE	M93-090	11318	61	36	141	ABDOMINAL PAIN
BODY AS A WHOLE	M93-090	11604	57	24	146	ABDOMINAL PAIN
BODY AS A WHOLE	M91-604	40119	10	6	219	ABDOMINAL PAIN
BODY AS A WHOLE	M91-604	50703	14	30	179	ABDOMINAL SYNDROME ACUTE
BODY AS A WHOLE	M91-578	351	29	4	604	ABSCESS
BODY AS A WHOLE	M91-565	7010	22	12	7	ABSCESS
BODY AS A WHOLE	M91-604	30101	41	80	617	ABSCESS
BODY AS A WHOLE	M91-578	351	29	24	1332	ACCIDENTAL INJURY
BODY AS A WHOLE	M91-578	351	29	24	1336	ACCIDENTAL INJURY
BODY AS A WHOLE	M90-481	4018	39	24	142	ACCIDENTAL INJURY
BODY AS A WHOLE	M90-481	4021	41	_	107	ACCIDENTAL INJURY
BODY AS A WHOLE	M91-578	101	39	64	590	ACCIDENTAL INJURY
BODY AS A WHOLE	M91-578	101	39	64	646	ACCIDENTAL INJURY

BODY AS A WHOLE	M91-578	101	39	48	786	ACCIDENTAL INJURY
BODY AS A WHOLE	M90-481	5012	43	24	72	ACCIDENTAL INJURY
BODY AS A WHOLE	M90-481	6006	36	32	181	ACCIDENTAL INJURY
BODY AS A WHOLE	M90-481	6025	32	8	103	ACCIDENTAL INJURY
BODY AS A WHOLE	M91-578	203	24	64	1204	ACCIDENTAL INJURY
BODY AS A WHOLE	M92-873	30405	30	48	986	ACCIDENTAL INJURY
BODY AS A WHOLE	M91-565	4024	28	16	14	ACCIDENTAL INJURY
BODY AS A WHOLE	M92-873	30110	30	32	894	ACCIDENTAL INJURY
BODY AS A WHOLE	M92-873	30508	39	56	491	ACCIDENTAL INJURY
BODY AS A WHOLE	M91-603	10202	40	_	52	ACCIDENTAL INJURY
BODY AS A WHOLE	M91-603	10807	39	_	-118	ACCIDENTAL INJURY
BODY AS A WHOLE	M91-604	31116	43	32	253	ACCIDENTAL INJURY
BODY AS A WHOLE	M91-604	31121	27	52	876	ACCIDENTAL INJURY
BODY AS A WHOLE	M91-604	31121	27	52	877	ACCIDENTAL INJURY
BODY AS A WHOLE	M91-604	31209	33	70	850	ACCIDENTAL INJURY
BODY AS A WHOLE	M91-604	31410	50	68	368	ACCIDENTAL INJURY
BODY AS A WHOLE	M91-603	11501	59	32	65	ACCIDENTAL INJURY
BODY AS A WHOLE	M91-603	11508	61	32	56	ACCIDENTAL INJURY
BODY AS A WHOLE	M91-604	31512	22	44	417	ACCIDENTAL INJURY
BODY AS A WHOLE	M91-604	31603	23	none/ unk	415	ACCIDENTAL INJURY
BODY AS A WHOLE	M91-604	31609	43	64	471	ACCIDENTAL INJURY
BODY AS A WHOLE	M91-604	31707	49	32	222	ACCIDENTAL INJURY
BODY AS A WHOLE	M91-604	31808	41	24	266	ACCIDENTAL INJURY
BODY AS A WHOLE	M91-604	31812	38	32	185	ACCIDENTAL INJURY
BODY AS A WHOLE	M91-604	32110	13	80	1026	ACCIDENTAL INJURY
BODY AS A WHOLE	M91-604	50416	35	56	576	ACCIDENTAL INJURY
BODY AS A WHOLE	M91-604	50606	23	64	592	ACCIDENTAL INJURY
BODY AS A WHOLE	M91-604	50611	42	48	200	ACCIDENTAL INJURY
BODY AS A WHOLE	M91-604	50703	14	32	308	ACCIDENTAL INJURY
BODY AS A WHOLE	M91-604	50814	38	44	572	ACCIDENTAL INJURY
BODY AS A WHOLE	M91-604	50818	53	36	336	ACCIDENTAL INJURY

BODY AS A WHOLE	M91-604	51011	26	80	480	ACCIDENTAL INJURY
BODY AS A WHOLE	M91-604	51108	54	40	121	ACCIDENTAL INJURY
BODY AS A WHOLE	M91-604	51118	50	_	116	ACCIDENTAL INJURY
BODY AS A WHOLE	M91-604	51403	36	44	171	ACCIDENTAL INJURY
BODY AS A WHOLE	M91-604	51405	45	40	350	ACCIDENTAL INJURY
BODY AS A WHOLE	M91-604	51405	45	40	615	ACCIDENTAL INJURY
BODY AS A WHOLE	M91-604	51704	66	48	184	ACCIDENTAL INJURY
BODY AS A WHOLE	M91-604	51704	66	80	870	ACCIDENTAL INJURY
BODY AS A WHOLE	M91-604	52117	35	72	516	ACCIDENTAL INJURY
BODY AS A WHOLE	M91-604	52115	16	_	757	ACCIDENTAL INJURY
BODY AS A WHOLE	M91-604	52604	30	48	814	ACCIDENTAL INJURY
BODY AS A WHOLE	M92-873	70202	68	20	236	ACCIDENTAL INJURY
BODY AS A WHOLE	M92-873	70305	29	30	167	ACCIDENTAL INJURY
BODY AS A WHOLE	M92-775	13012	44	_	-173	ACCIDENTAL INJURY
BODY AS A WHOLE	M92-873	70405	18	36	394	ACCIDENTAL INJURY
BODY AS A WHOLE	M92-873	70803	62	60	428	ACCIDENTAL INJURY
BODY AS A WHOLE	M92-775	19003	34	_	-47	ACCIDENTAL INJURY
BODY AS A WHOLE	M92-775	19004	54	_	-11	ACCIDENTAL INJURY
BODY AS A WHOLE	M92-873	70904	54	36	121	ACCIDENTAL INJURY
BODY AS A WHOLE	M92-873	70911	59	42	716	ACCIDENTAL INJURY
BODY AS A WHOLE	M92-775	19023	40	_	-111	ACCIDENTAL INJURY
BODY AS A WHOLE	M92-813	116	39	80	330	ACCIDENTAL INJURY
BODY AS A WHOLE	M92-813	119	49	24	953	ACCIDENTAL INJURY
BODY AS A WHOLE	M92-813	1112	38	24	86	ACCIDENTAL INJURY
BODY AS A WHOLE	M92-813	1504	49	24	439	ACCIDENTAL INJURY
BODY AS A WHOLE	M92-813	1901	57	52	133	ACCIDENTAL INJURY
BODY AS A WHOLE	M92-813	2209	47	12	27	ACCIDENTAL INJURY
BODY AS A WHOLE	M92-813	2309	14	6	55	ACCIDENTAL INJURY
BODY AS A WHOLE	M92-813	2401	32	50	1048	ACCIDENTAL INJURY
BODY AS A WHOLE	M92-813	2503	16	72	967	ACCIDENTAL INJURY
BODY AS A WHOLE	M92-813	3102	14	30	112	ACCIDENTAL INJURY
BODY AS A WHOLE	M92-813	3304	28	_	207	ACCIDENTAL INJURY

BODY AS A WHOLE	M92-813	3808	50	40	109	ACCIDENTAL INJURY
BODY AS A WHOLE	M92-813	4401	41	24	222	ACCIDENTAL INJURY
BODY AS A WHOLE	M92-813	4407	24	_	251	ACCIDENTAL INJURY
BODY AS A WHOLE	M92-813C	6702	46	64	281	ACCIDENTAL INJURY
BODY AS A WHOLE	M92-825	1808	40	_	103	ACCIDENTAL INJURY
BODY AS A WHOLE	M92-873	30508	39	56	519	ACCIDENTAL INJURY
BODY AS A WHOLE	M93-047	1101	27	_	73	ACCIDENTAL INJURY
BODY AS A WHOLE	M93-047	1104	32	12	29	ACCIDENTAL INJURY
BODY AS A WHOLE	M93-047	1410	44	34	414	ACCIDENTAL INJURY
BODY AS A WHOLE	M93-047	1507	47	18	16	ACCIDENTAL INJURY
BODY AS A WHOLE	M93-047	1907	37	64	627	ACCIDENTAL INJURY
BODY AS A WHOLE	M93-047	1913	27	64	489	ACCIDENTAL INJURY
BODY AS A WHOLE	M93-047	2305	61	48	244	ACCIDENTAL INJURY
BODY AS A WHOLE	M93-047	2501	52	60	68	ACCIDENTAL INJURY
BODY AS A WHOLE	M93-047	3403	40	36	148	ACCIDENTAL INJURY
BODY AS A WHOLE	M93-047	3512	60	28	575	ACCIDENTAL INJURY
BODY AS A WHOLE	M93-047	3634	36	64	300	ACCIDENTAL INJURY
BODY AS A WHOLE	M93-065	1304	31	64	256	ACCIDENTAL INJURY
BODY AS A WHOLE	M93-065	1405	42	48	197	ACCIDENTAL INJURY
BODY AS A WHOLE	M93-065	1903	12	30	102	ACCIDENTAL INJURY
BODY AS A WHOLE	M93-065	2808	35	_	363	ACCIDENTAL INJURY
BODY AS A WHOLE	M93-065	3103	34	48	260	ACCIDENTAL INJURY
BODY AS A WHOLE	M91-604	90422	17	24	400	ACCIDENTAL INJURY
BODY AS A WHOLE	M93-090	10423	45	36	33	ACCIDENTAL INJURY
BODY AS A WHOLE	M93-090	11008	52	6	46	ACCIDENTAL INJURY
BODY AS A WHOLE	M91-604	91317	71	_	115	ACCIDENTAL INJURY
BODY AS A WHOLE	M93-090	11331	32	6	21	ACCIDENTAL INJURY
BODY AS A WHOLE	M91-604	50606	23	64	592	BACK PAIN
BODY AS A WHOLE	M92-813	1809	30	_	-7	BACK PAIN
BODY AS A WHOLE	M92-813	5902	45	64	171	BACK PAIN
BODY AS A WHOLE	M92-813	510	46	32	944	CARCINOMA
BODY AS A WHOLE	M92-813C	6706	35	32	282	CARCINOMA

BODY AS A WHOLE	M93-047	1925	44	16	319	CARCINOMA
BODY AS A WHOLE	M93-047	3619	49	_	-284	CARCINOMA
BODY AS A WHOLE	M91-605	11304	49	_	-15	CELLULITIS
BODY AS A WHOLE	M91-605	11317	46	_	-29	CELLULITIS
BODY AS A WHOLE	M91-604	51606	39	32	585	CELLULITIS
BODY AS A WHOLE	M92-873	70403	20	54	480	CELLULITIS
BODY AS A WHOLE	M92-813	1501	22	6	6	CELLULITIS
BODY AS A WHOLE	M92-813	2804	28	_	-17	CELLULITIS
BODY AS A WHOLE	M92-813	4801	32	48	293	CELLULITIS
BODY AS A WHOLE	M93-047	2112	51	24	55	CELLULITIS
BODY AS A WHOLE	M91-578	153	44	24	424	CHEST PAIN
BODY AS A WHOLE	M91-604	30809	39	64	122	CHEST PAIN
BODY AS A WHOLE	M92-813	4401	41	36	526	CHEST PAIN
BODY AS A WHOLE	M92-813	519	32	64	297	CONGENITAL ANOMALY
BODY AS A WHOLE	M92-813	1113	16	26	941	CONGENITAL ANOMALY
BODY AS A WHOLE	M92-813	3812	30	24	66	CONGENITAL ANOMALY
BODY AS A WHOLE	M91-604	30101	41	80	824	CYST
BODY AS A WHOLE	M91-605	12606	30	24	17	CYST
BODY AS A WHOLE	M92-813	5404	39	40	502	CYST
BODY AS A WHOLE	M93-092	2101	13	32	556	CYST
BODY AS A WHOLE	M91-604	52707	27	64	283	DRUG LEVEL INCREASED
BODY AS A WHOLE	M93-047	2112	51	36	213	DRUG LEVEL INCREASED
BODY AS A WHOLE	M91-604	32006	16	80	586	FEVER
BODY AS A WHOLE	M91-604	50606	23	64	592	FEVER
BODY AS A WHOLE	M91-604	50814	38	36	263	FEVER
BODY AS A WHOLE	M91-605	11120	53	_	-12	FEVER
BODY AS A WHOLE	M91-604	52207	26	52	667	FEVER
BODY AS A WHOLE	M92-813	4407	24	24	245	FEVER
BODY AS A WHOLE	M91-604	80302	27	40	343	FEVER
BODY AS A WHOLE	M93-047	1213	17	64	559	FEVER

BODY AS A WHOLE	M91-604	40108	4	6	135	FEVER
BODY AS A WHOLE	M91-605	11317	46	32	50	FLU SYNDROME
BODY AS A WHOLE	M92-775	13037	40	_	-109	FLU SYNDROME
BODY AS A WHOLE	M93-043	202	9	0.5	140	FLU SYNDROME
BODY AS A WHOLE	M91-604	51303	40	36	720	HERNIA
BODY AS A WHOLE	M92-775	13001	47	30	141	HERNIA-
BODY AS A WHOLE	M92-813	211	29	32	240	HERNIA
BODY AS A WHOLE	M91-604	91302	47	36	196	HERNIA
BODY AS A WHOLE	M91-604	91302	47	36	268	HERNIA
BODY AS A WHOLE	M91-603	12103	23	56	51	INFECTION
BODY AS A WHOLE	M91-604	51109	28	64	991	INFECTION
BODY AS A WHOLE	M91-604	52401	28	32	204	INFECTION
BODY AS A WHOLE	M92-813	1612	12	20	50	INFECTION
BODY AS A WHOLE	M92-813	1614	13	14	182	INFECTION
BODY AS A WHOLE	M92-813	2209	47	12	27	INFECTION
BODY AS A WHOLE	M92-813	3413	19	56	478	INFECTION
BODY AS A WHOLE	M92-813	3610	48	-	361	INFECTION
BODY AS A WHOLE	M92-813	4401	41	24	244	INFECTION
BODY AS A WHOLE	M93-092	2101	13	32	686	INFECTION
BODY AS A WHOLE	M93-047	1212	37	32	130	INFECTION
BODY AS A WHOLE	M93-047	1213	17	64	559	INFECTION
BODY AS A WHOLE	M93-047	1236	24	24	45	INFECTION
BODY AS A WHOLE	M93-047	2305	61	48	379	INFECTION
BODY AS A WHOLE	M93-047	2411	40	40	663	INFECTION
BODY AS A WHOLE	M91-604	50805	43	36	134	INTENTIONAL OVERDOSE
BODY AS A WHOLE	M92-813	409	22	56	324	INTENTIONAL OVERDOSE
BODY AS A WHOLE	M92-813	4407	24	24	245	MALAISE
BODY AS A WHOLE	M91-604	50606	23	64	592	NECK PAIN
BODY AS A WHOLE	M91-604	52306	47	60	469	NECK PAIN
BODY AS A WHOLE	M93-065	2001	48	30	76	NECK RIGIDITY

BODY AS A WHOLE	M91-604	51406	55	80	882	NEOPLASM
BODY AS A WHOLE	M92-873	70806	17	36	71	OVERDOSE
BODY AS A WHOLE	M91-604	40109	3	4	280	OVERDOSE
BODY AS A WHOLE	M92-873	70805	27	32	241	PAIN
BODY AS A WHOLE	M92-813	2102	60	24	25	PAIN
BODY AS A WHOLE	M92-813	4302	30	80	117	PAIN
BODY AS A WHOLE	M92-813	5003	62	20	332	PAIN
BODY AS A WHOLE	M92-813	5003	62	20	602	PAIN
BODY AS A WHOLE	M93-047	1207	58	_	626	PAIN
BODY AS A WHOLE	M93-047	1924	53	_	-14	PAIN
BODY AS A WHOLE	M91-604	90110	49	36	252	PAIN
BODY AS A WHOLE	M91-604	50703	14	32	314	SEPSIS
BODY AS A WHOLE	M91-604	51116	66	_	412	SEPSIS
BODY AS A WHOLE	M92-873	70902	49	12	134	SEPSIS
BODY AS A WHOLE	M92-813	916	51	44	245	SEPSIS
BODY AS A WHOLE	M92-813	409	22	56	324	SUICIDE ATTEMPT
BODY AS A WHOLE	M93-047	1206	28	64	389	SUICIDE ATTEMPT
CARDIOVASCULAR SYSTEM	M91-604	50321	51	64	394	ANGINA PECTORIS
CARDIOVASCULAR SYSTEM	M91-604	50321	51	64	420	ANGINA PECTORIS
CARDIOVASCULAR SYSTEM	M91-604	51116	66	72	227	ANGINA PECTORIS
CARDIOVASCULAR SYSTEM	M91-604	91403	41	50	162	ANGINA PECTORIS
CARDIOVASCULAR SYSTEM	M91-604	31305	18	_	159	ARTERIOSCLEROSIS
CARDIOVASCULAR SYSTEM	M92-813	3622	54	16	119	ATRIAL FIBRILLATION
CARDIOVASCULAR SYSTEM	M91-603	11118	61	_	-49	CEREBRAL ISCHEMIA
CARDIOVASCULAR SYSTEM	M91-604	31115	61	40	91	CEREBRAL ISCHEMIA

CARDIOVASCULAR SYSTEM	M91-604	30906	23	48	628	CEREBROVASCULAR ACCIDENT
CARDIOVASCULAR SYSTEM	M93-090	10119	75	_	94	CEREBROVASCULAR ACCIDENT
CARDIOVASCULAR SYSTEM	M93-090	11330	71	36	27	CORONARY ARTERY DISORDER
CARDIOVASCULAR SYSTEM	M91-603	11401	42	16	102	DEEP THROMBOPHLEBITIS
CARDIOVASCULAR SYSTEM	M91-604	52112	31	52	727	DEEP THROMBOPHLEBITIS
CARDIOVASCULAR SYSTEM	M93-047	2606	24	24	21	HEART ARREST
CARDIOVASCULAR SYSTEM	M91-604	31215	50	44	536	HYPOTENSION
CARDIOVASCULAR SYSTEM	M92-813	1514	18	40	366	INTRACRANIAL HEMORRHAGE
CARDIOVASCULAR SYSTEM	M92-873	30101	53	0	1081	INTRACRANIAL HEMORRHAGE
CARDIOVASCULAR SYSTEM	M91-604	50321	51	64	356	MYOCARDIAL INFARCT
CARDIOVASCULAR SYSTEM	M91-604	50818	53	36	278	MYOCARDIAL INFARCT
CARDIOVASCULAR SYSTEM	M91-604	51116	66	56	343	MYOCARDIAL INFARCT
CARDIOVASCULAR SYSTEM	M92-813	5105	57	48	99	MYOCARDIAL INFARCT
CARDIOVASCULAR SYSTEM	M93-047	1224	58	28	557	MYOCARDIAL INFARCT
CARDIOVASCULAR SYSTEM	M92-873	70902	49	_	198	MYOCARDIAL ISCHEMIA
CARDIOVASCULAR SYSTEM	M92-813	301	54	48	340	PULMONARY EMBOLUS
CARDIOVASCULAR SYSTEM	M93-090	11008	52	_	76	PULMONARY EMBOLUS

CARDIOVASCULAR SYSTEM	M91-604	31608	20	48	444	SUBARACHNOID HEMORRHAGE
CARDIOVASCULAR SYSTEM	M92-813	1901	57	52	133	SUBARACHNOID HEMORRHAGE
CARDIOVASCULAR SYSTEM	M91-604	32110	13	80	1026	SYNCOPE
CARDIOVASCULAR SYSTEM	M91-604	31215	50	44	536	TACHYCARDIA
CARDIOVASCULAR SYSTEM	M91-603	11401	42	16	54	THROMBOPHLEBITIS
CARDIOVASCULAR SYSTEM	M93-065	3101	31	36	85	THROMBOPHLEBITIS
CARDIOVASCULAR SYSTEM	M93-047	2101	33	36	588	VARICOSE VEIN
CARDIOVASCULAR SYSTEM	M91-604	31608	20	48	444	VASCULAR ANOMALY
DIGESTIVE SYSTEM	M91-604	50606	23	32	527	ANOREXIA
DIGESTIVE SYSTEM	M93-047	2512	20	_	-120	ANOREXIA
DIGESTIVE SYSTEM	M91-604	32106	24	80	734	BLOODY DIARRHEA
DIGESTIVE SYSTEM	M92-813	523	50	48	449	CHOLANGITIS
DIGESTIVE SYSTEM	M91-578	153	44	24	401	CHOLECYSTITIS
DIGESTIVE SYSTEM	M92-873	70403	20	54	652	CHOLECYSTITIS
DIGESTIVE SYSTEM	M92-813	509	55	80	717	CHOLECYSTITIS
DIGESTIVE SYSTEM	M91-604	50909	34	32	53	CHOLELITHIASIS
DIGESTIVE SYSTEM	M91-604	51406	55	80	882	CHOLELITHIASIS
DIGESTIVE SYSTEM	M92-873	70403	20	54	587	CHOLELITHIASIS
DIGESTIVE SYSTEM	M92-813	523	50	48	460	CHOLELITHIASIS
DIGESTIVE SYSTEM	M91-604	50409	43	64	547	COLITIS
DIGESTIVE SYSTEM	M91-604	50814	38	36	263	DIARRHEA
DIGESTIVE SYSTEM	M91-605	11317	46	32	50	DIARRHEA
DIGESTIVE SYSTEM	M91-604	52207	26	52	667	DIARRHEA
DIGESTIVE SYSTEM	M91-604	30702	35	48	169	DYSPHAGIA
DIGESTIVE SYSTEM	M91-605	11317	46	32	54	FECAL INCONTINENCE

DIGESTIVE SYSTEM	M91-604	31215	50	44	536	GASTROENTERITIS
DIGESTIVE SYSTEM	M91-604	50409	43	64	319	GASTROENTERITIS
DIGESTIVE SYSTEM	M91-604	52117	35	72	538	GASTROENTERITIS
DIGESTIVE SYSTEM	M92-873	70207	30	16	374	GASTROENTERITIS
DIGESTIVE SYSTEM	M92-813	1204	27	_	615	GASTROENTERITIS
DIGESTIVE SYSTEM	M92-813C	6712	49	64	236	GASTROENTERITIS
DIGESTIVE SYSTEM	M91-604	90103	26	12	292	GASTROENTERITIS
DIGESTIVE SYSTEM	M91-604	50819	46	34	850	GASTROINTESTINAL CARCINOMA
DIGESTIVE SYSTEM	M92-813C	6604	59	72	433	GASTROINTESTINAL CARCINOMA
DIGESTIVE SYSTEM	M93-091	7006	79	_	-1	GASTROINTESTINAL CARCINOMA
DIGESTIVE SYSTEM	M92-813	3610	48	_	73	GASTROINTESTINAL DISORDER
DIGESTIVE SYSTEM	M93-090	11311	47	6	63	GASTROINTESTINAL HEMORRHAGE
DIGESTIVE SYSTEM	M92-813C	6308	34	16	37	HEMATEMESIS
DIGESTIVE SYSTEM	M92-813	3610	48	32	68	HEMORRHAGIC GASTRITIS
DIGESTIVE SYSTEM	M92-813	211	29	32	243	INTESTINAL OBSTRUCTION
DIGESTIVE SYSTEM	M92-813	3610	48	_	78	INTESTINAL OBSTRUCTION
DIGESTIVE SYSTEM	M93-047	1222	53	12	276	INTESTINAL PERFORATION
DIGESTIVE SYSTEM	M93-047	1931	31	64	241	INTESTINAL PERFORATION
DIGESTIVE SYSTEM	M91-605	10821	46	24	22	LIVER FUNCTION TESTS ABNORMAL
DIGESTIVE SYSTEM	M92-813	1406	46	8	624	NAUSEA
DIGESTIVE SYSTEM	M93-092	2101	13	32	651	NAUSEA
DIGESTIVE SYSTEM	M91-604	90414	49	4	128	PEPTIC ULCER
DIGESTIVE SYSTEM	M91-604	50810	47	16	192	RECTAL DISORDER

DIGESTIVE SYSTEM	M91-604	90414	49	4	128	STOMACH ULCER
DIGESTIVE SYSTEM	M91-603	11126	47	_	-13	TOOTH DISORDER
DIGESTIVE SYSTEM	M93-047	1910	18	64	701	TOOTH DISORDER
DIGESTIVE SYSTEM	M91-603	12110	24	16	8	ULCERATIVE COLITIS
DIGESTIVE SYSTEM	M91-565	4019	25	64	96	VOMITING
DIGESTIVE SYSTEM	M91-604	51808	40	64	377	VOMITING
DIGESTIVE SYSTEM	M93-092	2110	11	20	229	VOMITING
DIGESTIVE SYSTEM	M91-604	40108	4	6	135	VOMITING
ENDOCRINE SYSTEM	M91-604	51406	55	80	882	ADH INAPPROPRIATE
ENDOCRINE SYSTEM	M91-604	51406	55	80	882	ADRENAL DISORDER
ENDOCRINE SYSTEM	M91-604	40119	10	6	233	DIABETES MELLITUS
ENDOCRINE SYSTEM	M91-604	30702	35	48	169	GOITER
HEMIC AND LYMPHATIC	M93-047	2113	41	36	87	ACUTE LEUKEMIA
HEMIC AND LYMPHATIC	M92-813	916	51	44	245	ANEMIA
HEMIC AND LYMPHATIC	M93-047	2218	23	32	476	ANEMIA
HEMIC AND LYMPHATIC	M91-605	11807	27	_	-1	APLASTIC ANEMIA
HEMIC AND LYMPHATIC	M92-813	5402	33	_	241	HEMOLYTIC ANEMIA
HEMIC AND LYMPHATIC	M92-813	4609	28	24	116	LEUKOPENIA
HEMIC AND LYMPHATIC	M92-813	2711	30	16	26	PANCYTOPENIA
HEMIC AND LYMPHATIC	M92-813	1504	49	24	78	THROMBOCYTOPENIA
METABOLIC AND	M91-604	31215	50	44	536	DEHYDRATION
METABOLIC AND	M91-604	50905	36	_	396	DEHYDRATION
METABOLIC AND	M93-092	2110	11	20	229	DEHYDRATION
METABOLIC AND	M93-047	1915	43	_	472	DEHYDRATION
METABOLIC AND	M91-604	40108	4	_	136	DEHYDRATION

METABOLIC AND	M93-090	10114	72	_	-50	HYPERGLYCEMIA
METABOLIC AND	M91-604	51406	55	80	882	HYPONATREMIA
METABOLIC AND	M91-605	11605	39	_	-45	HYPONATREMIA
METABOLIC AND	M92-813	4609	28	16	40	HYPONATREMIA
METABOLIC AND	M91-604	71802	36	28	102	HYPONATREMIA
MUSCULOSKELETAL SYSTEM	M92-813	4303	47	24	107	ARTHRALGIA
MUSCULOSKELETAL SYSTEM	M93-065	1101	68	72	545	ARTHROSIS
MUSCULOSKELETAL SYSTEM	M93-047	1230	44	_	-23	BONE DISORDER
MUSCULOSKELETAL SYSTEM	M93-065	1806	57	24	349	BONE DISORDER
MUSCULOSKELETAL SYSTEM	M91-604	51704	66	72	330	BONE NECROSIS
MUSCULOSKELETAL SYSTEM	M91-604	30808	19	64	685	JOINT DISORDER
MUSCULOSKELETAL SYSTEM	M92-813	1614	13	14	784	JOINT DISORDER
MUSCULOSKELETAL SYSTEM	M91-604	52306	47	60	469	MYASTHENIA
MUSCULOSKELETAL SYSTEM	M92-813	1504	49	24	78	MYASTHENIA
MUSCULOSKELETAL SYSTEM	M91-604	30101	41	80	617	OSTEOMYELITIS
MUSCULOSKELETAL SYSTEM	M91-604	30108	37	64	719	TENDINOUS CONTRACTURE
MUSCULOSKELETAL SYSTEM	M92-813	1613	12	18	301	TENDON DISORDER
MUSCULOSKELETAL SYSTEM	M92-813	1614	13	14	784	TENDON DISORDER
MUSCULOSKELETAL SYSTEM	M92-813	3405	12	80	974	TENOSYNOVITIS
NERVOUS SYSTEM	M91-604	31116	43	40	805	ABNORMAL GAIT

NERVOUS SYSTEM	M91-604	31608	20	48	444	ABNORMAL GAIT
NERVOUS SYSTEM	M92-813	4508	29	24	386	ADDICTION
NERVOUS SYSTEM	M91-604	31113	45	32	411	AGITATION
NERVOUS SYSTEM	M91-604	51407	38	56	275	AGITATION
NERVOUS SYSTEM	M91-604	51808	40	64	377	AGITATION
NERVOUS SYSTEM	M92-813	409	22	56	324	AGITATION
NERVOUS SYSTEM	M91-565	8003	26	_	-1	AMNESIA
NERVOUS SYSTEM	M92-813	4506	35	48	175	ANXIETY
NERVOUS SYSTEM	M92-813	5402	33	_	241	APATHY
NERVOUS SYSTEM	M91-604	30403	36	_	924	APHASIA
NERVOUS SYSTEM	M91-604	31309	18	24	306	APHASIA
NERVOUS SYSTEM	M92-813	1504	49	24	439	ATAXIA
NERVOUS SYSTEM	M93-047	1104	32	12	30	ATAXIA
NERVOUS SYSTEM	M93-047	2411	40	40	663	ATAXIA
NERVOUS SYSTEM	M91-604	52115	16	_	758	CNS NEOPLASIA
NERVOUS SYSTEM	M93-091	2058	31	7	45	CNS NEOPLASIA
NERVOUS SYSTEM	M91-604	30906	23	48	612	COMA
NERVOUS SYSTEM	M91-604	31116	43	40	805	CONFUSION
NERVOUS SYSTEM	M91-604	51808	40	64	377	CONFUSION
NERVOUS SYSTEM	M92-873	70101	41	12	55	CONFUSION
NERVOUS SYSTEM	M92-813	409	22	56	324	CONFUSION
NERVOUS SYSTEM	M92-813	4201	19	6	237	CONFUSION
NERVOUS SYSTEM	M92-813C	6407	59	80	68	CONFUSION
NERVOUS SYSTEM	M93-047	2405	32	56	201	CONFUSION
NERVOUS SYSTEM	M91-604	30401	45	24	341	DELUSIONS
NERVOUS SYSTEM	M92-813	4502	42	56	95	DELUSIONS
NERVOUS SYSTEM	M92-813	526	30	80	191	DEPERSONALIZATION
NERVOUS SYSTEM	M91-604	31113	45	32	411	DEPRESSION
NERVOUS SYSTEM	M91-604	32109	22	32	848	DEPRESSION
NERVOUS SYSTEM	M92-813	412	39	8	2	DEPRESSION
NERVOUS SYSTEM	M92-813	526	30	24	755	DEPRESSION
NERVOUS SYSTEM	M92-813	2207	19	36	252	DEPRESSION

NERVOUS SYSTEM	M92-813	3604	61	48	272	DEPRESSION
NERVOUS SYSTEM	M92-813	4502	42	56	95	DEPRESSION
NERVOUS SYSTEM	M92-813	6203	37	_	-6	DEPRESSION
NERVOUS SYSTEM	M91-604	90413	16	36	464	DEPRESSION
NERVOUS SYSTEM	M91-604	90420	13	36	252	DEPRESSION
NERVOUS SYSTEM	M93-090	11312	40	36	15	DEPRESSION
NERVOUS SYSTEM	M91-604	31116	43	40	805	DIPLOPIA
NERVOUS SYSTEM	M93-047	1104	32	12	30	DIPLOPIA
NERVOUS SYSTEM	M91-604	50606	23	32	527	DIZZINESS
NERVOUS SYSTEM	M92-813	4201	19	6	237	DIZZINESS
NERVOUS SYSTEM	M93-047	2411	40	40	663	DIZZINESS
NERVOUS SYSTEM	M91-604	90601	27	_	539	EMOTIONAL LABILITY
NERVOUS SYSTEM	M92-873	30108	19	32	429	HEADACHE
NERVOUS SYSTEM	M91-605	10821	46	24	22	HEADACHE
NERVOUS SYSTEM	M92-813	1504	49	24	78	HEADACHE
NERVOUS SYSTEM	M93-092	2101	13	32	651	HEADACHE
NERVOUS SYSTEM	M91-604	91301	32	88	557	HEADACHE
NERVOUS SYSTEM	M91-604	30403	36	_	924	HEMIPLEGIA
NERVOUS SYSTEM	M91-604	31115	61	40	91	HEMIPLEGIA
NERVOUS SYSTEM	M91-604	31309	18	24	306	HEMIPLEGIA
NERVOUS SYSTEM	M92-813	5910	46	_	140	HEMIPLEGIA
NERVOUS SYSTEM	M91-604	91301	32	88	488	HEMIPLEGIA
NERVOUS SYSTEM	M91-604	50318	22	80	780	HOSTILITY
NERVOUS SYSTEM	M92-813	109	14	60	720	HOSTILITY
NERVOUS SYSTEM	M92-813	409	22	56	324	HOSTILITY
NERVOUS SYSTEM	M92-813	1916	13	2	1000	HOSTILITY
NERVOUS SYSTEM	M92-813	2207	19	36	252	HOSTILITY
NERVOUS SYSTEM	M93-047	2002	24	40	133	HOSTILITY
NERVOUS SYSTEM	M93-047	2405	32	56	201	HOSTILITY
NERVOUS SYSTEM	M93-065	1405	42	48	197	HOSTILITY
NERVOUS SYSTEM	M91-604	50606	23	64	592	HYPERTONIA
NERVOUS SYSTEM	M91-604	52707	27	64	283	HYPERTONIA

NERVOUS SYSTEM	M91-604	90409	13	6	546	HYSTERIA
NERVOUS SYSTEM	M93-047	1905	25	32	178	INTRACRANIAL HEMORRHAGE
NERVOUS SYSTEM	M91-604	30403	36	_	930	MENINGITIS
NERVOUS SYSTEM	M92-813	4506	35	48	173	MIGRAINE
NERVOUS SYSTEM	M91-604	52103	13	80	411	MYOCLONUS
NERVOUS SYSTEM	M91-604	30401	45	24	341	PARANOID REACTION
NERVOUS SYSTEM	M92-873	70101	41	12	55	PARANOID REACTION
NERVOUS SYSTEM	M92-813	4002	33	32	76	PARANOID REACTION
NERVOUS SYSTEM	M91-604	52306	47	60	469	PARESTHESIA
NERVOUS SYSTEM	M92-813	5902	45	64	171	PARESTHESIA
NERVOUS SYSTEM	M91-604	50427	24	48	533	PERSONALITY DISORDER
NERVOUS SYSTEM	M91-604	50701	21	40	697	PERSONALITY DISORDER
NERVOUS SYSTEM	M91-604	90413	16	36	464	PERSONALITY DISORDER
NERVOUS SYSTEM	M92-873	30103	27	56	603	PSYCHOSIS
NERVOUS SYSTEM	M91-604	30715	29	40	472	PSYCHOSIS
NERVOUS SYSTEM	M91-604	30715	29	48	507	PSYCHOSIS
NERVOUS SYSTEM	M91-604	31410	50	68	261	PSYCHOSIS
NERVOUS SYSTEM	M92-813	510	46	80	359	PSYCHOSIS
NERVOUS SYSTEM	M92-813	510	46	80	518	PSYCHOSIS
NERVOUS SYSTEM	M92-813	510	46	64	599	PSYCHOSIS
NERVOUS SYSTEM	M92-813	510	46	32	749	PSYCHOSIS
NERVOUS SYSTEM	M92-813	510	46	32	963	PSYCHOSIS
NERVOUS SYSTEM	M92-813	2809	56	28	458	PSYCHOSIS
NERVOUS SYSTEM	M93-047	3403	40	36	213	PSYCHOSIS
NERVOUS SYSTEM	M91-604	50906	34	36	55	SCHIZOPHRENIC REACTION
NERVOUS SYSTEM	M92-813	409	22	56	324	SOMNOLENCE
NERVOUS SYSTEM	M92-813	1504	49	24	78	SOMNOLENCE
NERVOUS SYSTEM	M92-813	3902	22	40	83	SOMNOLENCE

NERVOUS SYSTEM	M92-813	5402	33	_	241	SOMNOLENCE
NERVOUS SYSTEM	M91-604	31706	77	80	312	SPEECH DISORDER
NERVOUS SYSTEM	M91-604	51407	38	56	275	SPEECH DISORDER
NERVOUS SYSTEM	M91-604	51808	40	64	377	SPEECH DISORDER
NERVOUS SYSTEM	M92-813	5402	33	_	241	SPEECH DISORDER
NERVOUS SYSTEM	M91-603	10202	40	_	52	STUPOR
NERVOUS SYSTEM	M93-090	10906	24	_	59	STUPOR
NERVOUS SYSTEM	M91-604	40109	3	4	280	STUPOR
NERVOUS SYSTEM	M91-604	31609	43	64	471	SUBDURAL HEMATOMA
NERVOUS SYSTEM	M91-604	50606	23	64	592	SUBDURAL HEMATOMA
NERVOUS SYSTEM	M92-813	5910	46	_	140	THINKING ABNORMAL
NERVOUS SYSTEM	M91-603	10104	18	32	107	TREMOR
NERVOUS SYSTEM	M91-605	10821	46	24	22	VERTIGO
RESPIRATORY SYSTEM	M92-813	1614	13	14	125	APNEA
RESPIRATORY SYSTEM	M92-813	1614	13	14	182	APNEA
RESPIRATORY SYSTEM	M92-813C	6705	34	_	806	ASPHIXIATION SECONDARY TO SEIZURE
RESPIRATORY SYSTEM	M93-047	2105	29	_	286	ASPHYXIA
RESPIRATORY SYSTEM	M91-605	11020	27	32	57	ASTHMA
RESPIRATORY SYSTEM	M91-604	32208	22	80	663	BRONCHITIS
RESPIRATORY SYSTEM	M91-604	51116	66	72	252	BRONCHITIS
RESPIRATORY SYSTEM	M92-813	1208	16	40	985	BRONCHITIS
RESPIRATORY SYSTEM	M93-090	10708	27	6	25	BRONCHITIS
RESPIRATORY SYSTEM	M91-604	91307	54	32	147	BRONCHITIS

RESPIRATORY SYSTEM	M91-605	11317	46	32	47	COUGH INCREASED
RESPIRATORY SYSTEM	M92-813	1614	13	14	125	COUGH INCREASED
RESPIRATORY SYSTEM	M92-813	4401	41	36	526	DYSPNEA
RESPIRATORY SYSTEM	M92-813C	6407	59	80	68	HYPERVENTILATION
RESPIRATORY SYSTEM	M92-813	1614	13	14	182	LUNG EDEMA
RESPIRATORY SYSTEM	M92-813	1203	52	24	301	NASAL SEPTUM DISORDER
RESPIRATORY SYSTEM	M91-604	30815	12	80	718	PHARYNGITIS
RESPIRATORY SYSTEM	M92-813	1113	16	26	508	PHARYNGITIS
RESPIRATORY SYSTEM	M93-065	2803	18	36	216	PHARYNGITIS
RESPIRATORY SYSTEM	M93-090	11305	33	6	21	PHARYNGITIS
RESPIRATORY SYSTEM	M91-604	31108	46	40	86	PNEUMONIA
RESPIRATORY SYSTEM	M91-603	11401	42	_	-41	PNEUMONIA
RESPIRATORY SYSTEM	M91-604	31813	54	68	343	PNEUMONIA
RESPIRATORY SYSTEM	M91-604	32208	22	80	269	PNEUMONIA
RESPIRATORY SYSTEM	M91-604	32208	22	80	663	PNEUMONIA
RESPIRATORY SYSTEM	M91-604	32208	22	120	943	PNEUMONIA
RESPIRATORY SYSTEM	M91-604	50605	13	56	581	PNEUMONIA

RESPIRATORY SYSTEM	M91-604	50703	14	32	313	PNEUMONIA
RESPIRATORY SYSTEM	M91-604	51116	66	48	360	PNEUMONIA
RESPIRATORY SYSTEM	M92-775	12008	30	_	-87	PNEUMONIA
RESPIRATORY SYSTEM	M92-813	203	42	48	412	PNEUMONIA
RESPIRATORY SYSTEM	M92-813	301	54	24	123	PNEUMONIA
RESPIRATORY SYSTEM	M92-813	916	51	44	243	PNEUMONIA
RESPIRATORY SYSTEM	M92-813	1208	16	40	985	PNEUMONIA
RESPIRATORY SYSTEM	M92-813	1809	30	60	994	PNEUMONIA
RESPIRATORY SYSTEM	M92-813	4406	56	12	242	PNEUMONIA
RESPIRATORY SYSTEM	M92-813C	6407	59	40	34	PNEUMONIA
RESPIRATORY SYSTEM	M93-065	1303	29	48	211	PNEUMONIA
RESPIRATORY SYSTEM	M93-065	1304	31	36	400	PNEUMONIA
RESPIRATORY SYSTEM	M93-065	2901	27	20	84	PNEUMONIA
RESPIRATORY SYSTEM	M93-065	3103	34	36	98	PNEUMONIA
RESPIRATORY SYSTEM	M93-090	10119	75	_	103	PNEUMONIA
RESPIRATORY SYSTEM	M91-604	91310	48	28	192	PNEUMONIA
RESPIRATORY SYSTEM	M91-604	51116	66	56	343	PNEUMOTHORAX

RESPIRATORY SYSTEM	M93-047	2112	51	36	212	PULMONARY INFARCT
RESPIRATORY SYSTEM	M91-578	102	43	36	847	RESPIRATORY DISORDER
RESPIRATORY SYSTEM	M92-873	30404	46	32	1065	RESPIRATORY DISORDER
RESPIRATORY SYSTEM	M92-813	5910	46	_	140	RESPIRATORY DISORDER
RESPIRATORY SYSTEM	M91-604	80302	27	80	342	RESPIRATORY DISORDER
RESPIRATORY SYSTEM	M91-604	31215	50	44	536	SINUSITIS
RESPIRATORY SYSTEM	M93-047	2317	20	36	302	SINUSITIS
SKIN AND APPENDAGES	M92-873	70202	68	24	662	RASH
SKIN AND APPENDAGES	M92-813	4407	24	24	245	RASH
SKIN AND APPENDAGES	M91-604	31507	52	40	112	SKIN BENIGN NEOPLASM
SKIN AND APPENDAGES	M91-578	301	57	_	-849	SKIN CARCINOMA
SKIN AND APPENDAGES	M91-604	50904	52	48	556	SKIN CARCINOMA
SKIN AND APPENDAGES	M91-604	51108	54	80	302	SKIN CARCINOMA
SKIN AND APPENDAGES	M93-091	2044	46	_	88	SKIN CARCINOMA
SKIN AND APPENDAGES	M93-047	1223	43	24	45	SKIN MELANOMA
SKIN AND APPENDAGES	M91-604	30707	38	28	955	SKIN ULCER
SKIN AND APPENDAGES	M91-605	11317	46	_	-29	SKIN ULCER

SKIN AND APPENDAGES	M92-813	4401	41	36	526	SWEATING
SPECIAL SENSES	M91-604	31215	50	44	536	OTITIS MEDIA
SPECIAL SENSES	M92-873	70603	34	30	525	RETINAL DETACHMENT
SPECIAL SENSES	M93-047	2411	40	40	663	VESTIBULAR DISORDER
UROGENITAL SYSTEM	M92-813	1113	16	unk	949	ABORTION
UROGENITAL SYSTEM	M92-813	1706	38	72	530	ABORTION
UROGENITAL SYSTEM	M92-813	1911	29	0	1055	ABORTION
UROGENITAL SYSTEM	M92-813	2701	31	32	1037	ABORTION
UROGENITAL SYSTEM	M92-813	3901	29	_	153	ABORTION
UROGENITAL SYSTEM	M92-813	3904	22	40	97	ABORTION
UROGENITAL SYSTEM	M93-047	2505	33	36	121	ABORTION
UROGENITAL SYSTEM	M93-090	10410	16	6	34	ABORTION
UROGENITAL SYSTEM	M93-090	11336	33	6	43	ABORTION
UROGENITAL SYSTEM	M92-813	1701	24	76	371	BLADDER CALCULUS
UROGENITAL SYSTEM	M91-604	50607	43	104	890	BREAST CARCINOMA
UROGENITAL SYSTEM	M91-604	51012	44	58	545	BREAST CARCINOMA
UROGENITAL SYSTEM	M93-091	2044	46	_	93	BREAST NEOPLASM
UROGENITAL SYSTEM	M91-605	12606	30	24	17	CERVICITIS
UROGENITAL SYSTEM	M91-604	51712	38	56	316	CERVIX CARCINOMA IN SITU
UROGENITAL SYSTEM	M93-065	3103	34	48	657	DYSMENORRHEA
UROGENITAL SYSTEM	M91-604	31609	43	8	141	ENDOMETRIAL CARCINOMA
UROGENITAL SYSTEM	M91-605	12606	30	24	17	ENDOMETRIAL DISORDER
UROGENITAL SYSTEM	M93-047	2317	20	36	155	ENDOMETRIAL DISORDER
UROGENITAL SYSTEM	M93-090	11318	61	6	60	HEMATURIA
UROGENITAL SYSTEM	M93-047	1212	37	32	130	KIDNEY FAILURE
UROGENITAL SYSTEM	M92-873	70404	44	48	188	MENORRHAGIA
UROGENITAL SYSTEM	M91-578	156	35	24	1348	METRORRHAGIA
UROGENITAL SYSTEM	M92-813C	6508	35	12	316	METRORRHAGIA

UROGENITAL SYSTEM	M92-775	21001	29	_	-77	ORCHITIS
UROGENITAL SYSTEM	M92-813	1204	27	38	587	PREGNANCY DISORDER
UROGENITAL SYSTEM	M92-813	2709	60	8	75	PROSTATIC CARCINOMA
UROGENITAL SYSTEM	M92-813	2709	60	24	733	PROSTATIC CARCINOMA
UROGENITAL SYSTEM	M92-813	916	51	48	547	PYELONEPHRITIS
UROGENITAL SYSTEM	M92-813	2711	30	8	9	PYELONEPHRITIS
UROGENITAL SYSTEM	M91-603	10511	32	none/ unk	-89	SALPINGITIS
UROGENITAL SYSTEM	M91-605	12606	30	24	17	SALPINGITIS
UROGENITAL SYSTEM	M92-813	1103	38	32	57	SALPINGITIS
UROGENITAL SYSTEM	M91-578	301	57	_	307	URINARY FREQUENCY
UROGENITAL SYSTEM	M91-604	50810	47	16	192	URINARY INCONTINENCE
UROGENITAL SYSTEM	M92-813	1504	49	24	78	URINARY INCONTINENCE
UROGENITAL SYSTEM	M93-047	1915	43	_	472	URINARY TRACT DISORDER
UROGENITAL SYSTEM	M91-603	11309	22	8	8	URINARY TRACT INFECTION
UROGENITAL SYSTEM	M92-873	70902	49	12	134	URINARY TRACT INFECTION
UROGENITAL SYSTEM	M92-775	21018	49	30	31	URINARY TRACT INFECTION
UROGENITAL SYSTEM	M92-813	2201	35	48	621	URINARY TRACT INFECTION
UROGENITAL SYSTEM	M91-604	52401	28	24	151	UTERINE DISORDER
UROGENITAL SYSTEM	M92-813	1214	45	16	695	UTERINE FIBROIDS ENLARGED

Appendix 7.2 Serious Adverse Experiences Considered Possibly/Probably Related to Study Drug

Body System	Study Number	Patient Number	Age	Dose mg/day	Time from 1st Dose to AE Onset (days)	Adverse Event
BODY AS A WHOLE	M91-605	12607	28	32	94	ABDOMINAL PAIN
BODY AS A WHOLE	M92-775	13022	42		-34	ABDOMINAL PAIN
BODY AS A WHOLE	M91-604	90409	13	12	141	ABDOMINAL PAIN
BODY AS A WHOLE	M91-604	90412	17	36	243	ABDOMINAL PAIN
BODY AS A WHOLE	M91-578	101	39	48	903	ACCIDENTAL INJURY
BODY AS A WHOLE	M91-604	52401	28	32	36	ACCIDENTAL INJURY
BODY AS A WHOLE	M92-873	70706	30	24	52	ACCIDENTAL INJURY
BODY AS A WHOLE	M92-775	18003	45	30	93	ACCIDENTAL INJURY
BODY AS A WHOLE	M92-873	70803	62	60	532	ACCIDENTAL INJURY
BODY AS A WHOLE	M92-775	19006	34		-104	ACCIDENTAL INJURY
BODY AS A WHOLE	M92-813	3409	13	80	234	ACCIDENTAL INJURY
BODY AS A WHOLE	M91-604	30102	45	72	316	ACCIDENTAL OVERDOSE
BODY AS A WHOLE	M91-604	31214	29	48	338	CHEST PAIN
BODY AS A WHOLE	M91-603	12104	59		-43	CHEST PAIN
BODY AS A WHOLE	M92-813	4304	38	28	322	CHEST PAIN
BODY AS A WHOLE	M92-813	4406	56	16	8	CHEST PAIN
BODY AS A WHOLE	M93-065	2802	28	36	32	CHEST PAIN
BODY AS A WHOLE	M91-604	30203	26	56	168	DRUG INTERACTION
BODY AS A WHOLE	M91-604	31107	35	48	240	DRUG INTERACTION
BODY AS A WHOLE	M91-604	31115	61	40	53	DRUG INTERACTION
BODY AS A WHOLE	M91-604	31606	30	32	77	DRUG INTERACTION
BODY AS A WHOLE	M91-604	52202	29	8	42	DRUG INTERACTION
BODY AS A WHOLE	M92-813	1001	36	36	65	DRUG INTERACTION

BODY AS A WHOLE	M91-604	30102	45	72	316	DRUG LEVEL INCREASED
BODY AS A WHOLE	M91-604	30203	26	56	168	DRUG LEVEL INCREASED
BODY AS A WHOLE	M91-604	31107	35	48	240	DRUG LEVEL INCREASED
BODY AS A WHOLE	M91-604	31608	20	56	66	DRUG LEVEL INCREASED
BODY AS A WHOLE	M91-604	31606	30	32	77	DRUG LEVEL INCREASED
BODY AS A WHOLE	M91-604	52202	29	8	42	DRUG LEVEL INCREASED
BODY AS A WHOLE	M92-813	1001	36	36	65	DRUG LEVEL INCREASED
BODY AS A WHOLE	M92-813	5108	43	64	173	DRUG LEVEL INCREASED
BODY AS A WHOLE	M91-604	51703	52	20	169	FEVER
BODY AS A WHOLE	M91-605	12607	28	32	94	FEVER
BODY AS A WHOLE	M92-813	5108	43	64	173	INTENTIONAL OVERDOSE
BODY AS A WHOLE	M93-091	3001	67		335	MYELOMA
BODY AS A WHOLE	M91-604	80302	27	80	342	OVERDOSE
BODY AS A WHOLE	M93-065	2814	19	24	20	OVERDOSE
BODY AS A WHOLE	M93-065	3103	34	48	475	OVERDOSE
BODY AS A WHOLE	M92-813	1001	36	36	65	SUICIDE ATTEMPT
BODY AS A WHOLE	M92-813	3409	13	80	234	SUICIDE ATTEMPT
BODY AS A WHOLE	M93-065	1307	69	36	592	SUICIDE ATTEMPT
CARDIOVASCULAR SYSTEM	M92-873	30503	45	64	399	EXTRASYSTOLES
CARDIOVASCULAR SYSTEM	M91-603	12104	59	_	-43	PALPITATION
CARDIOVASCULAR SYSTEM	M91-603	12104	59	_	-43	SUPRAVENTRICULAR TACHYCARDIA

CARDIOVASCULAR SYSTEM	M93-047	2223	18	64	538	SYNCOPE
CARDIOVASCULAR SYSTEM	M93-065	2405	61	12	32	SYNCOPE
DIGESTIVE SYSTEM	M91-604	52202	29	8	39	ANOREXIA
DIGESTIVE SYSTEM	M92-775	21005	39	30	95	CHOLECYSTITIS
DIGESTIVE SYSTEM	M91-604	31813	54	76	868	DIARRHEA
DIGESTIVE SYSTEM	M91-605	12607	28	32	94	DIARRHEA
DIGESTIVE SYSTEM	M92-873	70319	42	48	448	DYSPEPSIA
DIGESTIVE SYSTEM	M91-604	50604	36	56	848	GASTRITIS
DIGESTIVE SYSTEM	M91-605	10322	38		-63	GASTROENTERITIS
DIGESTIVE SYSTEM	M91-604	31813	54	76	868	GASTROINTESTINAL HEMORRHAGE
DIGESTIVE SYSTEM	M91-604	50606	23	32	527	NAUSEA
DIGESTIVE SYSTEM	M91-604	52117	35	28	235	NAUSEA
DIGESTIVE SYSTEM	M91-605	12203	27	8	1	NAUSEA
DIGESTIVE SYSTEM	M91-604	52202	29	8	40	NAUSEA
DIGESTIVE SYSTEM	M91-604	52401	28	32	36	NAUSEA
DIGESTIVE SYSTEM	M91-605	12607	28	32	93	NAUSEA
DIGESTIVE SYSTEM	M92-873	70319	42	48	448	NAUSEA
DIGESTIVE SYSTEM	M91-604	31115	61	40	53	NAUSEA AND VOMITING
DIGESTIVE SYSTEM	M91-604	50702	12	36	187	NAUSEA AND VOMITING
DIGESTIVE SYSTEM	M92-813	3801	29	16	55	NAUSEA AND VOMITING
DIGESTIVE SYSTEM	M92-775	19007	20	_	-25	RECTAL HEMORRHAGE
DIGESTIVE SYSTEM	M91-578	302	30	32	449	TOOTH DISORDER
DIGESTIVE SYSTEM	M91-578	356	37	40	444	VOMITING
DIGESTIVE SYSTEM	M91-604	31813	54	76	868	VOMITING
DIGESTIVE SYSTEM	M91-604	50606	23	32	527	VOMITING

DIGESTIVE SYSTEM	M91-604	50819	46	34	876	VOMITING
DIGESTIVE SYSTEM	M91-604	52117	35	28	235	VOMITING
DIGESTIVE SYSTEM	M91-605	12203	27	8	1	VOMITING
DIGESTIVE SYSTEM	M91-604	52202	29	8	40	VOMITING
DIGESTIVE SYSTEM	M91-604	52401	28	32	36	VOMITING
DIGESTIVE SYSTEM	M91-605	12607	28	32	94	VOMITING
DIGESTIVE SYSTEM	M92-873	70313	50	30	164	VOMITING
DIGESTIVE SYSTEM	M93-047	1402	22	24	18	VOMITING
DIGESTIVE SYSTEM	TIA/J/3/J	1609	34	20	101	VOMITING
HEMIC AND LYMPHATIC SYSTEM	M91-604	31111	70	48	819	LYMPHOMA LIKE REACTION
METABOLIC AND NUTRITIONAL DISORDERS	M93-047	2312	16	30	104	DEHYDRATION
METABOLIC AND NUTRITIONAL DISORDERS	M92-775	18010	30	30	28	HYPOGLYCEMIA
METABOLIC AND NUTRITIONAL DISORDERS	M92-873	30506	29	32	735	HYPOGLYCEMIC REACTION
METABOLIC AND NUTRITIONAL DISORDERS	M91-604	51405	45	40	615	HYPONATREMIA
MUSCULOSKELETAL SYSTEM	M93-091	3001	67	_	335	BACK PAIN
MUSCULOSKELETAL SYSTEM	M93-047	3617	49	16	283	MYASTHENIA
MUSCULOSKELETAL SYSTEM	M93-090	10307	11	24	15	MYASTHENIA
MUSCULOSKELETAL SYSTEM	M91-604	90606	41	24	142	TWITCHING
NERVOUS SYSTEM	M91-604	50814	38	36	478	ABNORMAL GAIT
NERVOUS SYSTEM	M91-604	52202	29	8	42	ABNORMAL GAIT

NERVOUS SYSTEM	TIA/J/3/J	1609	34	20	101	ABNORMAL GAIT
NERVOUS SYSTEM	M91-604	30816	38	56	544	AGITATION
NERVOUS SYSTEM	M91-605	11113	66	32	106	AGITATION
NERVOUS SYSTEM	M91-604	51116	66	64	336	AGITATION
NERVOUS SYSTEM	M92-813	2405	41	80	260	AGITATION
NERVOUS SYSTEM	M92-813	4106	27	32	105	AGITATION
NERVOUS SYSTEM	M92-813	4704	39	32	134	AGITATION
NERVOUS SYSTEM	M91-604	80307	18	14	96	AGITATION
NERVOUS SYSTEM	M93-065	1307	69	36	592	AGITATION
NERVOUS SYSTEM	M93-090	10603	41	36	141	AGITATION
NERVOUS SYSTEM	M91-565	8005	25	64	58	AMNESIA
NERVOUS SYSTEM	M91-604	30102	45	72	316	AMNESIA
NERVOUS SYSTEM	M93-090	10210	43	36	147	AMNESIA
NERVOUS SYSTEM	M92-873	30202	56	32	162	ANXIETY
NERVOUS SYSTEM	M92-873	70304	63	36	72	ANXIETY
NERVOUS SYSTEM	M92-873	70319	42	64	503	ANXIETY
NERVOUS SYSTEM	M92-873	70407	38	30	106	ANXIETY
NERVOUS SYSTEM	M93-047	2601	48	24	15	ANXIETY
NERVOUS SYSTEM	M93-065	2305	38	48	120	ANXIETY
NERVOUS SYSTEM	M91-604	30102	45	72	316	APHASIA
NERVOUS SYSTEM	M92-813	3402	21	68	359	APHASIA
NERVOUS SYSTEM	M91-604	80308	46	64	584	APHASIA
NERVOUS SYSTEM	M91-604	31115	61	40	53	ASTHENIA
NERVOUS SYSTEM	M91-604	31606	30	32	77	ASTHENIA
NERVOUS SYSTEM	M91-604	51406	55	56	247	ASTHENIA
NERVOUS SYSTEM	M92-873	70320	43	64	446	ASTHENIA
NERVOUS SYSTEM	M92-813	3402	21	64	347	ASTHENIA
NERVOUS SYSTEM	M92-813C	6602	37	12	583	ASTHENIA
NERVOUS SYSTEM	M91-578	201	49	64	674	ATAXIA
NERVOUS SYSTEM	M91-604	30203	26	56	168	ATAXIA
NERVOUS SYSTEM	M91-604	31107	35	48	240	ATAXIA

NERVOUS SYSTEM	M91-604	31115	61	40	53	ATAXIA
NERVOUS SYSTEM	M91-604	31606	30	32	77	ATAXIA
NERVOUS SYSTEM	M92-775	12002	37	30	47	ATAXIA
NERVOUS SYSTEM	M92-873	70320	43	64	446	ATAXIA
NERVOUS SYSTEM	M92-813	1512	29	32	96	ATAXIA
NERVOUS SYSTEM	M92-813	4304	38	28	322	ATAXIA
NERVOUS SYSTEM	M93-047	1910	18	64	703	ATAXIA
NERVOUS SYSTEM	M93-065	2803	18	64	396	ATAXIA
NERVOUS SYSTEM	TIA/J/3/J	1609	34	20	101	ATAXIA
NERVOUS SYSTEM	M93-047	2601	48	24	15	CHOREOATHETOSIS
NERVOUS SYSTEM	M91-604	50807	44	32	827	CNS NEOPLASIA
NERVOUS SYSTEM	M90-481	4004	45	8	3	CONFUSION
NERVOUS SYSTEM	M91-565	8005	25	64	58	CONFUSION
NERVOUS SYSTEM	M91-604	30102	45	72	316	CONFUSION
NERVOUS SYSTEM	M91-604	30201	37	80	237	CONFUSION
NERVOUS SYSTEM	M91-604	30201	37	48	240	CONFUSION
NERVOUS SYSTEM	M91-604	30203	26	56	168	CONFUSION
NERVOUS SYSTEM	M91-604	30816	38	56	544	CONFUSION
NERVOUS SYSTEM	M91-604	31005	58	44	347	CONFUSION
NERVOUS SYSTEM	M91-604	31608	20	56	66	CONFUSION
NERVOUS SYSTEM	M91-604	31606	30	32	77	CONFUSION
NERVOUS SYSTEM	M91-604	50606	23	32	527	CONFUSION
NERVOUS SYSTEM	M91-604	50616	33	56	316	CONFUSION
NERVOUS SYSTEM	M91-605	11113	66	32	106	CONFUSION
NERVOUS SYSTEM	M91-604	51116	66	64	334	CONFUSION
NERVOUS SYSTEM	M92-813	705	14	64	95	CONFUSION
NERVOUS SYSTEM	M92-813	1001	36	36	59	CONFUSION
NERVOUS SYSTEM	M92-813	1111	43	64	113	CONFUSION
NERVOUS SYSTEM	M92-813	3402	21	66	364	CONFUSION
NERVOUS SYSTEM	M92-855	107	43	22	12	CONFUSION
NERVOUS SYSTEM	M91-604	80306	40	36	186	CONFUSION

NERVOUS SYSTEM	M91-604	80308	46	64	584	CONFUSION
NERVOUS SYSTEM	M93-047	1922	50	48	334	CONFUSION
NERVOUS SYSTEM	M93-047	2105	29	36	85	CONFUSION
NERVOUS SYSTEM	M93-047	3101	36	20	311	CONFUSION
NERVOUS SYSTEM	M93-065	1307	69	36	592	CONFUSION
NERVOUS SYSTEM	M93-090	10210	43	36	147	CONFUSION
NERVOUS SYSTEM	M91-604	30201	37	80	237	DELUSIONS
NERVOUS SYSTEM	M92-873	70304	63	36	72	DELUSIONS
NERVOUS SYSTEM	M90-481	9003	41	52	55	DEPRESSION
NERVOUS SYSTEM	M91-604	31007	40	40	380	DEPRESSION
NERVOUS SYSTEM	M91-604	31411	33	16	167	DEPRESSION
NERVOUS SYSTEM	M91-604	50314	43	72	413	DEPRESSION
NERVOUS SYSTEM	M91-604	50604	36	48	925	DEPRESSION
NERVOUS SYSTEM	M91-604	51111	21	32	221	DEPRESSION
NERVOUS SYSTEM	M91-604	51403	36	68	535	DEPRESSION
NERVOUS SYSTEM	M92-873	70319	42	36	283	DEPRESSION
NERVOUS SYSTEM	M91-604	80307	18	14	96	DEPRESSION
NERVOUS SYSTEM	M93-047	2414	38	42	268	DEPRESSION
NERVOUS SYSTEM	M93-047	3101	36	20	645	DEPRESSION
NERVOUS SYSTEM	M93-065	2407	58	12	519	DEPRESSION
NERVOUS SYSTEM	M93-065	2816	33	30	84	DEPRESSION
NERVOUS SYSTEM	M91-604	90702	32	44	338	DEPRESSION
NERVOUS SYSTEM	M93-090	11601	33	36	25	DEPRESSION
NERVOUS SYSTEM	M92-873	30405	30	64	426	DIPLOPIA
NERVOUS SYSTEM	M91-604	30203	26	56	168	DIPLOPIA
NERVOUS SYSTEM	M91-604	50819	46	34	876	DIPLOPIA
NERVOUS SYSTEM	M92-873	30405	30	64	426	DIZZINESS
NERVOUS SYSTEM	M91-565	8003	26	40	67	DIZZINESS
NERVOUS SYSTEM	M91-604	31608	20	56	66	DIZZINESS
NERVOUS SYSTEM	M91-604	31606	30	32	77	DIZZINESS
NERVOUS SYSTEM	M91-603	12104	59		-43	DIZZINESS

NERVOUS SYSTEM	M91-604	50814	38	36	478	DIZZINESS
NERVOUS SYSTEM	M91-604	51405	45	40	615	DIZZINESS
NERVOUS SYSTEM	M91-605	12203	27	8	1	DIZZINESS
NERVOUS SYSTEM	M92-775	21009	30	24	52	DIZZINESS
NERVOUS SYSTEM	M92-813	1001	36	36	59	DIZZINESS
NERVOUS SYSTEM	M93-047	2601	48	24	15	DIZZINESS
NERVOUS SYSTEM	M93-047	3305	54		2	DIZZINESS
NERVOUS SYSTEM	M93-047	3617	49	16	283	DIZZINESS
NERVOUS SYSTEM	M93-065	2405	61	12	32	DIZZINESS
NERVOUS SYSTEM	M93-065	2802	28	36	32	DIZZINESS
NERVOUS SYSTEM	M93-090	10401	13	36	138	DIZZINESS
NERVOUS SYSTEM	M91-604	90409	13	12	141	DIZZINESS
NERVOUS SYSTEM	M93-090	10603	41	12	132	DIZZINESS
NERVOUS SYSTEM	M92-813	4704	39	32	134	DYSKINESIA
NERVOUS SYSTEM	M93-065	2001	48	30	81	DYSKINESIA
NERVOUS SYSTEM	M92-813	1512	29	32	96	DYSTONIA
NERVOUS SYSTEM	M91-604	52202	29	8	40	EMOTIONAL LABILITY
NERVOUS SYSTEM	M92-775	11001	49	24	128	EMOTIONAL LABILITY
NERVOUS SYSTEM	M92-813	4106	27	32	105	EMOTIONAL LABILITY
NERVOUS SYSTEM	M91-604	31107	35	48	240	ENCEPHALOPATHY
NERVOUS SYSTEM	M92-813	607	52	32	174	ENCEPHALOPATHY
NERVOUS SYSTEM	M92-813	1512	29	32	96	ENCEPHALOPATHY
NERVOUS SYSTEM	M92-813	3106	19	72	313	ENCEPHALOPATHY
NERVOUS SYSTEM	M93-047	1508	51	12	14	ENCEPHALOPATHY
NERVOUS SYSTEM	M93-090	10307	11	24	15	ENCEPHALOPATHY
NERVOUS SYSTEM	M91-604	90304	54	36	150	ENCEPHALOPATHY
NERVOUS SYSTEM	M91-604	90401	20	56	223	ENCEPHALOPATHY
NERVOUS SYSTEM	M93-090	11604	57	32	157	ENCEPHALOPATHY

NERVOUS SYSTEM	M91-604	92401	25	64	74	ENCEPHALOPATHY
NERVOUS SYSTEM	M91-604	30201	37	48	240	HALLUCINATIONS
NERVOUS SYSTEM	M91-604	31411	33		173	HALLUCINATIONS
NERVOUS SYSTEM	M92-873	70407	38	30	106	HALLUCINATIONS
NERVOUS SYSTEM	M92-813	3402	21	66	364	HALLUCINATIONS
NERVOUS SYSTEM	M93-043	101	11	1	91	HALLUCINATIONS
NERVOUS SYSTEM	M93-090	10210	43		151	HALLUCINATIONS
NERVOUS SYSTEM	M91-604	31115	61	40	53	HEADACHE
NERVOUS SYSTEM	M91-604	51703	52	20	170	HEADACHE
NERVOUS SYSTEM	M91-604	52401	28	32	36	HEADACHE
NERVOUS SYSTEM	M93-047	3617	49	16	283	HEADACHE
NERVOUS SYSTEM	M90-481	4014	24	24	44	HOSTILITY
NERVOUS SYSTEM	M91-604	30102	45	72	316	HOSTILITY
NERVOUS SYSTEM	M91-604	31411	33	16	167	HOSTILITY
NERVOUS SYSTEM	M91-603	11512	19	56	48	HOSTILITY
NERVOUS SYSTEM	M91-604	51403	36	68	535	HOSTILITY
NERVOUS SYSTEM	M91-604	51703	52	20	168	HOSTILITY
NERVOUS SYSTEM	M92-873	70319	42	64	503	HOSTILITY
NERVOUS SYSTEM	M92-775	18011	21	30	57	HOSTILITY
NERVOUS SYSTEM	M92-813	519	32	64	522	HOSTILITY
NERVOUS SYSTEM	M92-813	5108	43	64	173	HOSTILITY
NERVOUS SYSTEM	M92-855	111	36	46	41	HOSTILITY
NERVOUS SYSTEM	M93-065	2806	23	24	45	HOSTILITY
NERVOUS SYSTEM	M92-873	71003	21	36	100	HYPOKINESIA
NERVOUS SYSTEM	M93-065	2803	18	64	396	HYPOKINESIA
NERVOUS SYSTEM	M93-047	2601	48	24	15	HYPOTONIA
NERVOUS SYSTEM	M92-813	1402	33	24	27	HYSTERIA
NERVOUS SYSTEM	M93-065	2901	27	20	83	ILEUS
NERVOUS SYSTEM	M93-065	2901	27	30	198	ILEUS
NERVOUS SYSTEM	M93-091	3001	67		311	ILEUS
NERVOUS SYSTEM	M91-578	101	39	64	665	INCOORDINATION

NERVOUS SYSTEM	M91-604	31107	35	48	240	INCOORDINATION
NERVOUS SYSTEM	M92-813	705	14	64	95	INCOORDINATION
NERVOUS SYSTEM	M92-855	203	31	24	33	INCOORDINATION
NERVOUS SYSTEM	M93-047	1515	47	6	21	MANIC REACTION
NERVOUS SYSTEM	M91-565	8003	26	32	39	MIGRAINE
NERVOUS SYSTEM	M91-604	30203	26	56	168	MOVEMENT DISORDER
NERVOUS SYSTEM	M91-604	31107	35	48	240	MOVEMENT DISORDER
NERVOUS SYSTEM	M91-604	31608	20	56	66	MOVEMENT DISORDER
NERVOUS SYSTEM	M92-813	705	14	64	95	MOVEMENT DISORDER
NERVOUS SYSTEM	M91-604	31608	20	56	66	MYOCLONUS
NERVOUS SYSTEM	M92-813	1513	22	40	130	MYOCLONUS
NERVOUS SYSTEM	M91-604	80302	27	80	342	MYOCLONUS
NERVOUS SYSTEM	M91-604	30203	26	56	168	NERVOUSNESS
NERVOUS SYSTEM	M91-604	31606	30	32	77	NERVOUSNESS
NERVOUS SYSTEM	M91-604	50606	23	32	527	NERVOUSNESS
NERVOUS SYSTEM	M92-813	1604	22	32	27	NERVOUSNESS
NERVOUS SYSTEM	M92-855	107	43	22	12	NERVOUSNESS
NERVOUS SYSTEM	M93-047	1910	18	64	703	NYSTAGMUS
NERVOUS SYSTEM	TIA/J/3/J	1609	34	20	101	NYSTAGMUS
NERVOUS SYSTEM	M91-604	31508	61	64	347	PARANOID REACTION
NERVOUS SYSTEM	M92-813	4110	45	64	222	PARANOID REACTION
NERVOUS SYSTEM	M91-604	31115	61	40	53	PARESTHESIA
NERVOUS SYSTEM	M92-813	607	52	32	174	PARESTHESIA
NERVOUS SYSTEM	M92-813	5108	43	64	173	PARESTHESIA
NERVOUS SYSTEM	M91-604	30201	37	64	238	PERSONALITY DISORDER
NERVOUS SYSTEM	M91-604	30201	37	48	240	PERSONALITY DISORDER

NERVOUS SYSTEM	M91-604	30808	19	64	988	PERSONALITY DISORDER
NERVOUS SYSTEM	M91-604	50408	31	80	978	PERSONALITY DISORDER
NERVOUS SYSTEM	M92-813	3412	23	40	238	PERSONALITY DISORDER
NERVOUS SYSTEM	M92-813	5108	43	64	173	PERSONALITY DISORDER
NERVOUS SYSTEM	M91-604	91002	49	80	406	PERSONALITY DISORDER
NERVOUS SYSTEM	M91-578	354	29	32	782	PSYCHOSIS
NERVOUS SYSTEM	M91-604	30212	35	80	292	PSYCHOSIS
NERVOUS SYSTEM	M91-604	30816	38	56	544	PSYCHOSIS
NERVOUS SYSTEM	M91-604	31407	44	36	1209	PSYCHOSIS
NERVOUS SYSTEM	M91-604	31411	33	unk	173	PSYCHOSIS
NERVOUS SYSTEM	M91-604	50604	36	48	898	PSYCHOSIS
NERVOUS SYSTEM	M92-813	4015	34	24	127	PSYCHOSIS
NERVOUS SYSTEM	M92-813	4015	34	24	163	PSYCHOSIS
NERVOUS SYSTEM	M92-813	4016	23	16	54	PSYCHOSIS
NERVOUS SYSTEM	M92-855	204	43	32	15	PSYCHOSIS
NERVOUS SYSTEM	M93-047	2308	35	unk	47	PSYCHOSIS
NERVOUS SYSTEM	M93-047	3607	39	36	334	PSYCHOSIS
NERVOUS SYSTEM	M93-090	11308	26	36	19	PSYCHOSIS
NERVOUS SYSTEM	M92-813	4704	39	32	134	PSYCHOTIC DEPRESSION
NERVOUS SYSTEM	M91-578	201	49	64	674	SOMNOLENCE
NERVOUS SYSTEM	M91-565	4024	28	20	19	SOMNOLENCE
NERVOUS SYSTEM	M92-873	30407	49	72	443	SOMNOLENCE
NERVOUS SYSTEM	M91-604	30102	45	72	316	SOMNOLENCE
NERVOUS SYSTEM	M91-604	50606	23	32	527	SOMNOLENCE
NERVOUS SYSTEM	M91-604	50814	38	36	478	SOMNOLENCE
NERVOUS SYSTEM	M91-604	52202	29	8	39	SOMNOLENCE

NERVOUS SYSTEM	M92-775	12002	37	30	47	SOMNOLENCE
NERVOUS SYSTEM	M92-873	70903	34	30	194	SOMNOLENCE
NERVOUS SYSTEM	M92-775	19013	49	18	16	SOMNOLENCE
NERVOUS SYSTEM	M92-813	1001	36	36	59	SOMNOLENCE
NERVOUS SYSTEM	M92-813	1513	22	40	130	SOMNOLENCE
NERVOUS SYSTEM	M92-813	1604	22	32	27	SOMNOLENCE
NERVOUS SYSTEM	M92-855	203	31	24	33	SOMNOLENCE
NERVOUS SYSTEM	M91-604	80302	27	80	342	SOMNOLENCE
NERVOUS SYSTEM	M93-092	2101	13	26	224	SOMNOLENCE
NERVOUS SYSTEM	M93-047	1402	22	24	18	SOMNOLENCE
NERVOUS SYSTEM	M93-065	2405	61	12	32	SOMNOLENCE
NERVOUS SYSTEM	M93-065	2803	18	64	396	SOMNOLENCE
NERVOUS SYSTEM	M93-090	10401	13	36	138	SOMNOLENCE
NERVOUS SYSTEM	M91-604	90409	13	12	141	SOMNOLENCE
NERVOUS SYSTEM	M91-604	31407	44	52	304	SPEECH DISORDER
NERVOUS SYSTEM	M92-813	4304	38	28	322	SPEECH DISORDER
NERVOUS SYSTEM	TIA/J/3/J	1609	34	20	101	SPEECH DISORDER
NERVOUS SYSTEM	M93-047	2803	29	24	9	STUPOR
NERVOUS SYSTEM	M90-481	7004	35	12	119	THINKING ABNORMAL
NERVOUS SYSTEM	M91-604	31005	58	48	344	THINKING ABNORMAL
NERVOUS SYSTEM	M91-604	31407	44	52	246	THINKING ABNORMAL
NERVOUS SYSTEM	M91-604	51405	45	40	615	THINKING ABNORMAL
NERVOUS SYSTEM	M92-813	703	23	44	180	THINKING ABNORMAL
NERVOUS SYSTEM	M92-813	1513	22	40	130	THINKING ABNORMAL
NERVOUS SYSTEM	M92-813	1604	22	32	27	THINKING ABNORMAL

NERVOUS SYSTEM	M92-873	30407	49	72	443	TREMOR
NERVOUS SYSTEM	M91-604	51406	55	56	247	TREMOR
NERVOUS SYSTEM	M92-873	71108	39	48	141	TREMOR
NERVOUS SYSTEM	M92-813	1111	43	64	113	TREMOR
NERVOUS SYSTEM	M92-813	1604	22	32	27	TREMOR
NERVOUS SYSTEM	M92-813	4304	38	28	322	TREMOR
NERVOUS SYSTEM	M91-604	80308	46	64	584	TREMOR
NERVOUS SYSTEM	M93-090	10401	13	36	138	TREMOR
NERVOUS SYSTEM	M91-604	90409	13	12	141	TREMOR
NERVOUS SYSTEM	M93-090	10603	41	24	142	TREMOR
NERVOUS SYSTEM	M93-047	3006	21	44	85	TWITCHING
NERVOUS SYSTEM	M93-065	2814	19	24	20	TWITCHING
NERVOUS SYSTEM	M91-604	50819	46	34	876	VERTIGO
NERVOUS SYSTEM	M91-604	52202	29	8	40	VERTIGO
RESPIRATORY SYSTEM	M91-604	80306	40	32	187	BRONCHITIS
RESPIRATORY SYSTEM	M90-481	5013	52	_	106	COUGH INCREASED
RESPIRATORY SYSTEM	M90-481	5013	52	_	106	DYSPNEA
RESPIRATORY SYSTEM	M92-775	13022	42	_	-33	HYPERVENTILATION
SKIN AND APPENDAGES	M91-604	30203	26	56	168	RASH
SKIN AND APPENDAGES	M91-604	31214	29	48	338	SWEATING
SKIN AND APPENDAGES	M91-604	31608	20	56	66	SWEATING
SKIN AND APPENDAGES	M91-603	12104	59	-	-43	SWEATING
UROGENITAL SYSTEM	M91-578	301	57	40	521	URINARY TRACT DISORDER

Appendix 7.3 Serious Adverse Events				
COSTART Body System		Phase II-III Studies	Placebo-Controlled Studies	
		Total N=(2468)	Tiagabine N=494	Placebo N=275
Body as a whole		225 (9)	11 (2)	10(4)
	Accidental injury	92 (4)	5 (1)	6 (2)
Cardiovascular		29 (1)	1 (<1)	2 (<1)
Digestive		55 (2)	5 (1)	4 (1)
Endocrine		3 (<1)	0	0
Hemic & Lymphatic		9 (<1)	1 (<1)	0
Laboratory		15 (<1)	3 (<1)	1
	Chemistry	8 (<1)	2 (<1)	1 (<1)
	Hematology	8 (<1)	1 (<1)	0
Metabolic & Nutritional		14 (<1)	2 (<1)	0
Musculoskeletal		16 (<1)	0	0
Nervous System		193 (8)	10 (2)	2 (<1)
	Asthenia	6 (<1)	-	-
	Confusion	31 (1)	-	-
	Depression	26 (1)	-	-
	Dizziness	20 (<1)	2 (<1)	1 (<1)
	Nervousness	5 (<1)	-	-
	Thinking Abnormal	8 (<1)	-	-
	Tremor	10 (<1)	1 (<1)	0
Respiratory		45 (2)	3 (<1)	2 (<1)
Skin		14 (<1)	1 (<1)	1 (<1)
Special Senses		3 (<1)	0	0
Urogenital		37 (1)	4 (<1)	1 (<1)

Appendix 8.b.1 Adverse Events for Which Two or More Tiagabine-Treated Patients Were Discontinued# Placebo-Controlled, Parallel-Group, Add-On Studies

Abbott + Results

Body System/ COSTART Term	Number (%) of Patients Discontinued with AE	
	Tiagabine (N=494)	Placebo (N=275)
Body as a Whole		
Abdominal Pain	3 (<1)	0
Chest Pain	2 (<1)	2 (<1)
Fever	2 (<1)	0
Infection	2 (<1)	0
Digestive System		
Anorexia	3 (<1)	0
Nausea	3 (<1)	1 (<1)
Vomiting	3 (<1)	1 (<1)
Nervous System		
Agitation	2 (<1)	1 (<1)
Asthenia	8 (2)	3 (1)
Ataxia	10 (2)	1 (<1)
Confusion	11 (2)	1 (<1)
Depression	4 (<1)	0
Diplopia	2 (<1)	1 (<1)
Dizziness	19 (4)	2 (<1)
Emotional Lability	2 (<1)	0
Hallucinations	2 (<1)	0
Headache	6 (1)	1 (<1)
Hostility	3 (<1)	0
Nervousness	5 (1)	1 (<1)
Paresthesia	2 (<1)	0
Somnolence	11 (2)	3 (1)
Speech Disorder	6 (1)	0
Thinking Abnormal	3 (<1)	0
Tremor	5 (1)	1 (<1)
Urogenital System		
Urinary Tract Infection	2 (<1)	0

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

Appendix 8.b.2 Adverse Events for Which ≥1% of Tiagabine-Treated Patients Were Discontinued and for Which the Incidence Was at Least Twice the Incidence of Placebo-Treated Patients#
Placebo-Controlled, Parallel-Group, Add-On Studies
Abbott + Results

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

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

Appendix 9.a.1.1 Incidence of Clinically Significant Blood Chemistry Abnormalities
Placebo-Controlled, Parallel-Group, Add-On Studies
Abbott Results

Chemistry Variable	Very Low (VL) and Very High (VH) Criteria	Number (%) of Patients Among Patients with Normal Baseline Values[1]	
		Tiagabine (N=417)	Placebo (N=198)
Glucose	VL $\leq$ 40 mg/dL	2/362 (<1)	2/180 (1)
	VH $\geq$ 175 mg/dL	3/362 (<1)	1/180 (<1)
Uric Acid	VH $\geq$ 10.5 mg/dL (male) VH $\geq$ 8.5 mg/dL (female)	0/318	0/158
BUN	VH $\geq$ 30 mg/dL	1/357 (<1)	0/180
Creatinine	VH $\geq$ 2 mg/dL	1/403 (<1)	0/197
Total Protein	VL $\leq$ 4.5 g/dL	0/380	0/191
	VH $\geq$ 10 g/dL	0/380	0/191
Albumin	VL $\leq$ 2.5 g/dL	1/401 (<1)	0/193
	VH $\geq$ 7.0 g/dL	0/401	0/193
Total Bilirubin	VH $\geq$ 2 mg/dL	0/404	0/196
Alkaline Phosphatase	VH $\geq$ 390 U/L	0/298	0/154
SGOT (AST)	VH $\geq$ 150 U/L	2/392 (<1)	0/188
SGPT (ALT)	VH $\geq$ 165 U/L	2/372 (<1)	0/179
LDH	VH $\geq$ 750 U/L	0/374	0/182
Sodium	VL $\leq$ 126 mEq/L	2/331 (<1)	0/161
	VH $\geq$ 156 mEq/L	1/331 (<1)	0/161
Potassium	VL $\leq$ 3 mEq/L	0/392	0/192
	VH $\geq$ 6 mEq/L	3/392 (<1)	0/192
Chloride	VL $\leq$ 90 mEq/L	4/366 (1)	1/178 (<1)
	VH $\geq$ 118 mEq/L	0/366	0/178
Bicarbonate	VL $\leq$ 10 mEq/L	0/372	0/185
	VH $\geq$ 45 mEq/L	0/372	0/185
Calcium	VL $\leq$ 8.2 mg/dL	19/389 (5)	8/185 (4)
	VH $\geq$ 12 mg/dL	0/389	0/185
Inorganic Phosphorus	VL $\leq$ 1.7 mg/dL	0/377	0/185
	VH $\geq$ 9 mg/dL	0/377	0/185
Cholesterol	VH $\geq$ 600 mg/dL	0/241	0/107

1 The denominator for each proportion is the number of patients with a normal baseline value for that variable, and at least one value after baseline.

Appendix 9.a.1.2 Incidence of Clinically Significant Blood Chemistry Abnormalities
Placebo-Controlled, Parallel-Group, Add-On Studies
Results

Chemistry Variable	Very Low (VL) and Very High (VH) Criteria	Number (%) of Patients Among Patients with Normal Baseline Values[1]	
		Tiagabine (N=77)	Placebo (N=77)
Glucose	VL $\leq$ 40 mg/dL	0/49	1/59 (2)
	VH $\geq$ 175 mg/dL	0/49	0/59
BUN	VH $\geq$ 30 mg/dL	0/68	0/70
Creatinine	VH $\geq$ 2 mg/dL	0/64	0/68
Total Protein	VL $\leq$ 4.5 g/dL	0/67	0/70
	VH $\geq$ 10 g/dL	0/67	0/70
Albumin	VL $\leq$ 2.5 g/dL	0/64	0/65
	VH $\geq$ 7.0 g/dL	0/64	0/65
Total Bilirubin	VH $\geq$ 2 mg/dL	0/66	0/66
Alkaline Phosphatase	VH $\geq$ 390 U/L	0/69	0/61
SGOT (AST)	VH $\geq$ 150 U/L	0/70	0/72
SGPT (ALT)	VH $\geq$ 165 U/L	0/58	0/61
GGT	VH $\geq$ 3 x ULN[2]	0/26	0/21
Sodium	VL $\leq$ 126 mEq/L	1/54 (2)	0/60
	VH $\geq$ 156 mEq/L	0/54	0/60
Potassium	VL $\leq$ 3 mEq/L	1/71 (1)	0/74
	VH $\geq$ 6 mEq/L	0/71	0/74
Calcium	VL $\leq$ 8.2 mg/dL	1/64 (2)	0/69
	VH $\geq$ 12 mg/dL	0/64	0/69

1 The denominator for each proportion is the number of patients with a normal baseline value for that variable, and at least one value after baseline.

2 ULN: Upper limit of normal.

Appendix 9.a.1.3 Incidence of Clinically Significant Blood Chemistry Abnormalities
Placebo-Controlled, Parallel-Group, Add-On Studies
Abbott + Results

Chemistry Variable	Very Low (VL) and Very High (VH) Criteria	Number (%) of Patients Among Patients with Normal Baseline Values[1]	
		Tiagabine (N=494)	Placebo (N=275)
Glucose	VL $\leq$ 40 mg/dL	2/411 (<1)	3/239 (1)
	VH $\geq$ 175 mg/dL	3/411 (<1)	1/239 (<1)
Uric Acid	VH $\geq$ 10.5 mg/dL (male)	0/318	0/158
	VH $\geq$ 8.5 mg/dL (female)		
BUN	VH $\geq$ 30 mg/dL	1/425 (<1)	0/250
Creatinine	VH $\geq$ 2 mg/dL	1/467 (<1)	0/265
Total Protein	VL $\leq$ 4.5 g/dL	0/447	0/261
	VH $\geq$ 10 g/dL	0/447	0/261
Albumin	VL $\leq$ 2.5 g/dL	1/465 (<1)	0/258
	VH $\geq$ 7.0 g/dL	0/465	0/258
Total Bilirubin	VH $\geq$ 2 mg/dL	0/470	0/262
Alkaline Phosphatase	VH $\geq$ 390 U/L	0/367	0/215
SGOT (AST)	VH $\geq$ 150 U/L	2/462 (<1)	0/260
SGPT (ALT)	VH $\geq$ 165 U/L	2/430 (<1)	0/240
GGT	VH $\geq$ 3 x ULN[2]	0/26	0/21
LDH	VH $\geq$ 750 U/L	0/374	0/182
Sodium	VL $\leq$ 126 mEq/L	3/385 (<1)	0/221
	VH $\geq$ 156 mEq/L	1/385 (<1)	0/221
Potassium	VL $\leq$ 3 mEq/L	1/463 (<1)	0/266
	VH $\geq$ 6 mEq/L	3/463 (<1)	0/266
Chloride	VL $\leq$ 90 mEq/L	4/366 (1)	1/178 (<1)
	VH $\geq$ 118 mEq/L	0/366	0/178
Bicarbonate	VL $\leq$ 10 mEq/L	0/372	0/185
	VH $\geq$ 45 mEq/L	0/372	0/185
Calcium	VL $\leq$ 8.2 mg/dL	20/453 (4)	8/254 (3)
	VH $\geq$ 12 mg/dL	0/453	0/254
Inorganic Phosphorus	VL $\leq$ 1.7 mg/dL	0/377	0/185
	VH $\geq$ 9 mg/dL	0/377	0/185
Cholesterol	VH $\geq$ 600 mg/dL	0/241	0/107

1 The denominator for each proportion is the number of patients with a normal baseline value for that variable, and at least one value after baseline.

2 ULN: Upper limit of normal.

Appendix 9.a.2.1 Incidence of Clinically Significant Hematology Abnormalities
Placebo-Controlled, Parallel-Group, Add-On Studies
Abbott Results

Hematology Variable	Very Low (VL) and Very High (VH) Criteria	Number (%) of Patients Among Patients with Normal Baseline Values[1]	
		Tiagabine (N=417)	Placebo (N=198)
Hemoglobin	VL $\leq$ 11.5 g/dL (males) $\leq$ 9.5 g/dl (females) VH $\geq$ 18.0 g/dL (males) $\geq$ 18.0 g/dL (females)	1/344 (<1) 0/344	1/164 (<1) 0/164
Hematocrit	VL $\leq$ 37% (males) $\leq$ 32% (females) VH $\geq$ 60% (males) $\geq$ 60% (females)	3/357 (<1) 0/357	1/177 (<1) 0/177
RBC	VL $\leq 3 \times 10^{12}$/L	0/310	0/159
Mean Cell Volume	VL $\leq$ 0.8 x LLN[2] VH $\geq$ 1.2 x ULN[2]	0/307 0/307	0/145 0/145
Mean Cell HGB Concentration	VL $\leq$ 0.8 x LLN[2] VH $\geq$ 1.2 x ULN[2]	0/262 0/262	0/126 1/126 (<1)
Platelets	VL $\leq 75 \times 10^9$/L VH $\geq 700 \times 10^9$/L	1/374 (<1) 0/374	0/188 0/188
WBC	VL $\leq 2.8 \times 10^9$/L VH $\geq 16 \times 10^9$/L	4/284 (1) 0/284	1/132 (<1) 0/132
Neutrophils	VL $\leq$ 15%	0/383	0/189
Lymphocytes	VH $\geq$ 75%	0/393	0/193
Monocytes	VH $\geq$ 15%	13/392 (3)	3/194 (2)
Eosinophils	VH $\geq$ 10%	9/391 (2)	4/189 (2)
Basophils	VH $\geq$ 10%	0/405	0/196
Bands	VH $\geq$ 10%	0/405	0/196
PT	VH $\geq$ 1.2 x ULN[2]	2/7 (29)	0/7
PTT	VH $\geq$ 1.2 x ULN[2]	1/4 (25)	0/3

1 The denominator for each proportion is the number of patients with a normal baseline value for that variable, and at least one value after baseline.

2 ULN: Upper limit of normal range. LLN: Lower limit of normal range.

Appendix 9.a.2.2 Incidence of Clinically Significant Hematology Abnormalities Placebo-Controlled, Parallel-Group, Add-On Studies Results

Hematology Variable	Very Low (VL) and Very High (VH) Criteria	Number (%) of Patients Among Patients with Normal Baseline Values[1]	
		Tiagabine (N=77)	Placebo (N=77)
Hemoglobin	VL $\leq$ 11.5 g/dL (males)	0/61	0/68
	$\leq$ 9.5 g/dl (females)		
	VH $\geq$ 18.0 g/dL (males)	0/61	0/68
	$\geq$ 18.0 g/dL (females)		
Hematocrit	VL $\leq$ 37% (males)	0/38	0/51
	$\leq$ 32% (females)		
	VH $\geq$ 60% (males)	0/38	0/51
	$\geq$ 60% (females)		
RBC	VL $\leq 3 \times 10^{12}$/L	0/55	0/58
Platelets	VL $\leq 75 \times 10^9$/L	0/71	0/72
	VH $\geq 700 \times 10^9$/L	0/71	0/72
WBC	VL $\leq 2.8 \times 10^9$/L	1/64 (2)	0/65
	VH $\geq 16 \times 10^9$/L	0/64	0/65
Neutrophils	VL $\leq$ 15%	0/64	0/64
Lymphocytes	VH $\geq$ 75%	0/54	0/66
Monocytes	VH $\geq$ 15%	1/63 (2)	1/65 (2)
Eosinophils	VH $\geq$ 10%	2/49 (4)	0/48
Basophils	VH $\geq$ 10%	0/57	0/59

1 The denominator for each proportion is the number of patients with a normal baseline value for that variable, and at least one value after baseline.

Appendix 9.a.2.3 Incidence of Clinically Significant Hematology Abnormalities Placebo-Controlled, Parallel-Group, Add-On Studies Abbott + Results

Hematology Variable	Very Low (VL) and Very High (VH) Criteria	Number (%) of Patients Among Patients with Normal Baseline Values[1]	
		Tiagabine (N=494)	Placebo (N=275)
Hemoglobin	VL $\leq$ 11.5 g/dL (males)	1/405 (<1)	1/232 (<1)
	$\leq$ 9.5 g/dl (females)		
	VH $\geq$ 18.0 g/dL (males)	0/405	0/232
	$\geq$ 18.0 g/dL (females)		
Hematocrit	VL $\leq$ 37% (males)	3/395 (<1)	1/228 (<1)
	$\leq$ 32% (females)		
	VH $\geq$ 60% (males)	0/395	0/228
	$\geq$ 60% (females)		
RBC	VL $\leq 3 \times 10^{12}$/L	0/365	0/217
Mean Cell Volume	VL $\leq$ 0.8 x LLN[2]	0/307	0/145
	VH $\geq$ 1.2 x LLN[2]		
Mean Cell HGB	VL $\leq$ 0.8 x LLN[2]	0/262	0/126
Concentration	VH $\geq$ 1.2 x LLN[2]	0/262	1/126 (<1)
Platelets	VL $\leq 75 \times 10^9$/L	1/445 (<1)	0/260
	VH $\geq 700 \times 10^9$/L	0/445	0/260
WBC	VL $\leq 2.8 \times 10^9$/L	5/348 (1)	1/197 (<1)
	VH $\geq 16 \times 10^9$/L	0/348	0/197
Neutrophils	VL $\leq$ 15%	0/447	0/253
Lymphocytes	VH $\geq$ 75%	0/447	0/259
Monocytes	VH $\geq$ 15%	14/455 (3)	4/259 (2)
Eosinophils	VH $\geq$ 10%	11/440 (3)	4/237 (2)
Basophils	VH $\geq$ 10%	0/462	0/255
Bands	VH $\geq$ 10%	0/405	0/196
PT	VH $\geq$ 1.2 x ULN[2]	2/7 (28)	0/7
PTT	VH $\geq$ 1.2 x ULN[2]	1/4 (25)	0/3

1 The denominator for each proportion is the number of patients with a normal baseline value for that variable, and at least one value after baseline.

2 ULN: Upper limit of normal range. LLN: Lower limit of normal range.

Appendix 9.c.1.1 Incidence of Clinically Significant Vital Sign Abnormalities Placebo-Controlled, Parallel-Group, Add-On Studies Abbott Results

Vital Sign Variable	Very Low (VL) and Very High (VH) Criteria	Number (%) of Patients Among Patients with Normal Baseline Values[1]	
		Tiagabine (N=417)	Placebo (N=198)
Systolic BP	VL $\leq$ 90 mm Hg and decreased $\geq$ 30 mm Hg from baseline	2/348 (<1)	1/174 (<1)
	VH $\geq$ 180 mm Hg and increased $\geq$ 40 mm Hg from baseline	0/348	0/174
Diastolic BP	VL $\leq$ 50 mm Hg and decreased $\geq$ 20 mm Hg from baseline	0/344	0/175
	VH $\geq$ 105 mm Hg and increased $\geq$ 30 mm Hg from baseline	0/344	0/175
Pulse	VL $\leq$ 50 bpm and decreased $\geq$ 30 bpm from baseline	0/359	0/181
	VH $\geq$ 120 bpm and increased $\geq$ 30 bpm from baseline	0/359	0/181
Temperature	VL decreased $\geq$ 2.5F from baseline	9/330 (3)	3/163 (2)
	VH $\geq$ 101.5F and increased $\geq$ 2.5F from baseline	0/330	0/163

1 The numerator and denominator were counted from post-randomization values associated with baseline which were within the lower and upper limits of normal, except for temperature, which had no normal limits.

Appendix 9.c.1.2 Incidence of Clinically Significant Vital Sign Abnormalities
Placebo-Controlled, Parallel-Group, Add-On Studies
Results

Vital Sign Variable	Very Low (VL) and Very High (VH) Criteria	Number (%) of Patients Among Patients with Normal Baseline Values[1]	
		Tiagabine (N=77)	Placebo (N=77)
Systolic BP	VL $\leq$ 90 mm Hg and decreased $\geq$ 30 mm Hg from baseline	0/62	0/67
	VH $\geq$ 180 mm Hg and increased $\geq$ 40 mm Hg from baseline	1/62 (2)	1/67 (1)
Diastolic BP	VL $\leq$ 50 mm Hg and decreased $\geq$ 20 mm Hg from baseline	0/56	0/65
	VH $\geq$ 105 mm Hg and increased $\geq$ 30 mm Hg from baseline	1/56 (2)	1/65 (2)
Pulse	VL $\leq$ 50 bpm and decreased $\geq$ 30 bpm from baseline	0/60	0/67
	VH $\geq$ 120 bpm and increased $\geq$ 30 bpm from baseline	0/60	0/67

1 The numerator and denominator were counted from post-randomization values associated with baseline which were within the lower and upper limits of normal.

Appendix 9.c.1.3 Incidence of Clinically Significant Vital Sign Abnormalities
Placebo-Controlled, Parallel-Group, Add-On Studies
Abbott - Results

Vital Sign Variable	Very Low (VL) and Very High (VH) Criteria	Number (%) of Patients Among Patients with Normal Baseline Values[1]	
		Tiagabine (N=494)	Placebo (N=275)
Systolic BP	VL $\leq$ 90 mm Hg and decreased $\geq$ 30 mm Hg from baseline	2/410 (<1)	1/241 (<1)
	VH $\geq$ 180 mm Hg and increased $\geq$ 40 mm Hg from baseline	1/410 (<1)	1/241 (<1)
Diastolic BP	VL $\leq$ 50 mm Hg and decreased $\geq$ 20 mm Hg from baseline	0/400	0/240
	VH $\geq$ 105 mm Hg and increased $\geq$ 30 mm Hg from baseline	1/400 (<1)	1/240 (<1)
Pulse	VL $\leq$ 50 bpm and decreased $\geq$ 30 bpm from baseline	0/419	0/248
	VH $\geq$ 120 bpm and increased $\geq$ 30 bpm from baseline	0/419	0/248
Temperature	VL decreased $\geq$ 2.5F from baseline	9/330 (3)	3/163 (2)
	VH $\geq$ 101.5F and increased $\geq$ 2.5F from baseline	0/330	0/163

1 The numerator and denominator were counted from post-randomization values associated with baseline which were within the lower and upper limits of normal, except for temperature, which had no normal limits.

Appendix 10.a.1 Treatment-Emergent Adverse Events Reported by ≥1% of Tiagabine-Treated Patients Placebo-Controlled, Parallel-Group, Add-On Studies Abbott Results

Body System/ COSTART Term #	Number (%) of Patients	
	Tiagabine (N=417)	Placebo (N=198)
Body as a Whole		
Abdominal Pain	34 (8)	5 (3)
Accidental Injury	70 (17)	40 (20)
Back Pain	8 (2)	2 (1)
Chest Pain	7 (2)	6 (3)
Fever	11 (3)	5 (3)
Flu Syndrome	34 (8)	12 (6)
Infection	52 (12)	30 (15)
Pain	19 (5)	6 (3)
Cardiovascular System		
Vasodilatation	8 (2)	3 (2)
Digestive System		
Anorexia	14 (3)	7 (4)
Constipation	6 (1)	6 (3)
Diarrhea	31 (7)	8 (4)
Dry Mouth	7 (2)	2 (1)
Dyspepsia	19 (5)	13 (7)
Increased Appetite	6 (1)	1 (<1)
Nausea	46 (11)	17 (9)
Nausea and Vomiting	5 (1)	3 (2)
Vomiting	27 (6)	10 (5)
Hemic and Lymphatic System		
Ecchymosis	6 (1)	1 (<1)
Musculoskeletal System		
Myalgia	10 (2)	10 (5)
Myasthenia	5 (1)	0
Twitching	6 (1)	3 (2)*
Nervous System		
Abnormal Gait	13 (3)	4 (2)
Agitation	5 (1)	1 (<1)
Amnesia	19 (5)	7 (4)
Anxiety	5 (1)	2 (1)
Aphasia	7 (2)	0
Asthenia	82 (20)	28 (14)

Appendix 10.a.1 Treatment-Emergent Adverse Events Reported by ≥1% of Tiagabine-Treated Patients Placebo-Controlled, Parallel-Group, Add-On Studies Abbott Results (Continued)

Body System/ COSTART Term #	Number (%) of Patients	
	Tiagabine (N=417)	Placebo (N=198)
Nervous System (Cont.)		
Ataxia	22 (5)	8 (4)
Confusion	17 (4)	8 (4)
Depression	14 (3)	1 (<1)
Diplopia	17 (4)	15 (8)
Dizziness	109 (26)	32 (16)
Emotional Lability	15 (4)	3 (2)
Headache	49 (12)	27 (14)
Hostility	10 (2)	2 (1)
Incoordination	8 (2)	5 (3)
Insomnia	23 (6)	6 (3)
Nervousness	47 (11)	6 (3)
Nystagmus	9 (2)	3 (2)
Paresthesia	16 (4)	3 (2)
Somnolence	79 (19)	29 (15)
Speech Disorder	17 (4)	5 (3)
Thinking Abnormal	29 (7)	5 (3)
Tremor	45 (11)	9 (5)
Respiratory System		
Cough Increased	18 (4)	7 (4)
Pharyngitis	27 (6)	9 (5)
Rhinitis	29 (7)	14 (7)
Sinusitis	7 (2)	5 (3)
Skin and Appendages		
Pruritus	8 (2)	1 (<1)
Rash	19 (5)	8 (4)
Special Senses		
Amblyopia	23 (6)	13 (7)
Conjunctivitis	6 (1)	2 (1)
Urogenital System		
Urinary Frequency	9 (2)	3 (2)
Urinary Tract Infection	9 (2)	4 (2)

Appendix 10.a.2 Treatment-Emergent Adverse Events Reported by ≥1% of Tiagabine-Treated Patients Placebo-Controlled, Parallel-Group, Add-On Studies Results

Body System/ COSTART Term #	Number (%) of Patients	
	Tiagabine (N=77)	Placebo (N=77)
Body as a Whole		
Abdominal Pain	1 (1)	3 (4)
Accidental Injury	6 (8)	10 (13)
Chest Pain	2 (3)	0
Flu Syndrome	3 (4)	9 (12)
Infection	11 (14)	11 (14)
Malaise	1 (1)	2 (3)
Pain	4 (5)	2 (3)
Cardiovascular System		
Palpitation	1 (1)	0
Syncope	1 (1)	0
Digestive System		
Cholecystitis	1 (1)	0
Constipation	2 (3)	2 (3)
Diarrhea	2 (3)	0
Dyspepsia	2 (3)	0
Flatulence	1 (1)	1 (1)
Gastroenteritis	4 (5)	6 (8)
Gastrointestinal Disorder	1 (1)	0
Increased Appetite	2 (3)	0
Mouth Ulceration	1 (1)	1 (1)
Nausea	9 (12)	8 (10)
Vomiting	5 (6)	1 (1)
Hemic and Lymphatic System		
Ecchymosis	1 (1)	2 (3)
Metabolic and Nutritional Disorder		
Hypoglycemia	1 (1)	0
Hypokalemia	1 (1)	0
Thirst	1 (1)	1 (1)
Weight Loss	2 (3)	0

Appendix 10.a.2 Treatment-Emergent Adverse Events Reported by ≥1% of Tiagabine-Treated Patients Placebo-Controlled, Parallel-Group, Add-On Studies Results (Continued)

Body System/ COSTART Term #	Number (%) of Patients	
	Tiagabine (N=77)	Placebo (N=77)
Musculoskeletal System		
Arthrosis	1 (1)	1 (1)
Joint Disorder	1 (1)	0
Myalgia	1 (1)	2 (3)
Myasthenia	1 (1)	0
Nervous System		
Agitation	1 (1)	0
Anxiety	1 (1)	2 (3)
Apathy	1 (1)	0
Aphasia	1 (1)	0
Asthenia	16 (21)	11 (14)
Ataxia	3 (4)	0
Confusion	5 (6)	0
Depression	3 (4)	1 (1)
Diplopia	5 (6)	5 (6)
Dizziness	22 (29)	8 (10)
Dry Mouth	1 (1)	0
Emotional Lability	1 (1)	1 (1)
Headache	15 (19)	12 (16)
Hostility	2 (3)	1 (1)
Hyperkinesia	1 (1)	0
Hypertonia	1 (1)	0
Insomnia	5 (6)	4 (5)
Nervousness	3 (4)	2 (3)
Paranoid Reaction	1 (1)	0
Paresthesia	2 (3)	1 (1)
Somnolence	11 (14)	13 (17)
Speech Disorder	3 (4)	0
Thinking Abnormal	1 (1)	1 (1)
Tremor	1 (1)	1 (1)
Vertigo	1 (1)	1 (1)

Appendix 10.a.2 Treatment-Emergent Adverse Events Reported by ≥1% of Tiagabine-Treated Patients Placebo-Controlled, Parallel-Group, Add-On Studies Results (Continued)

Body System/ COSTART Term #	Number (%) of Patients	
	Tiagabine (N=77)	Placebo (N=77)
Respiratory System		
Asthma	1 (1)	0
Cough Increased	1 (1)	1 (1)
Dyspnea	1 (1)	0
Laryngitis	1 (1)	0
Pharyngitis	6 (8)	1 (1)
Rhinitis	1 (1)	1 (1)
Sinusitis	1 (1)	3 (4)
Skin and Appendages		
Acne	3 (4)	2 (3)
Dry Skin	2 (3)	1 (1)
Maculopapular Rash	1 (1)	0
Pruritus	2 (3)	0
Rash	5 (6)	2 (3)
Urticaria	1 (1)	0
Special Senses		
Abnormal Vision	1 (1)	1 (1)
Amblyopia	1 (1)	0
Deafness	1 (1)	1 (1)
Eye Disorder	1 (1)	0
Tinnitus	1 (1)	0
Urogenital System		
Breast Pain	1 (1)	0
Cystitis	1 (1)	0
Metrorrhagia	1 (1)	0
Unintended Pregnancy	1 (1)	0
Urinary Frequency	1 (1)	2 (3)
Urinary Incontinence	1 (1)	1 (1)
Urinary Tract Infection	3 (4)	1 (1)

Appendix 10.a.3 Treatment-Emergent Adverse Events Reported by ≥1% of Tiagabine-Treated Patients Placebo-Controlled, Parallel-Group, Add-On Studies Abbott + Results

Body System/ COSTART Term #	Number (%) of Patients	
	Tiagabine (N=494)	Placebo (N=275)
Body as a Whole		
Abdominal Pain	35 (7)	8 (3)
Accidental Injury	76 (15)	50 (18)
Back Pain	8 (2)	4 (1)
Chest Pain	9 (2)	6 (2)
Fever	11 (2)	5 (2)
Flu Syndrome	37 (7)	21 (8)
Infection	63 (13)	41 (15)
Pain	23 (5)	8 (3)
Cardiovascular System		
Vasodilatation	8 (2)	3 (1)
Digestive System		
Anorexia	14 (3)	7 (3)
Constipation	8 (2)	8 (3)
Diarrhea	33 (7)	8 (3)
Dry Mouth	7 (1)	2 (<1)
Dyspepsia	21 (4)	13 (5)
Flatulence	5 (1)	2 (<1)
Gastroenteritis	6 (1)	7 (3)
Increased Appetite	8 (2)	1 (<1)
Mouth Ulceration	5 (1)	1 (<1)
Nausea	55 (11)	25 (9)
Nausea and Vomiting	5 (1)	3 (1)
Vomiting	32 (6)	11 (4)
Hemic and Lymphatic System		
Ecchymosis	7 (1)	3 (1)
Musculoskeletal System		
Myalgia	11 (2)	12 (4)
Myasthenia	6 (1)	0
Twitching	6 (1)	3 (1)

Appendix 10.a.3 Treatment-Emergent Adverse Events Reported by ≥1% of Tiagabine-Treated Patients Placebo-Controlled, Parallel-Group, Add-On Studies Abbott + Results (Continued)

Body System/ COSTART Term #	Number (%) of Patients	
	Tiagabine (N=494)	Placebo (N=275)
Nervous System		
Abnormal Gait	13 (3)	4 (1)
Agitation	6 (1)	1 (<1)
Amnesia	19 (4)	8 (3)
Anxiety	6 (1)	4 (1)
Aphasia	8 (2)	0
Asthenia	98 (20)	39 (14)
Ataxia	25 (5)	8 (3)
Confusion	22 (4)	8 (3)
Depression	17 (3)	2 (<1)
Diplopia	22 (4)	20 (7)
Dizziness	131 (27)	40 (15)
Emotional Lability	16 (3)	4 (1)
Headache	64 (13)	39 (14)
Hostility	12 (2)	3 (1)
Incoordination	8 (2)	5 (2)
Insomnia	28 (6)	10 (4)
Nervousness	50 (10)	8 (3)
Nystagmus	9 (2)	3 (1)
Paresthesia	18 (4)	4 (1)
Somnolence	90 (18)	42 (15)
Speech Disorder	20 (4)	5 (2)
Thinking Abnormal	30 (6)	6 (2)
Tremor	46 (9)	10 (4)
Respiratory System		
Cough Increased	19 (4)	8 (3)
Pharyngitis	33 (7)	10 (4)
Rhinitis	30 (6)	15 (5)
Sinusitis	8 (2)	8 (3)
Skin and Appendages		
Acne	5 (1)	3 (1)
Pruritus	10 (2)	1 (<1)
Rash	24 (5)	10 (4)

Appendix 10.a.3 Treatment-Emergent Adverse Events Reported by ≥1% of Tiagabine-Treated Patients Placebo-Controlled, Parallel-Group, Add-On Studies Abbott + . Results (Continued)

Body System/ COSTART Term #	Number (%) of Patients	
	Tiagabine (N=494)	Placebo (N=275)
Special Senses		
Amblyopia	24 (5)	13 (5)
Conjunctivitis	6 (1)	2 (<1)
Urogenital System		
Urinary Frequency	10 (2)	5 (2)
Urinary Tract Infection	12 (2)	5 (2)

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Appendix 10.d.1 Other Adverse Events Observed During the Premarketing Evaluation of Tiagabine

BODY AS A WHOLE : Frequent: Chills, Cyst, Malaise, Neck Pain, Reaction Unevaluable, Infrequent: Abscess, Aggravation Reaction, Allergic Reaction, Carcinoma, Cellulitis, Congenital Anomaly, Drug Interaction, Drug Level Increased, Face Edema, Halitosis, Hernia, Intentional Overdose, Lab Test Abnormal, Neck Rigidity, Neoplasm, Overdose, Pelvic Pain, Photosensitivity Reaction, Sepsis, Sudden Death, Suicide Attempt, Rare: Abdomen Enlarged, Abdominal Syndrome Acute, Accidental Overdose, Adenoma, Anticholinergic Syndrome, Chest Pain Substernal, Chills and Fever, Death, Gangrene, Generalized Edema, Hangover Effect, Injection Site Edema, Injection Site Hemorrhage, Injection Site Inflammation, Injection Site Pain, Injection Site Reaction, Mucous Membrane Disorder.

CARDIOVASCULAR SYSTEM : Frequent: Hypertension, Palpitation, Syncope, Infrequent: Angina Pectoris, Anisocoria, Arrhythmia, Cardiovascular Disorder, Cerebral Ischemia, Electrocardiogram Abnormal, Hemorrhage, Hypotension, Myocardial Infarct, Pallor, Peripheral Vascular Disorder, Phlebitis, Postural Hypotension, Tachycardia, Thrombophlebitis, Vascular Anomaly, Vascular Disorder, Rare: Arterial Thrombosis, Arteriosclerosis, Atrial Fibrillation, Bradycardia, Bundle Branch Block, Cerebrovascular Accident, Congestive Heart Failure, Coronary Artery Disorder, Deep Thrombophlebitis, Extrasystoles, Heart Arrest, Heart Failure, Intracranial Hemorrhage, Myocardial Ischemia, Pulmonary Embolus, Retinal Vascular Disorder, Subarachnoid Hemorrhage, Thrombosis, Varicose Vein, Ventricular Extrasystoles.

DIGESTIVE SYSTEM : Frequent: Gingivitis, Tooth Disorder, Infrequent: Abnormal Stools, Cholecystitis, Cholelithiasis, Dysphagia, Eructation, Esophagitis, Fecal Incontinence, Gastritis, Gastrointestinal Disorder, Gastrointestinal Hemorrhage, Glossitis, Gum Hemorrhage, Gum Hyperplasia, Hepatitis, Hepatomegaly, Increased Salivation, Liver Function Tests Abnormal, Melena, Periodontal Abscess, Rectal Disorder, Rectal Hemorrhage, Stomatitis, Thirst, Tongue Disorder, Tooth Caries, Ulcerative Stomatitis, Rare: Aphthous Stomatitis, Bloody Diarrhea, Cardiospasm, Cholangitis, Colitis, Duodenal Ulcer, Gastrointestinal Carcinoma, Hematemesis, Hemorrhagic Gastritis, Intestinal Obstruction, Intestinal Perforation, Jaundice, Liver Tenderness, Oral Moniliasis, Peptic Ulcer, Salivary Gland Enlargement, Stomach Ulcer, Tongue Discoloration, Tongue Edema, Tooth Discoloration, Tooth Malformation, Ulcerative Colitis.

ENDOCRINE SYSTEM : Infrequent: Goiter, Hypothyroidism, Rare: ADH Inappropriate, Adrenal Disorder, Diabetes Mellitus, Endocrine Disorder, Hyperthyroidism.

HEMIC AND LYMPHATIC SYSTEM : Frequent: Lymphadenopathy, Infrequent: Anemia, Erythrocytes Abnormal, Leukopenia, Petechia, Thrombocytopenia, Rare: Acute Leukemia, Antinuclear Antibody Present, Bleeding Time Increased, Cyanosis, Hemolytic Anemia, Hypochromic Anemia, Iron Deficiency Anemia, Lymphangitis, Lymphoma like Reaction, Macrocytic Anemia, Marrow Depression, Pancytopenia, Sedimentation Rate Increased, Spleen Disorder, Thrombocythemia.

METABOLIC AND NUTRITIONAL DISORDERS : Frequent: Edema, Peripheral Edema, Weight Gain, Weight Loss, Infrequent: Dehydration, Hypercholesteremia, Hyperglycemia, Hyperlipemia, Hypoglycemia, Hypokalemia, Hyponatremia, Thirst, Rare: Albuminuria, Alcohol Intolerance, Alkaline Phosphatase Increased, Avitaminosis, Bilirubinemia, BUN Increased, Creatinine Increased, Generalized Edema, Gout, Healing Abnormal, Hyperkalemia, Hyperuricemia, Hypocalcemia, Hypoglycemic Reaction, Hypoxia.

Appendix 10.d.1 Other Adverse Events Observed During the Premarketing Evaluation of Tiagabine (Continued)

MUSCULOSKELETAL SYSTEM : Frequent: Arthralgia, Infrequent: Arthritis, Arthrosis, Bone Disorder, Bone Pain, Bursitis, Generalized Spasm, Joint Disorder, Strabismus, Tendinous Contracture, Tendon Disorder, Tenosynovitis, Rare: Bone Necrosis, Extraocular Palsy, Myopathy, Osteomyelitis, Osteoporosis, Pathological Fracture.

NERVOUS SYSTEM : Frequent: Depersonalization, Dysarthria, Euphoria, Hallucinations, Hyperkinesia, Hypertonia, Hypesthesia, Hypokinesia, Migraine, Myoclonus, Personality Disorder, Reflexes Decreased, Stupor, Vertigo, Infrequent: Abnormal Dreams, Apathy, Choreoathetosis, Circumoral Paresthesia, CNS Neoplasia, CNS Stimulation, Coma, Convulsion, Delusions, Dry Mouth, Dyskinesia, Dystonia, Encephalopathy, Hemiplegia, Hypertension, Hypotonia, Increased Salivation, Leg Cramps, Libido Decreased, Libido Increased, Movement Disorder, Neuritis, Neurosis, Paralysis, Paranoid Reaction, Peripheral Neuritis, Psychosis, Psychotic Depression, Reflexes Increased, Sleep Disorder, Twitching, Urinary Retention, Rare: Abnormal Electroencephalogram, Addiction, Akathisia, Akinesia, Antisocial Reaction, Babinski Sign Positive, Brain Edema, Buccoglossal Syndrome, Catatonic Reaction, Cerebellar Ataxia, CNS Depression, Extrapyramidal Syndrome, Foot Drop, Hypalgesia, Hyperesthesia, Hysteria, Ileus, Intracranial Hemorrhage, Manic Reaction, Meningism, Meningitis, Mental Retardation, Neuralgia, Neuropathy, Oculogyric Crisis, Schizophrenic Reaction, Subdural Hematoma, Wrist Drop.

RESPIRATORY SYSTEM : Frequent: Bronchitis, Dyspnea, Epistaxis, Pneumonia, Infrequent: Apnea, Asthma, Hemoptysis, Hiccup, Hyperventilation, Laryngitis, Lung Disorder, Respiratory Disorder, Voice Alteration, Rare: Asphyxia, Hypoventilation, Lung Edema, Nasal Septum Disorder, Pleural Disorder, Pneumothorax, Pulmonary Infarct, Sputum Increased, Stridor.

SKIN AND APPENDAGES : Frequent: Alopecia, Sweating, Infrequent: Application Site Reaction, Contact Dermatitis, Dry Skin, Eczema, Exfoliative Dermatitis, Furunculosis, Hair Disorder, Herpes Simplex, Herpes Zoster, Hirsutism, Maculopapular Rash, Nail Disorder, Psoriasis, Skin Benign Neoplasm, Skin Carcinoma, Skin Discoloration, Skin Disorder, Skin Hypertrophy, Skin Nodule, Skin Ulcer, Subcutaneous Nodule, Urticaria, Vesiculobullous Rash, Rare: Fungal Dermatitis, Hair Discoloration, Melanosis, Petechial Rash, Pustular Rash, Seborrhea, Skin Melanoma.

SPECIAL SENSES : Frequent: Abnormal Vision, Ear Pain, Eye Disorder, Otitis Media, Tinnitus, Infrequent: Blepharitis, Blindness, Deafness, Dry Eyes, Ear Disorder, Eye Hemorrhage, Eye Pain, Hyperacusis, Keratoconjunctivitis, Lacrimation Disorder, Mydriasis, Otitis Externa, Parosmia, Photophobia, Taste Loss, Taste Perversion, Visual Field Defect, Vitreous Disorder, Rare: Cataract Specified, Chromatopsia, Corneal Lesion, Ophthalmitis, Partial Transitory Deafness, Pupillary Disorder, Refraction Disorder, Retinal Detachment, Scleritis, Vestibular Disorder.

Appendix 10.d.1 Other Adverse Events Observed During the Premarketing Evaluation of Tiagabine (Continued)

UROGENITAL SYSTEM : Frequent: Dysuria, Metrorrhagia, Urinary Incontinence, Vaginitis, Infrequent: Abortion, Amenorrhea, Breast Enlargement, Breast Pain, Cystitis, Dysmenorrhea, Endometrial Disorder, Fibrocystic Breast, Hematuria, Hypomenorrhea, Impotence, Kidney Failure, Menorrhagia, Menstrual Disorder, Nocturia, Papanicolau Smear Suspicious, Penis Disorder, Polyuria, Prostatic Disorder, Pyelonephritis, Salpingitis, Unintended Pregnancy, Urethritis, Urinary Tract Disorder, Urinary Urgency, Urine Abnormality, Vaginal Hemorrhage, Rare: Abnormal Ejaculation, Bladder Calculus, Breast Carcinoma, Breast Neoplasm, Cervicitis, Cervix Carcinoma In Situ, Cervix Disorder, Endometrial Carcinoma, Epididymitis, Female Lactation, Gynecomastia, Hemorrhagic Cystitis, Kidney Calculus, Kidney Pain, Menopause, Pregnancy Disorder, Prostatic Carcinoma, Testis Disorder, Urinary Retention, Urination Impaired, Uterine Disorder, Uterine Fibroids Enlarged, Uterine Hemorrhage.

Appendix 11.1 Drug (Tiagabine vs. Placebo) and Age Group (<65 vs. ≥ 65 yrs.) on Selected Adverse Experiences@ Abbott + Studies

		Incidence Rate: n (%)				Risk Ratios			C-M-H P-value	Estimate of Common Relative Risk		Breslow Day Homogeneity P-value
		Tiagabine (N=494)		Placebo (N=275)		RR_A	RR_B	RR_A/RR_B		Value	95% C.I.	
BODY AS A WHOLE	ABDOMINAL PAIN	35	(7.1)	8	(2.9)	2.720	0.0		0.015	0.380	0.175 - 0.827	0.220
DIGESTIVE SYSTEM	DIARRHEA	33	(6.7)	8	(2.9)	2.244			0.030	0.428	0.199 - 0.923	1.000
DIGESTIVE SYSTEM	INCREASED APPETITE	8	(1.6)	1	(0.4)	4.352			0.128	0.227	0.034 - 1.531	1.000
MUSCULOSKELETAL SYSTEM	MYASTHENIA	6	(1.2)	0	(0.0)				0.070	0.000		1.000
NERVOUS SYSTEM	AGITATION	6	(1.2)	1	(0.4)	3.264			0.244	0.304	0.041 - 2.256	1.000
NERVOUS SYSTEM	APHASIA	8	(1.6)	0	(0.0)				0.036	0.000		1.000
NERVOUS SYSTEM	ASTHENIA	98	(19.8)	39	(14.2)	1.403	0.0		0.059	0.677	0.451 - 1.016	0.351
NERVOUS SYSTEM	DEPRESSION	17	(3.4)	2	(0.7)	4.624			0.023	0.210	0.055 - 0.803	1.000
NERVOUS SYSTEM	DIZZINESS	131	(26.5)	40	(14.5)	1.799	3.6	0.5	0.000	0.471	0.320 - 0.693	0.500
NERVOUS SYSTEM	EMOTIONAL LABILITY	16	(3.2)	4	(1.5)	2.176			0.149	0.451	0.153 - 1.328	1.000
NERVOUS SYSTEM	HOSTILITY	12	(2.4)	3	(1.1)	1.995			0.161	0.424	0.128 - 1.405	0.332
NERVOUS SYSTEM	NERVOUSNESS	50	(10.1)	8	(2.9)	3.332			0.000	0.268	0.132 - 0.545	0.444
NERVOUS SYSTEM	PARESTHESIA	18	(3.6)	4	(1.5)	3.264	0.0		0.068	0.355	0.117 - 1.078	0.200
NERVOUS SYSTEM	SPEECH DISORDER	20	(4.0)	5	(1.8)	2.176			0.105	0.449	0.171 - 1.183	1.000
NERVOUS SYSTEM	THINKING ABNORMAL	30	(6.1)	6	(2.2)	2.720			0.017	0.353	0.150 - 0.830	1.000
NERVOUS SYSTEM	TREMOR	46	(9.3)	10	(3.6)	2.502			0.005	0.376	0.191 - 0.741	1.000
SKIN AND APPENDAGES	PRURITUS	10	(2.0)	1	(0.4)		0.0		0.045	0.101	0.011 - 0.946	0.019

@ Any adverse experience for which tiagabine incidence rate is greater than 1% and twice or more than placebo incidence rate. Adverse events for which overall incidence was statistically significantly higher for tiagabine than placebo also included..

RR_A : Relative Risk for patients <65 years - tiagabine rate in <65 yrs. patients / placebo rate in <65 yrs. patients.

RR_B : Relative Risk for patients ≥ 65 years - tiagabine rate in ≥ 65 yrs. patients / placebo rate in ≥ 65 yrs. patients.

Statistical Review and Evaluation

NDA#: 20-646

AUG 22 1997

Applicant: Abbott Laboratories

Drug: Gabitril™ (tiagabine)

Indication: Epilepsy

Documents reviewed: Vol. 2 of sponsor's response to October 31, 1996, approvable letter

Medical Reviewer: Bob Rappaport, M.D. (HFD-120)

Background

The sponsor has submitted a response to the October 31, 1996, approvable letter from the Medical Divsion, HFD-120. In the letter, the Division asked the sponsor to conduct additional analyses to support the indications of (1) partial seizures and (2) secondarily generalized seizures. The additional analyses of partial seizures involved two issues: (a) review of physician comments (verbatims) to determine whether or not under-reporting of partial seizures differed by treatment assignment and (b) re-analyses of data using only seizures with documented partial onset.

To support a claim for an effect on secondary generalization, the FDA asked the sponsor to perform an analysis looking at the (conditional) probability of experiencing a secondary generalized seizure following a partial onset seizure. As an illustration, the FDA suggested an analysis comparing the treatment groups on the proportion of patients experiencing a decrease from baseline to treatment in the percentage of partial onset seizures which secondarily generalize.

The above analyses were to be undertaken for M91-603, M91-605 and M92-775, the three parallel group placebo-controlled add-on trials in the original NDA submission.

Partial seizures: incomplete reporting

The sponsor reviewed case report forms from Trials 603, 605 and 775 with respect to investigator verbatims and the accuracy of seizure reporting. Appendix 1 summarizes entries mentioning "seizures or seizure-like activity" not recorded in patients' seizure diaries. Twenty-six (26) patients (21 tiagabine, 5 placebo) across the three studies had inaccurate reporting. Four of the 26 cases occurred during the Termination Period which was not included in the orginal efficacy analysis:

Table. Incomplete reporting of seizures:
Number of patients by study period

Drug	Period with incomplete reporting			Total
	Baseline	Experiment	Both	
Trial 603				
tiagabine	5	5	1	11
placebo	1	0	0	1
Trial 605				
tiagabine	1	3	0	4
placebo	0	1	1	2
Trial 775				
tiagabine	1	2	0	3
placebo	0	0	1	1

KEY: Seizure under-reporting favors: tiagabine placebo

A primary efficacy variable in all three trials was the (absolute) change from the Baseline Period to the Experiment Period in the 4-week partial seizure rate. Under-reporting of seizures during Baseline would make the drug (tiagabine or placebo) look worse than it should have. Under-reporting during the Experiment Period would make the drug look better. Thus the placebo group was favorably biased in 8 cases (lightly shaded cells in the Table) and tiagabine in 11 cases (heavily shaded cells). In 3 cases both periods were affected so the the overall effect was indeterminable (no shading). The sponsor concluded that "the difference of 3 cases favoring the tiagabine [sic] compared to placebo when nearly twice as many patients were exposed to the tiagabine [sic] compared to placebo justifies no need for reanalysis."

Reviewer comments

Obviously a complete assessment of bias requires not only knowledge of the direction of the change (favoring or not favoring a particular treatment group) but the magnitude of the change. Clearly the magnitude of the bias is not knowable here since in most instances physicians' notes

did not provide exact seizure counts for the incomplete data. One could impute nonzero quantities for the missing seizure counts. However, most of the verbatims are vague and contain scant information which might be used to produce estimates more reliable than the zero counts implied by the missing data. Nevertheless, the information is sufficient to cast serious doubt on any claim of systematic under-reporting of seizures, i.e., differential under-reporting with respect to treatment assignment.

Partial seizures: documented partial onset

The sponsor re-analyzed data from Trials 603, 605 and 775 using only seizures with documented partial onset. Appendix 2 lists patients whose partial seizure counts changed when only seizures with documented partial onset were used in the re-analyses. The sponsor cited p-value cutoffs only ($\leq .05$, $\leq .01$ or $\leq .001$) in their analyses and not specific p-values. They concluded that, in Trials 603 (32+56mg vs placebo) and 775, tiagabine was significantly more effective than placebo in reducing the median 4-week partial onset seizure rate. In Trial 605, the two pairwise comparisons between tiagabine and placebo did not reach statistical significance at .05.

Reviewer comments

This reviewer obtained the precise p-values to compare with p-values from the original submission. The Table below shows p-values from the statistical review of the original submission ("original") and from the analyses using only seizures with documented partial onset ("revised"). The two sets of p-values are virtually identical.

Table. Analyses of seizures with documented partial onset:
P-values for pairwise comparisons of tiagabine with placebo[a]

Target daily dose		16mg	30mg	32 mg		56 mg
Trial/regimen		qid	tid	16mg bid	8mg qid	qid
603	Original	.24			.018	<.001
	Revised	.29			.014	.001
605	Original			.097	.056	
	Revised			.084	.056	
775	Original		.019			
	Revised		.019			

[a] Reanalyses uses weighted van Eltern test, same statistical test used in original NDA submission

The virtual equality of the two sets of results is hardly surprising since only 16 patients out of 763 (2%) from the three trials had revised seizure counts, many of them trivial in nature.

Secondarily generalized seizures

The sponsor performed the conditional analysis described by the FDA in the approvable letter. According to the sponsor, "Insufficient data exists to support the indication for secondary generalized seizures as now defined by the Agency." (Vol 2, p. 009)

Conclusions

The re-analyses of partial seizure data do not alter the statistical results contained in the original submission.

J. Todd Sahlroot

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Mathematical Statistician

concur: Dr. Chi 5/25/97

cc: archive NDA 20-646
HFD-120
HFD-120/Dr. Leber
HFD-120/Dr. Katz
HFD-170/Dr. McCormick
HFD-344/Dr. Barton
HFD-120/Mr. Purvis
HFD-120/Ms. Ware
HFD-710/Dr. Chi
HFD-710/Dr. Sahlroot

Appendix 1

Investigator Comments Pertaining to Incomplete Reporting of Partial Seizures (Double-blind, Placebo-controlled, Parallel-group, Add-on Studies)

Study/Treatment Group/Patient No.	Baseline Period[a]	Treatment Period[a]	Termination Period
M91-603			
Placebo			
11101	(2.93)	(3.00)	2 seizures (unknown type) not recorded
12207	25 CP recorded on 8/6/92, comment is that it was "SECP" (62.53)	(50.09)	
16 mg			
11704	Estimated 60 seizures of unknown type over 2 weeks but none recorded (107.24)	(65.26)	
12007	(118.84)	1 month of SP record lost (85.50)	
12107	(66.74)	Had many seizures at school, only 2 CP recorded during titration, a second episode of "many SP" mentioned during maintenance but none were recorded (64.40)	
32 mg			
11009	(4.56)	No seizures recorded for 1 month (2.45)	
11109	No data for 2 weeks (4.07)	(1.89)	
11123	Estimate of 15-20 CP over 1 month but only 2 recorded (14.21)	(49.00)	
11220	(22.45)	2 SPCP recorded, had SECP (27.38)	
11706	(14.52)	(7.91)	No calendar for first part of termination
11707	(10.56)	(5.82)	
	< No CP counted in any phase, only SPCP >		
12109	Could not quantify 4 days of seizures (33.10))	(2.68)	

[a] 4-week rates of all partial seizures (with documented partial onset) shown in parentheses
Cross Reference Seizure, general comment fields and seizure counts from CRFs of M91-603, M91-605 and M92-775

Investigator Comments Pertaining to Incomplete Reporting of Partial Seizures (Double-blind, Placebo-controlled, Parallel-group, Add-on Studies)

Study Treatment Group Patient No.	Baseline Period[a]	Treatment Period[a]	Termination Period
M91-603 (Continued)			
56 mg			
10607	Clusters of CP not recorded because they could not be quantified (17.61)	(31.65)	
11705	(4.87)	No seizures for maintenance, diary was lost (1.19)	
M91-605			
Placebo			
10204	One "T" seizure was SECP (53.33)	One "T" seizure was SECP (54.65)	
11319	(109.00)	Increased seizures reported in comments, none recorded (57.93)	
8 mg QID			
10307	(11.56)	1 month of SP not recorded (10.87)	
10310	(19.19)	5 tonic seizures not recorded (24.00)	
16 mg BID			
10105	(23.48)	(11.33)	1 SP recorded on two days where seizures "lasted all day" in comments
10205	(12.28)	(25.85)	1 seizure (unknown type) not recorded
10617	(6.77)	Flurry of SP not recorded over one hour, could not count (10.77)	
10619	SP not recorded for early baseline (8.36)	(17.42)	

[a] 4-week rates of all partial seizures (with documented partial onset) shown in parentheses.
Cross Reference: Seizure, general comment fields and seizure counts from CRFs of M91-603, M91-605 and M92-775

Investigator Comments Pertaining to Incomplete Reporting of Partial Seizures (Double-blind, Placebo-controlled, Parallel-group, Add-on Studies)

Study/Treatment Group/Patient No.	Baseline Period[a]	Treatment Period[a]	Termination Period
M92-775			
Placebo			
19006	Seizures not recorded as faithfully for baseline and part of treatment period		
	(27.47)	(27.11)	
10 mg TID			
13006		No seizures recorded for 14 days	
	(61.32)	(67.78)	
14002	Lost seizure diary for part of baseline		
	(1.73)	(2.15)	
17007		Seizure accounting doubtful, time unclear but during treatment	
	(43.00)	(36.19)	

Cross Reference: Seizure, general comment fields and seizure counts from CRFs of M91-603, M91-605 and M92-775

Appendix 2

Patients Whose Partial Seizure Counts Changed
When Only Seizures with Documented Partial Onset Are Considered

Study / Treatment / Patient	- - - Partial Seizure Counts Which Have Changed - - - - Baseline Period - - - -Counts- Old	New	Reason Changed@	- - - Treatment Period - - -Counts- Old	New	Reason Changed@
M91-603						
16 mg						
10704	22	14	8 GTC seizures inappropriately coded as PGTC	28	19	9 GTC seizures inappropriately coded as PGTC
12008	20	18	2 GTC seizures inappropriately coded as PGTC			
12013	24	23	1 GTC seizure inappropriately coded as PGTC			
12216	123	114	9 GTC seizures inappropriately coded as PGTC	122	120	2 GTC seizures inappropriately coded as PGTC
32 mg						
11601	237	234	3 GTC seizures inappropriately coded as PGTC	219	218	1 GTC seizure inappropriately coded as PGTC
12215	381	370	11 GTC seizures inappropriately coded as PGTC	350	337	13 GTC seizures inappropriately coded as PGTC
56 mg						
11104	19	11	8 GTC seizures inappropriately coded as PGTC	13	12	1 GTC seizure inappropriately coded as PGTC

@ GTC = code for generalized tonic-clonic seizure;
PGTC = code for partial generalized tonic clonic seizure;
SEGTC = code for status epilepticus generalized tonic-clonic seizure.

Patients Whose Partial Seizure Counts Changed
When Only Seizures with Documented Partial Onset Are Considered

Study / Treatment / Patient	- - - Partial Seizure Counts Which Have Changed - - - - Baseline Period - - - -Counts- Old	New	Reason Changed@	- - - Treatment Period - - -Counts- Old	New	Reason Changed@
M91-605						
Placebo						
10807	25	23	2 GTC seizures inappropriately coded as PGTC			
12705	104	34	70 GTC seizures inappropriately coded as PGTC	94	26	68 GTC seizures inappropriately coded as PGTC
8 mg QID						
10902	24	23	1 GTC seizure inappropriately coded as PGTC			
11604				2	1	1 GTC seizure inappropriately coded as PGTC
12606	12	11	1 GTC seizure inappropriately coded as PGTC			
16 mg BID						
10808	41	29	12 GTC seizures inappropriately coded as PGTC	3	2	1 GTC seizure inappropriately coded as PGTC
12119	31	28	1 SEGTC seizure (assigned a partial seizure count of 3) inappropriately included in partial seizure count			

@ GTC = code for generalized tonic-clonic seizure;
PGTC = code for partial generalized tonic clonic seizure;
SEGTC = code for status epilepticus generalized tonic-clonic seizure.

Patients Whose Partial Seizure Counts Changed When Only Seizures with Documented Partial Onset Are Considered

Study / Treatment / Patient	- - - Partial Seizure Counts Which Have Changed - - - - Baseline Period - - - -Counts- Old	New	Reason Changed@	- - - - Treatment Period - - -Counts- Old	New	Reason Changed@
M91-605						
16 mg BID						
12701	19	17	2 GTC seizures inappropriately coded as PGTC	21	14	7 GTC seizures inappropriately coded as PGTC
M92-775						
Placebo						
12013				154	153	1 GTC seizure inappropriately included in partial seizure count

@ GTC = code for generalized tonic-clonic seizure;
PGTC = code for partial generalized tonic clonic seizure;
SEGTC = code for status epilepticus generalized tonic-clonic seizure.