7.1.2 Other Serious Adverse Events

Prior Submissions
In previous submissions, the sponsor did not present a comprehensive analysis of serious adverse events (SAEs), but instead presented separate analyses for hospitalizations, cancer diagnoses, status epilepticus events, events leading to disability, life threatening events, overdose events, and congenital anomalies. While these separate presentations included the adverse events that are captured by the regulatory definition of SAEs, the format of these presentations precluded calculation of overall SAE risks. In the following sections, I will summarize the data from prior submissions for hospitalizations, events resulting in disability, and life threatening events. I will not separately present information for overdose events, cancer diagnoses, or congenital malformations as part of the SAE section, but I will cover these events in later sections of this review.

NDA and NDA Amendment (Cutoff date 12/31/95)

For the pooled US epilepsy studies (controlled and uncontrolled), the sponsor reported that 18.7% (83/443) of vigabatrin exposed subjects were hospitalized. The most common reasons for hospitalization were convulsions (5.2%, 23/443), convulsions grand mal (2.7%, 12/443), and confusion and depression (1.1%, 5/443 each). In the pooled primary non-US epilepsy studies, 5.2% (39/765) of vigabatrin subjects were hospitalized. (Source Amendment review, p.25). The sponsor did not identify any events leading to disability or that were life threatening for the primary data group.

In the US controlled epilepsy studies, 6.8% (15/222) of vigabatrin subjects were hospitalized compared to 0.7% (1/135) of placebo subjects (Source: Amendment review, p.25). The most notable difference in risk for AEs leading to hospitalization in these studies was for convulsions/convulsions grand mal. In the US controlled studies 3.6% of vigabatrin subjects were hospitalized for convulsions/convulsions grand mal compared to 0.7% (1/135) of placebo subjects. The AEs leading to hospitalization for vigabatrin subjects are included in the table below.

Table 7.1. AEs that Led to Hospitalizations for US Controlled Epilepsy Trials in Original 1994 NDA Submission Study Patient AEs that led to hospitalization

Subject	AE(s) leading to Hospitalization
Study 71754-3-C-024	
054-003	Pneumonia, Sepsis, Fever
061-004	Convulsion
061-006	Vomiting
Study 71754-3-C-025	
010-111	Convulsions
011-104	Depression
013-008	Convulsions Grand Mal
013-011	Depression
069-003	Convulsions Grand mal, Personality Disorder, Convulsions

071-001	Emotional Lability, Personality Disorder, Psychosis, Suicide Attempt, Therapeutic Response Increased
071-004	Convulsions Grand Mal, Pneumonia, Stupor
071-007 (Placebo)	Convulsions
071-010	Bronchitis, Confusion, Convulsions, Fever
072-006	Convulsions
072-012	Hypertension
073-012	Pneumonia
089-003	Convulsions Grand Mal

Source: Ovation response to Division Questions, 4/15/08, p. 147

For primary non-US controlled trials, the comparisons made between vigabatrin and placebo groups are difficult to interpret because 6 of the 9 studies included in this group used a crossover design and only one of these studies included a washout period prior to crossover, potentially complicating classification of exposure at the time of the event (Source: Amendment review, pp.20-22).

The sponsor reported in the NDA Amendment that 51 vigabatrin exposed subjects from the secondary data group (5.3%, 51/968) were hospitalized. The most common reasons for hospitalization were from the CNS and psychiatric body systems. The sponsor noted that the non-CRF studies did not routinely capture hospitalizations and the only hospitalization reported for the non-CRF group was seizure related (Source: Amendment review, pp. 26-7). The sponsor did not identify any events leading to disability or that were life threatening for these groups.

In the NDA Amendment the sponsor identified 45 vigabatrin treated subjects from compassionate use programs that were hospitalized. The most common reasons for hospitalization for this group were psychosis (n=7), seizure (n=6), and status epilepticus (n=5). The group also included hospitalizations for an allergic skin rash (subject VGST SW01JA), for exfoliative erythematous rash (VGST MUMF-330) and hepatic and renal insufficiency (VGST MUMF 343).

In the NDA Amendment the sponsor identified 284 post marketing reports of patients that were hospitalized. Psychosis was the most commonly reported reason for hospitalization. Eight patients were hospitalized for hepatic injury (Source: Amendment review, pp.27-28).

The sponsor identified 14 eye-related events leading to disability from spontaneous reports, and 9 of these involved visual field loss. After visual events, the next most commonly identified event resulting in disability was behavioral event (event terms of psychosis and aggression) (Source Final Safety Update, p.5).

In the NDA Amendment, the sponsor identified 18 post marketing patients that experienced life threatening adverse events. The majority of these events were seizure related. In addition, the sponsor identified an event of hepatic failure. The patient (report #VGZ-9400-7742) developed fulminant hepatic failure and hepatic coma and was hospitalized. The patient received a liver transplant. The discharge summary for this patient noted that the event was "thought to be drug

induced, secondary to a recent anti-epileptic drug trial with vigabatrin." The patient was also taking gabapentin prior to the event (Source: Amendment review, p.33).

The sponsor reported that a 28 year old female patient (report number VGZ-9500-4387) with a history of elevated liver enzymes temporally related to treatment with carbamazepine and valproate, developed elevated liver enzymes with vigabatrin. A liver biopsy found mild acute and chronic inflammatory cell infiltrate and hepatic bridging necrosis, findings felt to be consistent with drug induced hepatitis. This patient's transaminases reportedly normalized after discontinuation of vigabatrin (Source Amendment review, p.33).

The sponsor also reported that a male pediatric patient (report number VGZ-9500-3964) was treated with vigabatrin for almost 1 year and developed elevated transaminases, prolonged PT and PTT, and coma. The sponsor stated that the patient did not die but admitted that follow up data was not available (Source Amendment review, p.34).

The sponsor identified 3 reports of feeding disorders in patients (7 months, 10 months, unknown) treated for infantile spasms. These patients stopped feeding within 24 hours of the first dose of vigabatrin, and two of the infants were given tube feedings. The reported noted that feeding improved in all three cases after vigabatrin was stopped (Source Amendment review, p.34).

Safety Update (1/1/96-3/15/97)

In the Safety update, the sponsor reported that the integrated (through 3/15/97) hospitalization risk for US epilepsy studies was 20.2% (285/1,409) compared to 9.2% (185/1,975) for non-US primary epilepsy studies. The most common reasons for hospitalizations for both groups were convulsions (US 3.5%, 49/1,409; non-US 2.2%, 44/1,975) and convulsions grand mal (US 4%, 56/1,409; non-US 1.4%, 27/1,975) (Source Final Safety Update Review, p.5).

For the combined data from controlled epilepsy trials presented in the safety update, the sponsor reported that 7.5% of vigabatrin and 2.2% of placebo exposed subjects were hospitalized. When examining the reasons for hospitalization, the most glaring disparity between vigabatrin and placebo was for convulsions. The sponsor reported that 3% (29/969) of vigabatrin subjects but only 0.4% (2/491) of placebo subjects were hospitalized for convulsions (Source Final Safety Update Review, p.5).

The sponsor identified a subject from an ongoing clinical trial that experienced an adverse event that led to disability. This subject experienced decreased vision that was diagnosed as macular degeneration (Source: Final Safety Update, p.5).

In the Safety Update, the sponsor presented all identified life threatening events from all sources. For the combined data the sponsor identified 47 vigabatrin exposed individuals with life threatening events. The most commonly reported life threatening events were increase in seizure frequency (n=12) and suicide attempt (n=9).

Current Submission

Overall Safety Population (3/16/97-6/30/07)

Ovation presented the SAEs pooled from 13 of the 15 safety update studies. The SAEs from the remaining 2 Current submission studies (0098 and 4021) were presented separately due to data quality issues (inconsistent capture of subject numbers or date of birth- 12/28/07 submission, p.77). The 13 studies included in the pooled SAE analyses included 1,299 subjects.

Ovation provided table 4.1.5.4 (p.7323) that summarized the SAEs for the pooled Safety Update population. Ovation reported that 44% (570/1,299) of subjects in the pooled analysis experienced one or more SAEs. The complete list of SAEs is included as an appendix to this review. In the following table, I present the SAEs reported by at least 1% of the Safety Update population.

SAEs Occurring in at Least 1% of Vigabatrin Exposed Subjects, Current Submission

SAE	% (n)
Visual field defect	26% (335)
Convulsion	2.8% (36)
Hemianopia	2.5% (32)
Status epilepticus	1.9% (24)

In response to a Division request, Ovation re-examined their database and identified 12 additional subjects with SAEs that were not included in the above analysis. The SAEs reported for these subjects were VFD (n=9), seizure (n=2), and abnormal behavior, dysarthria, convulsion, and cognitive disorder (Source 5/1/08 submission, pp.138-9).

In addition to identifying the common SAEs, I reviewed table 4.1.5.4 to identify less frequent, but potentially concerning SAEs. I summarize those findings below.

Four subjects had SAEs of rash, 2 had rash maculopapular, 1 had leukocytoclastic vasculitis, and 1 had Stevens Johnson syndrome. The narratives for the SAEs coded as Rash and one of the narratives for an SAE coded as rash maculopapuar described events that did not appear to be SAEs (subject was not hospitalized, event was not described as life threatening, etc.). When asked why these events were classified as SAEs, Ovation reported that the events were coded as SAEs by the previous sponsor and had no further explanation. The subject with an SAE of Stevens Johnson syndrome was also taking lamotrigine and carbamazepine at the time of the event and the narrative suggested that the patient experienced another occurrence suspicious for Stevens Johnson syndrome 3 months after discontinuing vigabatrin, factors suggesting that vigabatrin was not causally related to the event. Narratives for the remaining rash maculopapular SAE and the leukocytoclastic vasculitis SAE are provided below and narratives for the rest of the skin related SAEs are included in an appendix to this review.

Rash maculopapular

Subject 0201/1386-0002 This 14-year old female Caucasian with a history of complex partial seizures was hospitalized for increased seizure frequency. The subject was also noted to have a bilateral extremity erythematous

rash with crusts and excoriation that was described as moderate intensity. The subject was discontinued from the study. The narrative provides no diagnosis for the rash and does not indicate how the rash was treated. The rash was decreased when the subject was discharged from the hospital.

Leucocytoclastic vaculitis

Subject 0223/1480-0005 This 57 year old Caucasian female with a history of simple partial seizures, complex partial seizures and partial generalized seizures experienced leukocytoclastic vasculitis and shortness of breath while on vigabatrin. Subject was on vigabatrin for 23 days prior to the events. On [redacted] the subject noted a rash (described as bilateral petechia of the lower extremities) on the back of her legs (more severe on the left leg) which worsened the next day. Subject also complained of shortness of breath and wheezing. She took two of her husband's nitroglycerin tablets to relieve the shortness of breath. The outcome of the events was not provided but the subject was hospitalized due to the events. The physical and neurological exams were unremarkable. Lab and x-ray results were not provided. A dermatologist diagnosed leukocytoclastic vasculitis as 'commonly seen' in drug-type reactions. The intensity of the reaction was considered moderate, with a duration of four days. The event resolved. Vigabatrin was discontinued on 28Feb1996 due to the events. Medical history included renal failure, arthritis, left hip fracture 1995, hysterectomy due to carcinoma and fibroids with chemotherapy treatment, carpal tunnel syndrome of the right hand and release, poor memory and drug allergy to Feldene. Concomitant medications included Dilantin, Tegretol, Tylenol, Aleve, Didronel, aspirin, Premarin, Nitrostat and calcium carbonate.. b(6)

Two subjects had SAEs of acute renal failure, and 1 subject had SAEs of glomerulonephritis and proteinuria. One of the renal failure SAEs was attributed to dehydration and the subject's renal function improved with rehydration. The second renal failure SAE occurred in a 13 year old male during hospitalization for encephalitis and the subject's renal function improved with continued vigabatrin treatment. One subject experienced SAEs of proteinuria and glomerulonephritis. The narrative did not provide a clear diagnosis or etiology for these events. I provide excerpts from the narrative summary for the subject with proteinuria and glomerulonephritis below and for the 2 renal failure SAEs in an appendix to this review.

Proteinuria/Glomerulonephritis

Subject 1A/269 [redacted] This Caucasian male born on [redacted] was enrolled on 23Apr99 weighing 10.4 kilograms. The subject was assigned to the low-dose group and began vigabatrin on [redacted] for infantile spasms. Vigabatrin was dosed at 1500 mg/day until decreased to 500 mg/day on [redacted] b(6)

On [redacted] he experienced an SAE (seriousness criteria unknown) described as decreased blood albumin lasting 1 day. He recovered from the SAE with no sequelae and the relationship to study drug was judged as unlikely. There were no related AEs.

On [redacted] he experienced an SAE (seriousness criteria unknown) described as proteinuria lasting 1 day. He recovered from the SAE with no sequelae and the relationship to study drug was judged as not related. He had 3 related AEs including proteinuria of unknown intensity on [redacted] continuing to study completion. Treatment was 'Other' and the investigator assessed the AE as not reasonably attributable to vigabatrin. He also had mild kidney biopsy on [redacted] Treatment was 'None', the outcome was 'Recovered' and the investigator assessed the AE as not reasonably attributable to vigabatrin. He had mild hypoalbuminemia on [redacted] continuing to study completion. Treatment was 'Other' and the investigator assessed the AE as not reasonably attributable to vigabatrin. b(6)

On [redacted] he experienced an SAE described as focal glomerulonephritis continuing to study completion. The relationship to study drug was judged as not related. He had 5 related AEs including moderate nephrotic syndrome on [redacted] continuing to study completion. Treatment was 'Hospitalization' and the investigator assessed the AE as not reasonably attributable to vigabatrin. He also had mild hypertension for less than 1 week on [redacted] Treatment was 'Other', the outcome was 'Recovered' and the investigator assessed the AE as not reasonably attributable to vigabatrin. He had moderate peripheral edema for 1 week on [redacted] Treatment was b(6)

'Hospitalization', the outcome was 'Recovered' and the investigator assessed the AE as not reasonably attributable to vigabatrin. He had moderate nephrogenic anemia on [redacted] continuing to study completion. Treatment was 'Other', and the investigator assessed the AE as not reasonably attributable to vigabatrin. He had moderate anemia for 2 weeks on [redacted] Treatment was 'Other', the outcome was 'Recovered' and the investigator assessed the AE as not reasonably attributable to vigabatrin. Although there were 2 adverse events resulting in hospitalization (nephrotic syndrome and peripheral edema), these were not reported as an SAE by the investigator. b(6)

Concomitant AEDs included phenobarbital, prednisolone, methylprednisolone, furosemide, and clorazepate. Other concomitant medications included albumin iv, amoxicillin, aspirin, captopril, cefotaxime, Epogen, general anesthesia, albumin iv 25%, Lasix iv, sedation iv, Kayexalate, Mylicon, Pedialyte, Pepcid, prednisone, Solu-Medrol, calcium carbonate, Tranxene, Tylenol, Xylocaine, and Zithromax.

Two subjects had anemia SAEs and one subject had an SAE of decreased platelet count. One anemia SAE was attributed to epistaxis but the narrative and CRF included few details for this event. The narrative for the other anemia event did not provide sufficient information to characterize the event. The narrative for the decreased platelet count SAE attributed the event to vigabatrin. I provide the 2 anemia narratives and the decreased platelet count narrative below.

Anemia

0101/Subject 13300001 This 26 year old female with a history of partial complex seizures and anemia requiring iron replacement had an AE of anemia while being treated with vigabatrin. The subject discontinued and the narrative reported that the CRF documented the outcome of the anemia AE was study drug discontinued but other "notes" document that the subject voluntarily withdrew from the study. Tegretol was listed as the concomitant medication. The narrative did not provide any additional relevant details. To look for additional information about this event, I reviewed the subject's CRF. Interestingly, this subject's baseline medical history sheet included several AEs that were handwritten while anemia and post seizure headache entries were typed. Similarly, the "notes" that report the patient requested to drop from the study (ex. CRF page 105) were typed while most other CRF entries are handwritten. The CRF noted that the week 0 visit (beginning of titration) was 4/95. The labs from 3/95 (baseline) included a hemoglobin of 12.1mg/dL with a WBC of 9,400/mm3 and a platelet count of 241,000/mm3. The following table summarizes hematology related labs for this subject from study visits.

Date	Hemoglobin (g/dL)	WBC (/mm3)	PLT (/mm3)
6/95	11.2	4,500	250
11/95	10.3	10,100	228
6/96	11.4	6,100	210

CRF page 90 reports that the date of last vigabatrin dose received was 4/24/96. The lab result sheet from 11/95 included a handwritten request for a repeat CBC, in addition to iron and total iron binding capacity tests but results for these tests were not included in the CRF.

Subject 4020/00150039 This 17 year old male with a history of epilepsy was enrolled in Study 4020 and randomized on 8/25/99. The subject began vigabatrin 3000 mg daily treatment on an unknown date in Jul97 (this study of VFD included patients with previous vigabatrin exposure). The subject voluntarily withdrew from the study and was lost to follow-up. His last study visit was on 04Dec00, and at that time vigabatrin treatment was ongoing. The subject experienced a serious adverse event of anemia (acute anemia due to epistaxis) of unspecified severity on an unknown date in Nov00. The clinical investigator assessed the event as unrelated to vigabatrin treatment. The subject was treated with blood transfusion auxiliary products and recovered from the event. The CRF did not include a history of bleeding diathesis or any laboratory results for this subject.

Additional medical history was not provided. Concomitant antiepileptic medications at the time of the event included Lamictal. The narrative reported no additional concomitant medications but the CRF noted the subject was taking "depakine".

Decreased Platelet Count

Subject 0242/15430003 This 22 year old female subject with a history of seizures and headaches discontinued from a trial after 18 months of treatment with vigabatrin due to decreased platelet count. In a previous trial (0223) this subject had two platelet counts of 160 and 166 (Hgb 12.7 and 12.8, and WBC count 4.4 and 5.2). Platelets in December of 1997 were 128,000, Jan 23, 1998 they were 98,000 and Jan 30, 1998 they were 16,000. Work up included a bone scan with biopsy, CT scan, and HIV testing which were all negative. The patient was observed and then discharged home 2 days later. Two days afterward she was re-admitted for 4 days and was started on prednisolone. Doses ranged from 20 mg/d to 80 mg/d ultimately stabilizing at 40 mg/d which is her current dose. Study drug was stopped. The intensity of this event was considered severe by the investigator and the investigator felt the causality to be definitely related to study drug. The subject was lost to follow up. Concomitant medications included advil, neurontin, vitamin E, and oral contraceptive (Genora). I reviewed the CRF provided for this subject and it did not contain any lab results. I then proceeded to the study report for this study and found a listing of lab results for this subject. I summarize some of the hematology lab results from the study report in the table below.

Date	PLT (/mm3)	Hemoglobin (g/dL)	WBC (/mm3)
8/22/96 (Baseline)	170	12.8	5
11/19/95	228	12.9	5.8
2/12/97	159	12.9	4.2
9/4/97	97	12.9	6.7
12/11/97	123	13.1	7
2/26/98	76	13.6	15.5
4/7/98	182	15	8.6

The lab results in the study report did not correlate with the results provided in the narrative.

Three subjects had SAEs of respiratory failure and one of respiratory arrest. These respiratory SAEs all occurred in infantile spasms patients. The narratives for these events provided too few clinical details to allow assessment of potential causes of these events. I provide those narratives below.

Respiratory arrest

Subject 1A/112 [redacted] This Caucasian female born on [redacted] was enrolled on [redacted] at Site 1 weighing [redacted] kilograms. The subject was assigned to the low-dose group and began vigabatrin on [redacted] for infantile spasms. Vigabatrin was dosed at 250 mg/day, increasing to 375 mg/day on 30 Oct96, to 625 mg bid on 08Jan98, and finally decreased to 500 mg bid on 11Mar98. b(6)

On [redacted] the subject experienced an SAE described as respiratory arrest, ending on the same day. Non-drug therapy was administered (details not provided), outcome was listed as recovered with no sequelae, and the relationship to study drug was judged as not related. Seriousness criteria for the SAE was not specified. However an adverse event of mild drug hypersensitivity was also reported on 2 occasions on [redacted], one of these events was life-threatening (but not reported as an SAE). Both events continued to study completion. The investigator assessed the events as not reasonably attributed to vigabatrin. Treatment was 'Other,' but no details were provided. b(6)

Concomitant AEDs included clonazepam and topiramate. Other reported concomitant medications included albuterol, Auralgan otic, baby lax, Bactroban, Cefzil, Decadron, Donatussin, Murine eye drops, Mylanta, Phenergan, Poly-DM, Tylenol, and Ventolin.

Subject 1A-209 This Caucasian male born on [redacted] was enrolled on [redacted], weighing [redacted] kilograms. The subject was assigned to the low-dose group and began vigabatrin on 27Sep96 for infantile spasms. Vigabatrin was dosed at 250 mg/day, increased to 1250 mg/day on 25Oct96, to 1750 mg/day on 23Nov96, to 2500 mg/day on 03Feb97, and finally decreased to 2000 mg/day on 21Nov97. This subject experienced several SAEs during the study including pneumonia, ear infection, hydrocephalus, gastrointestinal disorder, b(6)

On [redacted] he experienced an SAE lasting 2 days while hospitalized described as cardio-respiratory. The outcome was recovered with no sequelae and the relationship to study drug was assessed as not related. He had 2 temporally related AEs including severe cardiorespiratory arrest for 2 weeks on [redacted] Treatment was 'Hospitalization', the outcome was 'Recovered' and the investigator assessed the AE as not reasonably attributable to vigabatrin. He also had severe ventriculoperitoneal shunt malfunction for 2 weeks on [redacted] Treatment was 'Hospitalization', the outcome was 'Recovered' and the investigator assessed the AE as not reasonably attributable to vigabatrin. Although the 2 adverse events resulted in hospitalization, they were not reported as SAEs by the investigator. b(6)

On [redacted] he experienced an SAE described as respiratory arrest, ending the same day, and was hospitalized. The outcome was recovered with no sequelae and the relationship to study drug was assessed as not related. There were no related AEs.

Subject 1A-658 This male (Race = 'Other') born on [redacted] was enrolled on [redacted] weighing [redacted] kilograms. The subject was assigned to the high-dose group and began vigabatrin on [redacted] for infantile spasms. Vigabatrin was dosed at 750 mg/day, decreasing to 500 mg/day on [redacted], and finally to 250 mg/day on [redacted] b(6)

On [redacted], he experienced an SAE described as respiratory arrest lasting 1 day and was hospitalized. He recovered with no sequelae and the relationship to study drug was assessed as not related. He also had moderate convulsion for 1 week on [redacted] with seriousness listed as 'Life-Threatening', but treatment was 'None'. The outcome was 'Recovered' and the investigator assessed the AE as not reasonably attributed to vigabatrin.

Concomitant AEDs included phenobarbital and lorazepam. There were no other concomitant medications reported.

Respiratory Failure

Subject 1A/103 This 2 year and 8- month old Caucasian male, weight [redacted] kilograms, with a history of infantile spasms, complex partial seizures, partial seizures with generalization, tonic seizures and myoclonic seizures experienced respiratory failure. The subject had been on vigabatrin for approximately two years when the respiratory failure occurred. Vigabatrin dose was 1500mg/day at the time of the event. The subject was admitted for respiratory insufficiency secondary to tonsillar enlargement and a tonsillectomy and adenoidectomy. The investigator assessed the event of respiratory failure as not related to vigabatrin. Severity was not provided; no action was taken. The outcome was "other." Concomitant medications included Topamax 62.5mg TID. The subject terminated from the study because he was "spasm free" with last dose of drug on [redacted] b(6)

Ovation reported SAEs of drug hypersensitivity, hypersensitivity, and tongue edema. The narrative for the drug hypersensitivity event mentions an "itchy rash", along with swelling of the lips and tongue, findings suspicious for angioedema. The narrative for the tongue edema event provided insufficient clinical details to evaluate the event. The hypersensitivity event was not described in detail but the narrative reported that the patient was rechallenged with vigabatrin without recurrence. I provide the narratives for the drug hypersensitivity event below and for the hypersensitivity and tongue edema events in an appendix to this review.

Drug Hypersensitivity

Subject R003/0405-011 This 32 year old Caucasian female with a history of simple partial, complex partial and secondary generalized seizures experienced drug hypersensitivity, diagnosed as allergic reaction with lips, tongue and gums swelling and a generalized itchy rash, while on vigabatrin 1000 mg/day. The subject's tongue swelled after the first dose of study medication (evening of [redacted], and treatment consisted of Benadryl 100 mg. After the second dose (morning of [redacted], the subject experienced lips and gum swelling and a generalized red itchy rash and she was treated with another dose of Benadryl 100 mg. Later that same day [redacted], she was given one dose of Reactine 20 mg. Study drug was discontinued and the subject was withdrawn from the study due to this event. On [redacted] her symptoms were resolved somewhat and she was given Solu-Medrol 125 mg IV, Benadryl 50 mg IV and prednisone 50 mg daily (for two days). The drug hypersensitivity symptoms gradually resolved b(6)

(unknown date in [redacted] without sequelae. The investigator assessed that the drug hypersensitivity was related to study medication and was moderate in intensity. Seriousness criteria were assessed as medically important. Medical history included numerous drug allergies, depression, feelings of anxiety, suicidal thoughts, fractured right wrist and left ankle 1991, right temporal lobectomy, use of glasses or contact lenses, nonsmoker, no alcohol use. Concomitant medications included valproic acid, Neurontin, clobazam, and lorazepam. b(6)

Ovation identified psychiatric SAEs of hallucination, hallucination auditory, hallucination visual, and suicide attempt. The description of the hallucination SAE is included in the narrative describing the rash SAE (subject 0118/1272-0002), in an appendix to this review. I provide summaries for the hallucination auditory, hallucination visual, and suicide attempt SAEs below.

Hallucination visual

Subject R003/0405-001 This 50 year old Caucasian female with a history of simple partial, complex partial, and secondary generalized seizures experienced visual hallucinations and restless legs syndrome while on vigabatrin 1000 mg/day. The subject also experienced affective disorder (diagnosed as severe mood disorder/depression with symptoms of labile mood, sleep disturbance and emotional change). These three events occurred 23Dec2000, which was 11 days after the first dose of study medication. The subject was withdrawn from the study 31Dec2000 due to the affective disorder, visual hallucinations, and restless legs syndrome. The events resolved without sequelae on 11Jan2001 without countermeasures. The investigator judged that the visual hallucination and restless legs syndrome were related to study medication and were moderate in intensity. Seriousness criteria was assessed as medically important for these three symptoms. Concomitant medications included phenytoin, oxcarbamazepine, Apo-Salvent, Atrovent, Cefprozil, and Flovent.

Hallucination auditory

Subject 0201/1387-0002 This 73 pound, 8 year old, Caucasian female with a history of complex partial seizures experienced depression on two occasions, suicidal ideation, auditory hallucination and headache. The patient entered a previous double-blind vigabatrin epilepsy clinical study on 13Jul1995 and received placebo until 5Oct1995. The patient entered this study on 5Oct1995 and received vigabatrin (15 mL BID; 20, 40, 60 or 80 mg/mL) during the 4 week double-blind dose adjustment phase and then entered the open-label phase of the study on 7Nov1995 at which time the subject was receiving 15 mL BID (60 mg/mL = 1.8 gm/day). On 01Nov1995, the subject experienced symptoms of depression and suicidal thoughts. Three weeks later, the subject experienced auditory hallucinations. Length of time on study drug in relation to event onset could not be determined due to the study being blinded at the time of the events.

Lab results included carbamazepine level (08Dec1995) of 6.0, and valproic acid level (08Dec1995) of 62. b(6)

On [redacted] the subject was admitted to the hospital for a psychological evaluation.

The subject reported to her mother that she had wanted to hurt herself and her mother, and heard voices. The subject was maintained on her usual dose of divalproex and carbamazepine; her vigabatrin was decreased to 600 mg BID (10ml BID; 60mg/ml), and she responded well to the decrease of vigabatrin with no seizure activity noted. The subject was discharged from the hospital on [redacted]. The subject underwent individual and family therapy. The event of auditory hallucination resolved 3 weeks after onset and the events of depression and suicidal ideation resolved 6 weeks after onset. The investigator assessed that the depression, suicidal ideation and auditory hallucinations were moderate in intensity and definitely related to study medication. Treatment information was not provided. Concomitant medications included Advil 1-2 tablets PRN, hydrocortisone cream 0.05% PRN, Depakote 250 mg BID, Depakote 375 mg QHS, and Tegretol 100 mg TID. b(6)

On 20Sep1996, the subject experienced depression and headache while on vigabatrin TID a (total of 25 mL (10-5-10) per day at 60 mg/mL). Length of time on study drug in relationship onset could not be determined due to the study being blinded at the time of the initial events. The subject was hospitalized for observation and treatment. Treatment received was ibuprofen, paracetamol and Tylenol 3. The events did not resolve and the investigator

deemed that no follow-up was necessary. However, the events were still under treatment. The investigator assessed the events of depression and headache as moderate in intensity and unlikely related to study drug. An alternative etiology provided was stress at home and school. Concomitant medications at the time of the depression and headache included ibuprofen, Advil 1-2 tablets PRN, hydrocortisone cream 0.05% BID, Depakote 125 mg BID, and Depakote 250 mg QHS.

Medical history included oligodendroglioma at age six associated with mild memory problems, learning difficulties, sleepiness, tiredness and headaches. The subject rolled over into the 098 study.

Suicide attempt

Subject 0223/1669-0001 This 49 year old Caucasian male with a history of simple partial seizures and complex partial seizures experienced depression and suicide attempt while on vigabatrin. Subject was on vigabatrin for 18 days prior to the events. On 17Jun1996 the subject became depressed due to family conflicts. On 18Jun1996, the subject appeared to be more severely depressed and was not able to go to work. On [redacted], the subject attempted suicide, incurred no physical harm to self and was hospitalized in the evening for suicidal tendency and observation. Date of last dose of study medication was on 18Jun1996. Subject was hospitalized for 10 days and discharged on [redacted]. Subject was instructed to follow-up with a psychiatrist, continue medications, limit stress, limit time in the sunshine and eat a regular diet. The investigator assessed the events as possibly related to study medication and severe in intensity. The subject was discontinued from the study due to the events and the events resolved. Medical history included depression, hypertension, kidney stones, red and green color deficiency and left lobectomy 1990. Subject experienced gingival hyperplasia with Dilantin. Concomitant medications included Dilantin, Neurontin, Phenobarbital, Dynacin, Metoprolol, allopurinol, Toprol XL and Cozaar.

b(6)

One subject had an SAE coded as psychotic disorder but Ovation explained that this event was miscoded. The subject (4020/0021-0064) actually experienced an SAE of hemianopia heteronymous with "psychogenic AE" listed as an alternative etiology (Source 3/14/08 submission).

One subject had SAEs of hepatic failure and hepatic necrosis and these events were discussed above with the deaths (narrative is included in an appendix to this review).

SAEs in Studies 0098 and 4021

As noted above, Ovation presented these SAEs separately from the pooled safety data in the current submission due to data quality issues (inconsistent capture of subject numbers or date of birth- 12/28/07 submission, p.77). In these 2 studies there were 151 subjects experiencing 1 or more SAEs. The SAEs reported by at least 5 subjects were visual field defect (n=38), convulsion (n=27), status epilepticus (n=14), chest pain (n=8), and pneumonia (n=7).

In response to a Division request, Ovation re-examined their database and identified 16 additional subjects from study 0098 with 17 SAEs not included in the above analysis. Ovation provided 16 narratives describing these 17 SAEs. The SAEs reported for these subjects were VFD (n=6), increased seizure frequency, basal cell carcinoma, basal call carcinoma recurrence, acute cholecystitis, COPD exacerbation, psychosis, hysterectomy for menometrorrhagia, degenerative arthritis of the ankle, MVA with L3 fracture, left carotid cavernous fistula following surgery for pituitary adenoma, and ACL rupture following fall (Source 5/1/08 submission, pp.163-213).

I reviewed table 2.1 (pp. 11197-11241) to identify less frequently occurring but potentially concerning SAEs from studies 0098 and 4021. The list included 3 subjects with suicide attempts, 2 subjects with psychotic disorder, 1 subject with a rash (that resolved with discontinuation of lamotrigine), and 1 subject with ITP/anemia. I provide summaries for these events below. There were no SAEs of acute hepatic failure, acute renal failure, pancreatitis, aplastic anemia, Stevens Johnson syndrome, Toxic epidermal necrolysis, or hypersensitivity reported for these studies.

Suicide attempt

Subject 1216-0009 This 55 year old Caucasian male with a history of complex partial seizures and partial generalized seizures was hospitalized due to a suicide attempt by cutting wrists, ataxia, mental slowing, dysarthria and depression while on vigabatrin. Subject was on vigabatrin for four years prior to the events. Family noted subject, who lives in a group home, to be dysarthric, ataxic, and intermittently confused. Blood level testing, on an unspecified date, suggested probable overdose due to increased phenytoin and phenobarbital levels. On 29Aug1997, the subject, in a somewhat confused state of mind and depressed about his inability to function more independently cut his wrists. (Two months prior to this event, the subject suffered a leg fracture. The subject subsequently had to go to rehabilitation due to the fracture and was upset with going to rehabilitation). Subject was hospitalized [redacted] and evaluated by psychiatry. They felt his suicide attempt was not well-thought out and subject's depression was no longer present. Also, they thought that the toxicity from his drugs may have played a role in his suicide attempt and they did not feel that he needed any supervision for suicidal risk. Phenytoin level was 17 and phenobarbital level was 40 on an unspecified date. It was also thought that his intermittent adverse events might be due to Mysoline (primidone) and an attempt was made to reduce his dose to 250 mg BID. Following this reduction the subject had several seizures and the Mysoline was increased back to TID. Vigabatrin therapy continued unchanged. After stabilization, subject was discharged to a chronic care facility and the events were considered resolved. The investigator considered the event of suicide attempt by cutting wrists as not related to vigabatrin but possibly related to the subject being upset over rehabilitation or the possibility of toxicity from phenytoin or primidone. Subject has no history of depression or psychiatric disorders. Medical history included tonsillectomy, constipation, rectal polyps and hemorrhoids, acne, ankle fracture and right-sided partial seizures since age 17. Concomitant medications included phenytoin and Mysoline. b(6)

Subject 1316-0009 (AVENTIS-050523-0000857) This 23 year old male subject with a history of epilepsy experienced a suicide attempt (jumped from bridge), sustained an open compound tibia and fibula fracture of right leg, and L2 vertebrae compression fracture (due to the injury accident) [redacted] while on vigabatrin 3 gm/day. The subject was on vigabatrin for one year and six months. He was out with a friend, became depressed about his epilepsy condition and under the influence of alcohol, jumped off a bridge approximately 17 feet high. The subject was brought to the emergency room and was found to have an open fracture of the right lower extremity and a nonoperative L2 compression fracture. He underwent a right tibia/fibula I&D (incision and drainage), external fixation after reduction for a right grade 2 open tibia/fibula fracture which was well tolerated. Treatment medications included morphine, heparin, clindamycin, levofloxacin, and Vicodin. Vigabatrin therapy remained unchanged. A psychiatry consult evaluated that this subject was not at risk for further suicide attempts and that this current episode was not a suicide attempt. Psychiatry also felt that this subject needed no further psychiatric care but did need to participate in an alcohol rehabilitation program. The subject recovered in 12 days [redacted]. The investigator assessed the events as not related to study medication, but rather associated with depression due to the subject's epilepsy condition. Medical history was not provided. Concomitant medication included lamotrigine, lorazepam, clonazepam, and ethanol. b(6)

Subject 1204-0008 (AVENTIS-050523-0000832) This 26 year old female with a history of simple and complex partial seizures experienced increase in seizures and was hospitalized on [redacted] while on vigabatrin 3 gm/day. The subject was taken off Paxil and prescribed Prozac (dates not provided). The investigator assessed that the increase in seizures was not related to the vigabatrin, and an alternative etiology was Paxil usage, which was exacerbating her seizures. On [redacted] the subject was hospitalized for the event of worsening depression. The depression continued to worsen and on [redacted] the subject overdosed on 75.5 mg of lorazepam and alcohol. According to the subject's mother, the subject ingested 151 0.5- milligram tablets in an apparent suicidal gesture and b(6)

was admitted to the medical floor. On [redacted] the subject left the hospital on her own; however she was located by the police on the same day and was subsequently admitted to the psychiatric floor. Admission plans included individual psychotherapy, medication management and a more structured educational program regarding interactions. The subject recovered and was discharged to her apartment with follow- up care provided by her neurologist and psychiatrist. The investigator assessed that the worsening major depression and suicidal gesture **were not related to vigabatrin but instead associated with the subject's underlying history of depression, job loss and** seizures. Vigabatrin ultimately was discontinued on 15Aug1997 since Topamax was an exclusionary concomitant medication. b(6)

Psychotic disorder

Subject 1250-0006 (AVENTIS-050523-0001211) This 38 year old female with a history of complex partial seizures with rare secondary generalization experienced psychosis and bipolar affective disorder while on vigabatrin. Subject was on vigabatrin ranging from 2 grams to 6 grams/day for 3 years and 21 days prior to the events. The subject was on vigabatrin 6 grams/day at the time of the event. The subject had no prior psychiatric history, but began exhibiting bizarre and manic behavior. On [redacted] the subject, while in church, began lifting her dress in front of the congregation and caused a commotion. The next evening, she **rode her bicycle to her mother's apartment complex,** took off all her clothes and ran around screaming and yelling about God and sex. Police and paramedics arrived. The subject was combative, incoherent and had to be physically restrained. She was taken to the Emergency Room and a complete medical work up was performed. The subject experienced a seizure and after her post- ictal state subsided, she continued to exhibit pronounced manic symptoms. She spoke rapidly and incoherently. Subject remained agitated and was kept in four point restraints. Urine toxicology screen was negative. Phenytoin serum levels were within normal limits upon hospital admission. Subject denied suicidal or homicidal ideations or thoughts of impending doom. On [redacted] subject was discharged from the hospital with a discharge diagnosis of bipolar affective disorder with psychosis. Prozac and Depakote were added to her medication regime. Vigabatrin dosing was continued at 6 grams/day unchanged. The event was considered to be resolved. The investigator assessed the events as not related to vigabatrin but rather to an idiopathic cause since the subject had been on vigabatrin for slightly more than 3 years at the time of event onset. Medical history included hypertension. Concomitant medication included phenytoin, hydrochlorothiazide, and enalapril. b(6)

Subject 1265-0004 (AVENTIS-050523-0001487, AVENTIS-050523- 0002241)
This 32 year old male was hospitalized due to psychotic thoughts and post ictal psychotic disorder. Subject was on vigabatrin for at least three years five months prior to the event of psychotic thoughts. Subject presented to the **emergency room stating that he was "not being able to get thoughts out of my head, feel like I want to hurt young people, feel like devils are working against the left side of my head". Subject had experienced these thoughts off and** on for a several months. The subject described the feeling on the left side of his head as a pressure that was not painful, but felt sometimes as if the pressure was strong enough to push through his left eye and he expressed that sometimes he wanted to take his left eye out. Vital signs and neurological exam were normal. Mental status examination revealed; subject was pleasant, calm and cooperative. Good eye contact and impulse control. Speech was normal rate, tone and volume; however, he appeared to have difficulty expressing himself. Mood was worried. Affect was restricted. Thought processes were circumstantial and tangential. No paranoia. Denied auditory and visual hallucinations. Subject appeared delusional about the evil force in his head. Denied suicidal thoughts but did confirm homicidal thoughts toward kids but was rather vague and had no plan. The subject did express that he was angry sometimes with the way that kids treated their parents or upset that they were using drugs and felt that he would like to show them how to live a better way. **Subject was able to spell the word "WORLD" forward and** backward. Subject was oriented to person, place and time. Subject was able to name presidents back to Ford. Memory was 3/3 at zero minutes, 3/3 at five minutes. Intelligence was average. Judgment and insight were poor. Upon admission to the hospital unit, the subject was pleasant and cooperative and did not appear to be responding to any internal stimuli. Study drug remained unchanged due to the event. The event resolved without sequelae. He had a history of depression, without prior hospitalizations, and was treated with fluoxetine for the first time a few months ago. The investigator assessed the psychotic thoughts as not related to study drug and indicated fluoxetine as suspect.

Six months later, the subject was hospitalized for post ictal psychotic disorder related to temporal lobe epilepsy. Subject was on vigabatrin for at least four years prior to the event. Action taken was not provided. The event resolved without sequelae and the subject was discharged five days later. The investigator assessed the event as not related. An alternative etiology provided was underlying seizure. Relevant medical history included left temporal lobectomy 1988, motor vehicle accident 1985. Concomitant medications included carbamazepine, fluoxetine, olanzapine, naproxen and ibuprofen.

Rash

Subject 1202-0006 (AVENTIS-050523-0000941) This 48 year old female with a history of complex partial seizures with secondary generalization experienced an acute extensive rash on face and arms [redacted] while on vigabatrin 5 gm/day. The subject was on study medication for three years and thirteen days. The site examined the subject and felt that the rash appeared typical for cutaneous reaction to lamotrigine. **Due to the subject's social status and fearing that the discontinuance of lamotrigine would worsen the subject's poor seizure control, the subject was** prophylactically admitted to the hospital. The rash started one day prior to the hospital admission. The subject was loaded with phenytoin and put on seizure monitoring. The seizures were well controlled with the addition of phenytoin (serum phenytoin 06Dec: 13.7; serum phenytoin 07Dec: 17.3). The rash was treated with oral Benadryl (diphenhydramine) and lamotrigine taper. The event abated and the subject was discharged [redacted] with a diagnosis of skin rash secondary to lamotrigine. Vigabatrin continued unchanged. The investigator assessed the event as not related to vigabratin but rather to lamotrigine. Medical history included mental retardation and chronic static encephalopathy. Concomitant medications included lamotrigine, diazepam, Docusate, sorbitol, multivitamin, Dyazide and Lescol. b(6)

ITP/Anemia

Subject 1234-0016 (AVENTIS-050523-0000652, AVENTIS-050523- 0000753, AVENTIS-050523-0000769, AVENTIS-050523-0000902) This 45 year old female with a history of complex partial and simple partial seizures experienced hypotension (50/40 mmHg), anemia and idiopathic thrombocytopenia (platelet count 6,000 uL) and was admitted to the hospital through the emergency room on [redacted] after two years and three months on vigabatrin therapy. Treatment included packed RBCs and platelets. The vigabatrin dose was 4.5 gm/day. The events were resolving. The investigator assessed these events as unlikely related to vigabatrin therapy; an alternative explanation was stated as undefined underlying disease. b(6)

Pediatric Subpopulation (non IS, age 3-<16)

Ovation reported that 141 pediatric subjects from the Overall Safety Population experienced SAEs (32.4%, 141/435; note-total does not include pediatric subjects from trials 0098 and 4021 because the SAEs from these trials were presented separately- see above; Source 12/28/07 submission, p.144). The percentage of pediatric subjects with SAEs (32%) was slightly lower than the percentage reported for the Overall population (44%) in the current submission. The SAEs reported for at least 1% of pediatric subjects were visual field defect (20.2%, 88/435), convulsion (3.5%, 15/435), hemianopia (3%, 13/435), and status epilepticus (1.8%, 8/435). Less frequently reported SAEs of special interest included 3 pediatric subjects with depression, 1 with suicidal ideation, 1 with hallucination, 1 with hallucination auditory, 1 subject with a rash, 1 with rash maculopapular, 1 with Stevens Johnson syndrome and 1 with acute renal failure. There were no SAEs of suicide, suicide attempt, acute hepatic failure, pancreatitis, aplastic anemia, or hypersensitivity reported for the pediatric subjects in the included studies.

IS Subpopulation

Ovation reported that 34% (75/223) of IS subjects in the Overall Safety Population experienced one or more SAEs (Source 12/28/07 Submission, p.166). The SAEs reported by at least 1% of subjects in the IS subpopulation were status epilepticus (4.9%, n=11), pneumonia (4.5%, n=10),

pyrexia (2.7%, n=6), convulsion (2.2%, n=5), bronchospasm (1.8%, n=4), viral infection (1.8%, n=4), and gastroesophageal reflux disease (1.4%, n=3), dehydration (1.4%, n=3), vomiting (1.4%, n=3), respiratory arrest (1.4%, n=3), lobar pneumonia (1.4%, n=3) and infantile spasms (1.4%, n=3).

SAEs Integrated Data

Ovation provided SAE risks by submission and combined for the development program studies. **Those risks are included in the table below. The "Prior" column of the table includes information** from US, primary non-US, and secondary studies through the 1998 Safety Update (3/1/07 **submission, p.194). The "Current"** column of the table includes information from the studies in this submission except for studies 0098 and 4021, which were reported separately (3/1/07 submission, p.193). The following table includes the SAEs that were reported for more than one subject.

SAEs Reported by More than One Subject, Integrated Data

Event Category Adverse Event	Prior Data (N=3440) % (n)	Current Data (N=1297) % (n)	Combined (N=4737) % (n)
Any SAE	10.7% (369)	43.7% (567)	19.8% (936)
Blood and Lymphatic Disorders			
Anemia	0.03% (1)	0.15% (2)	0.06% (3)
DIC	0.03% (1)	0.08% (1)	0.04% (2)
Cardiac Disorders			
Myocardial Infarction	0.06% (2)	0.08% (1)	0.06% (3)
Cardiac arrest	0.06% (2)	0	0.04% (2)
Ventricular Tachycardia	0.06% (2)	0	0.04% (2)
Congenital, Familial, and Genetic Disorders			
Tuberous sclerosis	0	0.15% (2)	0.04% (2)
Eye Disorders			
Scotoma	0.03% (1)	0.23% (3)	0.08% (4)
Visual disturbance	0	0.15% (2)	0.04% (2)
Gastrointestinal Disorders			
Vomiting	0.15% (5)	0.62% (8)	0.27% (13)
Abdominal pain	0.09% (3)	0.23% (3)	0.13% (6)
Diarrhea	0.06% (2)	0.23% (3)	0.08% (4)
Gastroesophageal reflux disease	0.03% (1)	0.23% (3)	0.08% (4)
Dyspepsia	0	0.23% (3)	0.06% (3)
Colitis ulcerative	0.06% (2)	0	0.04% (2)
Pancreatitis	0.06% (2)	0	0.04% (2)
Tooth disorder	0	0.15% (2)	0.04% (2)
General Disorders and Administration Site Conditions			
Pyrexia	0.29% (10)	0.85% (11)	0.44% (21)
Chest pain	0.15% (5)	0.08% (1)	0.13% (6)
Fatigue	0.03% (1)	0.39% (5)	0.13% (6)
Death	0	0.31% (4)	0.08% (4)

Drug interaction	0.12% (4)	0	0.08% (4)
Asthenia	0.09% (3)	0	0.06% (3)
Cyst	0.03% (1)	0.15% (2)	0.06% (3)
Unevaluable event	0	0.23% (3)	0.06% (3)
Drowning	0.06% (2)	0	0.04% (2)
Hepatobiliary Disorders			
Cholecystitis	0.12% (4)	0.08% (1)	0.11% (5)
Cholelithiasis	0.03% (1)	0.08% (1)	0.04% (2)
Infections and Infestations			
Pneumonia	0.35% (12)	0.93% (12)	0.51% (24)
Bronchitis	0.06% (2)	0.46% (6)	0.17% (8)
Urinary tract infection	0.15% (5)	0.15% (2)	0.15% (7)
Gastroenteritis	0.06% (2)	0.31% (4)	0.13% (6)
Influenza	0.06% (2)	0.31% (4)	0.13% (6)
Upper Respiratory tract infection	0	0.46% (6)	0.13% (6)
Viral infection	0.03% (1)	0.39% (5)	0.13% (6)
Cellulitis	0.12% (4)	0.08% (1)	0.11% (5)
Infection	0.06% (2)	0.23% (3)	0.11% (5)
Osteomyelitis	0.09% (3)	0.08% (1)	0.08% (4)
Otitis media	0.03% (1)	0.23% (3)	0.08% (4)
Sinusitis	0.06% (2)	0.15% (2)	0.08% (4)
Appendicitis	0.06% (2)	0.08% (1)	0.06% (3)
Lobar pneumonia	0	0.23% (3)	0.06% (3)
Pneumonia viral	0.03% (1)	0.15% (2)	0.06% (3)
Sepsis	0.06% (2)	0.08% (1)	0.06% (3)
Bronchitis acute	0.06% (2)	0	0.04% (2)
Candidiasis	0	0.15% (2)	0.04% (2)
Endocarditis	0.03% (1)	0.08% (1)	0.04% (2)
Gastroenteritis viral	0.03% (1)	0.08% (1)	0.04% (2)
Pharyngitis	0.03% (1)	0.08% (1)	0.04% (2)
Postoperative infection	0	0.15% (2)	0.04% (2)
Pyelonephritis	0.06% (2)	0	0.04% (2)
Respiratory syncytial virus	0	0.15% (2)	0.04% (2)
Injury, Poisoning, and Procedural Complications			
Injury	0.03% (1)	0.62% (8)	0.19% (9)
Overdose	0.15% (5)	0.15% (2)	0.15% (7)
Fall	0.17% (6)	0	0.13% (6)
Ankle fracture	0.12% (4)	0	0.08% (4)
Hip fracture	0.12% (4)	0	0.08% (4)
Joint dislocation	0.06% (2)	0.15% (2)	0.08% (4)
Accidental overdose	0.03% (1)	0.08% (1)	0.04% (2)
Cervical vertebral fracture	0.06% (2)	0	0.04% (2)
Facial bones fracture	0.06% (2)	0	0.04% (2)
Laceration	0.06% (2)	0	0.04% (2)
Lower limb fracture	0.06% (2)	0	0.04% (2)
Near drowning	0.03% (1)	0.08% (1)	0.04% (2)
Road traffic accident	0.03% (1)	0.08% (1)	0.04% (2)
Snake bite	0.06% (2)	0	0.04% (2)
Thermal burn	0.03% (1)	0.08% (1)	0.04% (2)
Tibia fracture	0.06% (2)	0	0.04% (2)

Wrist fracture	0	0.15% (2)	0.04% (2)
Investigations			
Electroencephalogram	0.03% (1)	0.08% (1)	0.04% (2)
Metabolism and Nutrition Disorders			
Dehydration	0.03% (1)	0.23% (3)	0.08% (4)
Hyponatremia	0.09% (3)	0	0.06% (3)
Anorexia	0	0.15% (2)	0.04% (4)
Diabetes mellitus inadequate control	0.06% (2)	0	0.04% (2)
Musculoskeletal and Connective Tissue Disorders			
Back pain	0.12% (4)	0.15% (2)	0.13% (6)
Osteoarthritis	0.09% (3)	0.15% (2)	0.11% (5)
Intervertebral disc protrusion	0.09% (3)	0	0.06% (3)
Arthralgia	0	0.15% (2)	0.04% (2)
Spinal osteoarthritis	0.06% (2)	0	0.04 (2)
Neoplasms Benign, Malignant, and Unspecified (incl Cysts and Polyps)			
Basal cell carcinoma	0.09% (3)	0	0.06% (3)
Breast cancer	0.06% (2)	0	0.04% (2)
Lung neoplasm malignant	0.06% (2)	0	0.04% (2)
Meningioma	0.03% (1)	0.08% (1)	0.04% (2)
Neoplasm malignant	0.06% (2)	0	0.04% (2)
Uterine leiomyoma	0.06% (2)	0	0.04% (2)
Nervous System Disorders			
Visual field defect	0.06% (2)	24.83% (322)	6.84% (324)
Convulsion	2.79% (96)	2.78% (36)	2.79% (132)
Status epilepticus	1.54% (53)	1.85% (24)	1.63% (77)
Hemianopia homonomous	0	1.46% (19)	0.4% (19)
Grand mal convulsion	0.38% (13)	0.23% (3)	0.34% (16)
Complex partial seizures	0.35% (12)	0.23% (3)	0.32% (15)
Hemianopia	0	1.16% (15)	0.32% (15)
Headache	0.12% (4)	0.77% (10)	0.3% (14)
Postictal state	0.35% (12)	0	0.25% (12)
Dizziness	0.09% (3)	0.62% (8)	0.23% (11)
Somnolence	0.15% (5)	0.39% (5)	0.21% (10)
Epilepsy	0.06% (2)	0.54% (7)	0.19% (9)
Partial seizures	0.09% (3)	0.39% (5)	0.17% (8)
Coordination abnormal	0.06% (2)	0.31% (4)	0.13% (6)
Tremor	0.09% (3)	0.23% (3)	0.13% (6)
Cerebrovascular accident	0.15% (5)	0	0.11% (5)
Lethargy	0.09% (3)	0.15% (2)	0.11% (5)
Hemiparesis	0.09% (3)	0.08% (1)	0.08% (4)
Simple partial seizures	0.09% (3)	0.08% (1)	0.08% (4)
Amnesia	0.06% (2)	0.08% (1)	0.06% (3)
Depressed level of consciousness	0.03% (1)	0.15% (2)	0.06% (3)
Disturbance in attention	0	0.23% (3)	0.06% (3)
Infantile spasms	0	0.23% (3)	0.06% (3)
Cerebral hemorrhage	0.06% (2)	0	0.04% (2)
Coma	0	0.15% (2)	0.04% (2)
Dyskinesia	0	0.15% (2)	0.04% (2)

Encephalopathy	0.06% (2)	0	0.04% (2)
Febrile convulsion	0	0.15% (2)	0.04% (2)
Hydrocephalus	0	0.15% (2)	0.04% (2)
Intracranial pressure increased	0.03% (1)	0.08% (1)	0.04% (2)
Memory impairment	0.06% (2)	0	0.04% (2)
Migraine	0.03% (1)	0.08% (1)	0.04% (2)
Partial seizures with secondary generalization	0.03% (1)	0.08% (1)	0.04% (2)
Syncope	2 (0.06%)	0	0.4% (2)
Psychiatric disorders			
Depression	0.32% (11)	0.77% (10)	0.44% (21)
Confusional state	0.38% (13)	0.54% (7)	0.42% (20)
Psychotic disorder	0.38% (13)	0.08% (1)	0.3% (14)
Aggression	0.29% (10)	0.23% (3)	0.27% (13)
Suicidal ideation	0.32% (11)	0.08% (1)	0.25% (12)
Suicide attempt	0.26% (9)	0.08% (1)	0.21% (10)
Abnormal behavior	0.12% (4)	0.23% (3)	0.15% (7)
Anxiety	0.12% (4)	0.23% (3)	0.15% (7)
Agitation	0.09% (3)	0.23% (3)	0.13% (6)
Acute psychosis	0.12% (4)	0	0.08% (4)
Disorientation	0.09% (3)	0.08% (1)	0.08% (4)
Irritability	0.09% (3)	0.08% (1)	0.08% (4)
Affect liability	0.03% (1)	0.15% (2)	0.06% (3)
Conversion disorder	0.03% (1)	0.15% (2)	0.06% (3)
Delusion	0.09% (3)	0	0.06% (3)
Hallucination, auditory	0.06% (2)	0.08% (1)	0.06% (3)
Mental status changes	0.06% (2)	0.08% (1)	0.06% (3)
Alcoholism	0.06% (2)	0	0.04% (2)
Delirium	0.03% (1)	0.08% (1)	0.04% (2)
Depression suicidal	0.06% (2)	0	0.04% (2)
Hallucination	0.03% (1)	0.08% (1)	0.04% (2)
Hostility	0	0.15% (2)	0.04% (2)
Insomnia	0	0.15% (2)	0.04% (2)
Mood disorder due to general medical condition	0.06% (2)	0	0.04% (2)
Paranoia	0.03% (1)	0.08% (1)	0.04% (2)
Personality disorder	0.06% (2)	0	0.04% (2)
Sleep disorder	0.03% (1)	0.08% (1)	0.04% (2)
Renal and Urinary Disorders			
Renal failure acute	0	0.15% (2)	0.04% (2)
Reproductive System and Breast Disorders			
Ovarian cyst	0.06% (2)	0	0.04% (2)
Respiratory, Thoracic, and Mediastinal Disorders			
Pneumonia aspiration	0.29% (10)	0.15% (2)	0.25% (12)
Dyspnea	0.12% (4)	0.15% (2)	0.13% (6)
Hypoxia	0.12% (4)	0.08% (1)	0.11% (5)
Respiratory arrest	0.06% (2)	0.23% (3)	0.11% (5)
Aspiration	0.09% (3)	0.08% (1)	0.08% (4)
Bronchospasm	0	0.31% (4)	0.08% (4)
Asthma	0.09% (3)	0	0.06% (3)

Respiratory distress	0.03% (1)	0.15% (2)	0.06% (3)
Respiratory failure	0.06% (2)	0.08% (1)	0.06% (3)
Acute respiratory distress syndrome	0.06% (2)	0	0.04% (2)
Apnea	0.03% (1)	0.08% (1)	0.04% (2)
Pneumothorax	0.06% (2)	0	0.04% (2)
Skin and Subcutaneous Tissue Disorders			
Rash	0	0.31% (4)	0.08% (4)
Rash maculopapular	0	0.15% (2)	0.04% (2)
Surgical and Medical Procedures			
Brain lobectomy	0.09% (3)	0.15% (2)	0.11% (5)
Hospitalization	0	0.15% (2)	0.04% (2)
Surgery	0	0.15% (2)	0.04% (4)
Vascular Disorders			
Deep vein thrombosis	0.06% (2)	0	0.04% (2)
Hematoma	0.06% (2)	0	0.04% (2)
Hypertension	0.03% (1)	0.08% (1)	0.04% (2)

Additional Analyses

The Division asked Ovation to submit a pooled comparative analysis of SAEs using the same 12 controlled trials that they used for the comparative mortality analysis (see above). In this pooled analysis, the SAE incidence was 31.2/100 PY (139/446 PY) for vigabatrin compared to 12.7/100 PY (21/166 PY) for carbamazepine, 14.7/100 PY (10/68 PY) for valproate, 0/100 PY (0/1.7PY) for gabapentin, and 49.5/100 PY (50/101 PY) for placebo. I reviewed the results of this analysis and identified the SAEs occurring in at least 5 vigabatrin subjects. I list those events below (gabapentin not shown since there were no SAEs).

SAEs by Treatment Group for Pool of Phase 2-3 Studies

Serious Adverse Event	Vigabatrin 446 PY (n=952) Rate/100 PY (n)	Carbamazepine 166 PY (n=229) Rate/100 PY (n)	Valproate 68 PY (n=113) Rate/100 PY (n)	Placebo 101 PY (n=393) Rate/100 PY (n)
Convulsion	5.6 (25)	1.2 (2)	5.9 (4)	7.9 (8)
Status epilepticus	2.9 (13)	0	1.5 (1)	2.0 (2)
Headache	2.2 (10)	0.6 (1)	0	5.9 (6)
Depression	2.2 (10)	2.4 (4)	0	2.0 (2)
Confusional State	1.8 (8)	0	0	0
Dizziness	1.6 (7)	0	0	2.0 (2)
Bronchitis	1.3 (6)	0.6 (1)	0	0
Upper Resp Tract Infect	1.3 (6)	0	0	6.9 (7)
Pneumonia	1.3 (6)	0	0	0
Injury	1.3 (6)	0	0	1.0 (1)
Fatigue	1.1 (5)	0	0	0

Source 3/14/08 Submission, Table 14.2; Person years from p.83.

In this pooled analysis, SAEs of status epilepticus, depression, confusional state, pneumonia, and fatigue occurred more frequently among vigabatrin subjects than placebo subjects.

Post Marketing Reports

Current Submission

Ovation provided a summary of serious AEs reported during the post marketing period for 3/15/97 through 6/30/07. Ovation identified 190 reports with 317 serious adverse events for the 10 year period. Post marketing report events were considered serious if reported as such, or if the event resulted in death. The highest percentage of SAE reports were for the Nervous System disorders (135 reports, 7.5% of total) and Eye disorders (23 reports, 1.3% of the total). The most common SAEs reported were visual field defect (107 events) and convulsions (7 events). In the following table, I list the post marketing SAEs with 3 or more event reports.

MedDRA SOC **MedDRA Preferred Term**	**Patients**	**Events**
Any SAE	190	317
Nervous System Disorders	135	151
Visual field defect	103	107
Convulsion	7	7
Somnolence	4	4
Tunnel vision	4	4
Brain edema	3	3
Encephalopathy	3	3
Status Epilepticus	3	3
Eye disorders	23	30
Visual disturbance	8	8
Strabismus	4	4
Optic atrophy	3	3
General Disorders and Administration Site Conditions	17	19
Death	3	3
Developmental delay	3	3
Condition aggravated	2	3
Injury, Poisoning, and Procedural Complications	14	14
Drug exposure during pregnancy	9	9
Congenital, Familial, and Genetic Disorders	12	36
Dysmorphism	4	4
Multiple congenital abnormalities	3	3
Dentofacial anomaly	2	3
Investigations	12	12
Nuclear magnetic resonance imaging brain abnormal	7	7
Psychiatric disorders	10	16
Surgical and Medical Procedures	6	6
Abortion induced	6	6
Musculoskeletal and Connective Tissue Disorders	4	4
Gastrointestinal Disorders	3	3
Infections and Infestations	3	3
Metabolism and Nutritional Disorders	3	3
Respiratory, Thoracic, and Mediastinal Disordes	3	5
Skin and Subcutaneous Tissue Disorders	2	4

Source Amendment Submission 12/28/07, Post Marketing Reports Section, Table 1.6a, pp. 147-155.

There were no SAE post marketing reports of anemia, liver failure, or hepatitis. Ovation identified one SAE of angioedema, one of rash, and one of rash maculopapular.

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

Previous Submissions
NDA and NDA Amendment
Forty-five percent (198/443) of vigabatrin exposed subjects discontinued prematurely from US epilepsy studies. Almost 23% (101/443) of enrolled vigabatrin subjects discontinued for lack of efficacy while 17.2% (76/443) discontinued for adverse events. In primary non-US epilepsy studies 29.2% (223/765) of vigabatrin exposed subjects discontinued prematurely. For this group, lack of efficacy (14.2%, 109/765) and adverse event (9.9%, 76/765) were the most commonly recorded reasons for discontinuation. The sponsor acknowledged that 2% (15/765) of the vigabatrin subjects enrolled in these studies discontinued for unknown reasons (Source: Amendment review, pp.20-21, and attachment table C-18).

In US controlled epilepsy studies, 14.4% (32/222) of vigabatrin subjects discontinued prematurely compared to 3.7% (5/135) of placebo subjects. The most common reason for withdrawal in these trials was adverse event with 10.8% (24/222) of vigabatrin subjects discontinuing for AEs compared to 2.2% (3/135) of placebo subjects. In non-US primary controlled epilepsy trials, 19.4% (65/335) of vigabatrin subjects discontinued prematurely. In those trials, 8.4% (28/335) of vigabatrin subjects discontinued for AEs compared to 2.5% (7/284) of placebo patients. As previously noted comparisons from these trials should be interpreted cautiously because 6 of the nine studies used a crossover design and only one of these used a washout period prior to crossover (Source: Amendment review, pp.20-23, attachment table C-18).

Safety Update (1/1/96-3/15/97)
For the epilepsy studies in the Safety Update, the sponsor reported that 42% (708/1,667) of enrollees withdrew prior to completion of the studies. The most common reasons for discontinuation were loss of efficacy (18%, 304/1,667) and adverse event (14%, 225/1,667). (Source Final Safety Update Review, p.4).

Current Submission

Overall Safety Population (3/16/97-6/30/07)

Ovation reported that 66% (1,416/2,146) of the subjects in the included Overall Safety Population studies discontinued due to the following reasons: lack of efficacy 16.1% (n=345), administrative reasons 12.2% (n=261), other 11.8% (n=254), adverse event 9.3% (n=199), lost to follow up 9.1% (n=196), voluntarily withdrew 3.4% (n=74), protocol violation 3.2% (n=69), unknown 0.5% (n=10), death 0.2% (n=4), withdrawn by investigator 0.1% (n=2), and failed to meet entry criteria 0.1% (n=2) (Table 7, p.36). The subject disposition data that appear in table 7 come from the CRF termination pages. Subsequent presentations of discontinuations due to AEs were based on outcome information included in CRF AE pages. This distinction is important because inconsistencies between these two sources of information led to differences in the number of subjects identified as discontinuing due to AEs when comparing disposition table 7 with subsequent presentations of discontinuations due to AEs.

7.1.3.2 Adverse events associated with dropouts

Prior Submissions

NDA and NDA Amendment (Cutoff date 12/31/95)
As noted above, 17.2% (76/443) of vigabatrin subjects in US epilepsy studies discontinued for adverse events. For vigabatrin subjects who discontinued for AEs in these studies, the most commonly reported AEs leading to discontinuation were drowsiness (n=12), seizures (convulsions + convulsions grand mal, n=9), depression (n=9), agitation (n=9), fatigue, headache, amnesia (n=7 each), paranoid reaction (n=6) and thinking abnormal (n=5). In primary non-US epilepsy studies, 9.9% (76/765) of vigabatrin exposed subjects discontinued for AEs. The most commonly reported AEs leading to discontinuation from the primary non-US epilepsy studies were seizures (convulsions +convulsions grand mal, n=14), depression (n=13), drowsiness, fatigue, insomnia (n=6, each), dizziness, headache, and aggressive reaction (n=5, each) (Source: Amendment Review, p23, attachment table C-18).

In US controlled epilepsy studies 10.8% of vigabatrin and 2.2% of placebo subjects discontinued for AEs (RR=4.9). In non US primary controlled trials, 8.4% of vigabatrin subjects and 2.5% of placebo subjects discontinued for AEs (RR 3.4) (Source: Amendment review, p.23 and attachment table C-18). Given the previously stated caveat about comparisons within non US primary epilepsy trials, 3.3% (11/335) of vigabatrin subjects and no placebo subjects discontinued for depression. No subjects from primary studies discontinued for hepatic injury or hepatic failure related events (Source Amendment review p.23 and attachment table C-18).

Secondary, non-CRF Data
In Secondary epilepsy studies, AEs led to discontinuation of 11.1% (100/900) vigabatrin exposed subjects. The most commonly reported AEs leading to discontinuation were drowsiness (1.3%, n=12), aggressive reactions, (1.2%, n=11), fatigue (1.1%, n=10), psychosis (0.9%, n=8) and agitation (0.9%, n=8). The sponsor did not summarize in tabular format the AEs leading to discontinuation for the non-CRF cohort (Source Amendment review, p.24, and attachment table C-19).

Safety Update (1/1/96-3/15/97)
The sponsor reported that 234 subjects (13%, 234/1,773) discontinued for adverse events from the trials included in the safety update. The sponsor did not provide a separate summary of the discontinuations due to AE's for this group and the remainder of the presentation focused on the discontinuations for the integrated data through the end of this Safety Update period (Source: Final Safety Update Review, p.4).

Current Submission

Overall Safety Population (3/16/97-6/30/07)

In the current submission, the sponsor reported that 7.8% (168/2,146) of vigabatrin subjects discontinued from trials for adverse events. The AEs leading to discontinuation of at least 5

subjects were convulsions (1.4%, 29/2,146), depression (0.7%, 14/2146), visual field defect (0.6%, 12/2,146), coordination abnormal (0.3%, 7/2,146), weight increased (0.3%, 7/2,146), status epilepticus (0.3%, 6/2,146), abnormal behavior (0.2%, 5/2146), and somnolence (0.2%, 5/2,146). Less frequently occurring, but potentially concerning AEs leading to discontinuation included rash (n=4), anemia (n=1), platelet count decreased (n=1), drug hypersensitivity (n=1), hypersensitivity (n=1), depression suicidal (n=1), suicide attempt (n=1), major depression (n=1), hallucination (n=1), hallucination visual (n=1), leukocytoclastic vasculitis, (n=1), Stevens Johnson Syndrome (n=1), renal failure acute (n=1), and hepatic failure (n=1) (Source: 10/10/06 Submission, pp.78-9). Most of these events were also SAEs and I discussed them above. Below, I summarize information from potentially concerning AEs leading to discontinuation that were not previously discussed.

Rash

0101/Subject 13420003 This 42 year old female subject with a history of eczema developed circular patches of burning and itching skin after 6 months of vigabatrin treatment. The rash was treated with cetaphil and mometasone furoate cream and the rash resolved with study drug taper. The subject was withdrawn from the study. The listed concomitant medication was tegretol.

1A/ Subject 280 This 1 year old male with a history of infantile spasms was terminated from a study for a skin rash and was lost to follow up.

Depression Suicidal

0098/Subject 12230014 This 47 year old male subject with a history of seizures, cortical blindness, hypertension, intermittent UTIs, decubitus ulcers, left hemiparesis, intractable headaches, allergies, depression, and suicidal ideation discontinued from the trial after 336 days of vigabatrin for depression and suicidal ideation. The event resolved one day after stopping study medication.

Pediatric Subpopulation (non IS, age 3-<16)

Ovation reported that 12% (53/444) of the pediatric patients included in the Overall Safety Population discontinued for adverse events. The discontinuation due to AE risk among these pediatric subjects was slightly higher than the risk observed in the overall population (8%). The adverse events leading to discontinuation of at least 1% of vigabatrin pediatric subjects were convulsion (4.3%, 19/444), and abnormal behavior (1.1%, 5/444). Other adverse events leading to discontinuation included depression (0.5%, 2/444), major depression (0.2%, 1/444), hallucination (0.2%, 1/444), Stevens Johnson Syndrome (0.2%, 1/444), and rash (0.2%, 1/444). For the pediatric subjects, there were no discontinuations for AEs of suicide, suicide attempt, acute hepatic failure, pancreatitis, aplastic anemia, or hypersensitivity (Source 12/28/07 submission, pp.151-3).

IS Subpopulation

Ovation reported that 7.6% (17/223) of the IS patients included in the Overall Safety Population discontinued for adverse events. The adverse events leading to discontinuation of more than one IS subjects were pneumonia (n=2), infantile spasms (n=2), and convulsions (n=2). Otitis media, sedation, hypertension, fecaloma, blood ALP increased, irritability, rash, pulmonary hemorrhage, gastrointestinal infection, postoperative infection, and somnolence led to discontinuation of one subject each (Source 12/28/07 submission, pp.171).

Integrated Data

Ovation provided discontinuation or AE risks by submission and combined for the development program studies. The following table includes the AEs that led to discontinuation of at least 3 subjects.

AEs that Led to Discontinuation of More than One Subject, Integrated Data

Event Category Adverse Event	Prior Data (N=3440) % (n)	Current Data (N=2148) % (n)	Combined (N=4855) % (n)
Any AE Leading to Discontinuation	14.3% (493)	7.8% (168)	13.6% (661)
Blood and Lymphatic Disorders			
Anemia	0.06% (2)	0.05% (1)	0.06% (3)
Cardiac Disorders			
Palpitations	0.09% (3)	0	0.06% (3)
Ear and Labyrinth Disorders			
Vertigo	0.26% (9)	0	0.19% (9)
Tinnitus	0.09% (3)	0	0.06% (3)
Eye Disorders			
Vision blurred	0.35% (12)	0.14% (3)	0.31% (15)
Diplopia	0.26% (9)	0.09% (2)	0.23% (11)
Visual disturbance	0.06% (2)	0.05% (1)	0.06% (3)
Gastrointestinal Disorders			
Nausea	0.44% (15)	0	0.31% (15)
Constipation	0.23% (8)	0.09% (2)	0.21% (10)
Vomiting	0.23% (8)	0.05% (1)	0.19% (9)
Diarrhea	0.23% (8)	0	0.16% (8)
Abdominal pain	0.17% (6)	0	0.12% (6)
Abdominal pain upper	0.12% (4)	0.05% (1)	0.10% (5)
General Disorders and Administration Site Conditions			
Fatigue	1.10% (38)	0.09% (2)	0.82% (40)
Gait disturbance	0.17% (6)	0	0.12% (6)
Feeling abnormal	0.15% (5)	0	0.10% (5)
Edema peripheral	0.09% (3)	0.09% (2)	0.10% (5)
Asthenia	0.12% (4)	0	0.08% (4)
Pain	0.09% (3)	0.05% (1)	0.08% (4)
Chest pain	0.09% (3)	0	0.06% (3)
Immune System Disorders			
Hypersensitivity	0.06% (2)	0.05% (1)	0.06% (3)
Infections and Infestations			
Pneumonia	0.03% (1)	0.09% (2)	0.06% (3)
Urinary tract infection	0.09% (3)	0	0.06% (3)
Injury, Poisoning, and Procedural Complications			
Investigations			
Weight increased	0.7% (24)	0.33% (7)	0.64% (31)
Metabolism and Nutrition Disorders			
Anorexia	0.12% (4)	0.05% (1)	0.10 (5)
Increased appetite	0.09% (3)	0.05% (1)	0.08% (4)
Musculoskeletal and Connective Tissue Disorders			

Arthralgia	0.17% (6)	0	0.12% (6)
Muscle twitching	0.09% (3)	0	0.06% (3)
Neoplasms Benign, Malignant, and Unspecified (incl Cysts and Polyps)			
Glioma	0.06% (2)	0.05% (1)	0.06% (3)
Nervous System Disorders			
Convulsion	1.13% (39)	1.35% (29)	1.4% (68)
Somnolence	1.10% (38)	0.23% (5)	0.89% (43)
Dizziness	0.81% (28)	0.14% (3)	0.64% (31)
Headache	0.84% (29)	0.05% (1)	0.62% (30)
Status epilepticus	0.58% (20)	0.28% (6)	0.54% (26)
Coordination abnormal	0.41% (14)	0.33% (7)	0.43% (21)
Memory impairment	0.49% (17)	0.09% (2)	0.39% (19)
Tremor	0.44% (15)	0.14% (3)	0.37% (18)
Visual field defect	0.03% (1)	0.56% (12)	0.27% (13)
Disturbance in attention	0.23% (8)	0.14% (3)	0.23% (11)
Lethargy	0.26% (9)	0.09% (2)	0.23% (11)
Balance disorder	0.23% (8)	0	0.16% (8)
Sedation	0.17% (6)	0.09% (2)	0.16% (8)
Parasthesia	0.17% (6)	0.05% (1)	0.14% (7)
Amnesia	0.15% (5)	0.05% (1)	0.12% (6)
Myoclonus	0.17% (6)	0	0.12% (6)
Nystagmus	0.17% (6)	0	0.12% (6)
Dyskinesia	0.12% (4)	0.05% (1)	0.10% (5)
Grand mal convulsion	0.15% (5)	0	0.10% (5)
Hyperkinesia	0.15% (5)	0	0.10% (5)
Partial seizures	0.12% (4)	0.05% (1)	0.10% (5)
Cognitive disorder	0.03% (1)	0.14% (3)	0.08% (4)
Complex partial seizures	0.09% (3)	0.05% (1)	0.08% (4)
Movement disorder	0.09% (3)	0.05% (1)	0.08% (4)
Postictal state	0.12% (4)	0	0.08% (4)
Dysarthria	0.03% (1)	0.09% (2)	0.06% (3)
Psychomotor hyperactivity	0.6% (2)	0.05% (1)	0.06% (3)
Simple partial seizures	0.06% (2)	0.05% (1)	0.06% (3)
Speech disorder	0.06% (2)	0.05% (1)	0.06% (3)
Psychiatric disorders			
Depression	1.66% (57)	0.65% (14)	1.46% (71)
Confusional state	0.78% (27)	0.14% (3)	0.62% (30)
Irritability	0.73% (25)	0.19% (4)	0.60% (29)
Aggression	0.70% (24)	0.19% (4)	0.58% (28)
Abnormal behavior	0.58% (20)	0.23% (5)	0.51% (25)
Insomnia	0.41% (14	0.14% (3)	0.35% (17)
Psychotic disorder	0.39% (17)	0	0.35% (17)
Agitation	0.20% (7)	0.19% (4)	0.23% (11)
Anxiety	0.26% (9)	0.09% (2)	0.23% (11)
Paranoia	0.23% (8)	0.09% (2)	0.21% (10)
Suicidal ideation	0.29% (10)	0	0.21% (10)
Expressive language disorder	0.23% (8)	0	0.16% (8)
Mental disorder	0.20% (7)	0.05% (1)	0.16% (8)
Hallucination	0.17% (6)	0.05% (1)	0.14% (7)
Affect liability	0.15% (5)	0.05% (1)	0.12% (6)
Hallucination, auditory	0.15% (5)	0	0.10% (5)

Mood swings	0.09% (3)	0.09% (2)	0.10% (5)
Suicide attempt	0.12% (4)	0.05% (1)	0.10% (5)
Delusion	0.09% (3)	0.05% (1)	0.08% (4)
Disorientation	0.06% (2)	0.09% (2)	0.08% (4)
Mental status changes	0.06% (2)	0.09% (2)	0.08% (4)
Nervousness	0.12% (4)	0	0.08% (4)
Abnormal dreams	0.09% (3)	0	0.06% (3)
Anger	0.09% (3)	0	0.06% (3)
Conversion disorder	0.03% (1)	0.09% (2)	0.06% (3)
Crying	0.09% (3)	0	0.06% (3)
Dysphemia	0.09% (3)	0	0.06% (3)
Hallucination visual	0.06% (2)	0.05% (1)	0.06% (3)
Panic attack	0.09% (3)	0	0.06% (3)
Sleep disorder	0.09% (3)	0	0.06% (3)
Thinking abnormal	0.09% (3)	0	0.06% (3)
Renal and Urinary Disorders			
Dysuria	0.12% (4)	0	0.08% (4)
Respiratory, Thoracic, and Mediastinal Disorders			
Dyspnea	0.12% (4)	0.09% (2)	0.12% (6)
Skin and Subcutaneous Tissue Disorders			
Rash	0.23% (8)	0.19% (4)	0.25% (12)
Dermatitis allergic	0.12% (4)	0	0.08% (4)
Pruritis generalized	0.09% (3)	0	0.06% (3)
Vascular Disorders			
Hypertension	0.03% (1)	0.09% (1)	0.06% (3)

Source NDA Amendment Table 66, pp. 193-205

Additional Analyses

The Division asked Ovation to submit a pooled comparative analysis of AEs leading to dropout using the same 12 controlled trials that they used for the comparative mortality analysis and SAE analysis (see above). In this pooled analysis, the incidence for any AE leading to dropout was 32.3/100 PY (144/446 PY) for vigabatrin compared to 40.0/100 PY (63/166 PY) for carbamazepine, 20.6/100PY (14/113) for valproate, 58.8/100 PY (1/1.7 PY) for gabapentin, and 13.9/100 PY (14/101) for placebo. I reviewed the results of this analysis and identified the AEs leading to dropout of at least 5 vigabatrin subjects. I list those events below.

Discontinuations for Adverse Events by Treatment Group for Pool of Phase 2-3 Studies

Adverse Event Leading to Dropout	Vigabatrin 446 PY (n=952) Rate/100 PY (n)	Carbamazepine 166 PY (n=229) Rate/100 PY (n)	Valproate 68 PY (n=113) Rate/100 PY (n)	Gabapentin 1.7 PY (n=9) Rate/100 PY (n)	Placebo 101 PY (n=393) Rate/100 PY (n)
Depression	3.2 (15)	1.2 (2)	2.9 (2)	0	1.0 (1)
Headache	3.0 (14)	0.6 (1)	0	0	2.0 (2)
Convulsion	2.4 (11)	0	2.9 (2)	0	2.0 (2)
Fatigue	1.9 (9)	5.4 (9)	1.5 (1)	0	1.0 (1)
Somnolence	1.7 (8)	1.9 (9)	2.9 (2)	0	2.0 (2)
Rash	1.7 (8)	7.2 (12)	0	0	0
Dizziness	1.5 (7)	2.4 (4)	0	0	0
Disturbance	1.5 (7)	1.8 (3)	0	0	0

in Attention					
Agitation	1.5 (7)	0	0	0	0
Confusional state	1.3 (6)	0	0	0	0
Weight increased	1.3 (6)	1.8 (3)	0	0	1.0 (1)
Insomnia	1.3 (6)	0.6 (1)	0	0	3.0 (3)
Irritability	1.1 (5)	1.2 (2)	1.5 (1)	58.8 (1)	0
Status epilepticus	1.1 (5)	0	0	0	0
Lethargy	1.1 (5)	1.8 (3)	1.5 (1)	0	0
Vomiting	1.1 (5)	1.2 (2)	5.9 (4)	0	1.0 (1)

Source 3/14/08 Submission, Table 14.3; Person years data from p.83

In this pooled analysis, AEs of headache, agitation, confusional state, and status epilepticus appeared to lead to dropout more commonly among vigabatrin subjects than control subjects. Depression AEs occurred more frequently among vigabatrin, carbamazepine and valproate subjects than placebo subjects

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

Prior Submissions

NDA and NDA Amendment (Cutoff date 12/31/95)

As noted in the Amendment review, for most of the primary data studies, CRFs recorded responses to open ended questions about adverse events. In addition to recording the AE, the CRF AE sheets were designed to also capture information about severity, action taken and opinions about causality. The sponsor took a different approach to collecting adverse events from non US studies. In addition to capturing the AEs recorded on the CRF AE sheets, the sponsor extracted AEs from comment fields, concomitant medication pages, physical and neurological exams, laboratory pages, and letters. AEs from sources other than the CRF AE sheets had no information about severity, action taken or opinions about causality (Amendment review, p.12).

Treatment emergent AEs were defined as those AEs that occurred for the first time or that worsened during the study period, regardless of investigator assessment of causality (Amendment review, p.12).

Current Submission

Overall Safety Population (3/16/97-6/30/07)

Investigators recorded responses to open ended questions about adverse events on adverse event sheets in the CRF. Ovation defined treatment-emergent adverse events as any adverse event that occurred after the subject had taken one or more doses of vigabatrin (adverse events recorded during placebo baseline periods before active dose of vigabatrin were not included). If a medical

condition or adverse event present before the first dose of medication worsened in severity after taking study medication, the worsening of the condition was considered a treatment-emergent adverse event (12/28/07 submission, p.33).

During the course of the review, the Division discovered information in narrative summaries (lab data, clinical details, etc.) that was not present in the CRFs. When asked about this, Ovation explained that for a number of studies included in the current submission, the previous sponsor did not record SAE data in the CRF but instead captured this information in a separate database (GADERS). The studies using this procedure were 0294, 0223, 0221, 0192, 0222, 0101, 0098, 0118, 4103, 0201, and 0242. Ovation stated that the procedure for reporting SAEs required investigators to notify clinical monitors by fax, overnight mail, or telephone call within one working day. The clinical monitor completed an SAE form and forwarded the form to the company for entry into the GADERS database. Clinical monitors were required to provide the SAE form to the study sites. The investigators apparently did not have to sign off on the information included in the SAE form. When asked if there were any data included in GADERS that were not submitted in the Amendment, Ovation re-queried their database and identified 25 SAE reports that had not been submitted. Ovation submitted narratives for 21 of the SAEs (5 VFD defects were mentioned in the text of a study report but no narratives were written). As part of a broader effort, Ovation also identified 4 SAEs from studies that captured SAEs on the CRFs (R003 and 4020). (Source 5/1/08 Submission, pp. 136-9).

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

In their 3/1/07 submission, Ovation provided a table that listed the adverse event investigator verbatim terms and the MedDRA preferred terms to which the verbatim terms were coded. The table included the terms for the Integrated Data (all epilepsy studies) and provided separate columns for events from prior submissions, the current submission, and a column for combined data (prior data plus current data).

The coding of adverse events generally appeared appropriate although there were several notable examples of unhelpful and inappropriate coding. Ovation used preferred terms that were too nonspecific to be useful. In addition, the result of coding in some cases was to split seemingly related events and to lump unrelated events. Lastly there were infrequent occurrences where the coding appeared incorrect.

An example of the use of a nonspecific term was the preferred term of "Pain". Ovation coded a number of events including ankle pain, leg pain, and chest pain. Relying on this preferred term does not provide a useful summary of the subsumed events.

An example of splitting of related events was use of the preferred terms laceration and skin laceration. These preferred terms appeared to subsume many of the same type of events with no obvious reason as to why one preferred term was selected over the other in any particular instance. Another example of splitting was when despite having a preferred term of "Iron Deficiency Anemia", Ovation coded the adverse event of iron deficient microcytic anemia to the

preferred term "Microcytic anemia". Another splitting example was the use of preferred terms Otitis media and Ear infection which appeared to subsume similar events.

An example of lumping unrelated items was the use of the preferred term General symptom. This preferred term included events such as feet swollen/painful, abdomen and back pain, embedded earrings, bad dreams, blurred vision and sleepiness, chills and diarrhea, and ankle pain.

Lastly, there were occasional eamples where the coding of the verbatim term appeared incorrect. The verbatim term microcytic hyperchromic anemia was coded to hypochromic anemia. The verbatim term "Parent reports Pt's head us "hot" but not rest of body; crying unconsol" was coded to "Tympanic Membrane disorder". In another instance, the verbatim term "Split lip requiring stitches when playing basketball" was coded to chapped lips. Two cases of mycosis (funfgal skin infections) were coded to mycosis fungoides (cutaneous T-cell lymphoma).

7.1.5.3 Incidence of common adverse events

Prior Submissions

NDA and NDA Amendment (Cutoff date 12/31/95)

Primary Data
The NDA Amendment review included a table (Appendix F2) that reported the pooled AE risks from the 2 US controlled epilepsy trials (024,025), a Canadian placebo controlled trial (021), and the first period crossover for selected non US primary trials. Table F2 included AEs that occurred in at least 1% of vigabatrin subjects and were numerically more frequent compared to placebo The sponsor proposed using information from table F2 in labeling (but using a 2% cutoff) to illustrate adverse event risks in controlled trials. I present information from Table F2 below.

Most Frequently Reported Adverse Events in Placebo-Controlled Epilepsy Trials (>=1% of SABRIL Patients and Numerically More Frequent Than Placebo Patients)

Body System/Adverse event	Vigabatrin (n=406)	Placebo (n=311)
Neurologic		
Headache	28.1%	26.0%
Drowsiness	25.9%	15.1%
Dizziness	19.2%	13.5%
Nystagmus	11.6%	5.1%
Tremor	10.8%	7.7%
Amnesia	9.4%	3.5%
Ataxia	8.1%	4.5%
Confusion	6.9%	2.6%
Parasthesia	6.2%	1.9%
Coordination abnormal	5.2%	2.9%
Gait abnormal	4.9%	3.5%
Concentration impaired	4.7%	1.6%
Speech disorder	3.7%	1.0%

Vertigo	3.7%	2.3%
Hypoesthesia	3.2%	2.3%
Hyporeflexia	3.0%	0.3%
Hyperreflexia	1.7%	1.3%
Tinnitus	1.7%	1.3%
Convulsion Grand Mal	1.5%	1.3%
Twitching	1.5%	0.3%
Hearing impaired	1.0%	0
Myopathy	1.0%	0.3%
Neuropathy	1.0%	0
Psychiatric		
Depression/psychotic depression	12.1%	3.5%
Agitation	10.8%	8.0%
Anxiety	7.1%	4.2%
Emotional lability	4.7%	2.9%
Thinking abnormal	4.2%	0.6%
Aggressive Reaction	3.0%	1.6%
Nervousness	3.0%	2.6%
Personality Disorder	1.5%	1.0%
Dreaming abnormal	1.2%	0.3%
Nightmare	1.2%	0.3%
Paranoid reaction	1.2%	0.3%
Euphoria	1.0%	0
Suicide attempt	1.0%	0
Gastrointestinal System		
Nausea	9.1%	8.0%
Diarrhea	6.9%	5.5%
Abdominal Pain	6.2%	4.2%
Constipation	5.9%	3.5%
Vomiting	5.7%	4.8%
Tooth disorder	3.4%	1.6%
Hemorrhoids	1.2%	0
Body as a Whole		
Fatigue	26.1%	15.8%
Asthenia	5.2%	5.1%
Fever	3.7%	2.6%
Chest pain	2.7%	2.6%
Malaise	2.2%	1.3%
Generalized edema (including edema)	2.0%	0.6%
Face edema	1.5%	0.3%
Rigors	1.2%	0
Respiratory System		
Throat Irritation	6.7%	5.8%
Upper Respiratory Tract Infection	5.4%	3.2%
Sinusitis	2.0%	1.9%
Dyspnea	1.5%	0.3%
Infectious Disease		
Infection Viral	14.3%	12.2%
Infection Fungal	1.5%	0.6%
Dermatologic		
Pruritis	1.5%	0.3%
Sweating Increased	1.5%	0.6%

Musculoskeletal System		
Arthralgia	7.4%	4.2%
Back pain	5.9%	4.2%
Arthrosis	2.5%	1.9%
Myalgia	1.7%	1.6%
Metabolic & Nutritional		
Weight Increase	7.9%	3.9%
Appetite Increased	2.7%	2.6%
Reproductive, Female		
Dysmenorrhea	3.9%	1.6%
Menstrual Disorder	2.0%	1.0%
Amenorrhea	1.2%	0.6%
Vaginitis	1.2%	0.3%
Urinary System		
Urinary Tract Infection	3.2%	0.3%
Urinary Disorder	1.2%	0
Urinary Retention	1.0%	0
Cardiovascular		
Peripheral edema (including dependent and leg)	5.7%	1.0%
Ophthalmologic		
Vision abnormal	10.1%	6.1%
Diplopia	7.9%	5.5%
Eye Pain	2.5%	0.6%
Eye Abnormality	1.7%	0.6%
Hematologic		
Purpura	4.4%	3.5%
Anemia/hypochromic anemia	1.5%	0.6%
Lymphadenopathy	1.0%	0.3%
Ear, Nose, and Throat		
Earache	2.0%	1.3%
Immunologic		
Allergy	1.2%	0.3%
Other adverse events reported in >=1% of patients but equally or more frequent in the placebo group include **Neurologic:** convulsions (including condition aggravated), aphasia, hypokinesia, hypertonia. **Psychiatric:** insomnia, depersonalization, apathy. **GI:** dyspepsia, anorexia, abdominal distension. **Body as a Whole:** pain, trauma, injury, hot flushes. **Respiratory:** congestion, coughing, rhinorrhea, bronchitis, epistaxis, rhinitis. **Infectious Disease:** influenza-like symptoms, infection, herpes simplex. **Dermatologic:** rash, acne, alopecia, eczema, erythema, urticaria, furunculosis. **Metabolic and Nutritional:** weight decrease, phosphatase alkaline increased. **Urinary System:** urinary frequency, urinary incontinence. **Hepatic and Biliary:** GGT increased. **Hematologic:** leucopenia. **Ophthalmologic:** conjunctivitis.		

Source Amendment Review, Appendix Table F2

Safety Update (1/1/96-3/15/97)

The controlled epilepsy trials in the safety update used active comparator groups (valproate and carbamazepine). The percentage of subjects reporting AEs was 83% (280/338) for Sabril, 66% (75/113) for valproate and 85% (194/229) for carbamazepine. Notably, valproate was less

frequently associated with CNS and psychiatric AEs than Sabril. Carbamazepine had an increased risk of skin AEs compared to the other treatments. The following table compares the commonly reported adverse events for Sabril, valproate, and carbamazepine.

A comparison of selected adverse events from the newly completed controlled trials included in the final safety update

Event	Sabril®	Valproate	Carbamazepine
Drowsiness	23% (78/338)	16% (18/113)	28% (64/229)
Fatigue	18% (60/338)	13% (15/113)	21% (49/229)
Dizziness	12% (42/338)	6% (7/113)	13% (29/229)
Weight increase	10% (34/338)	10% (11/113)	5% (11/229)

Compared to the data presented in the NDA amendment (Table F1: Incidence of Adverse events by preferred terms for US and Primary Non US placebo controlled epilepsy trials), the percentage of vigabatrin subjects reporting these events had not substantially changed.

For both the US and non-US uncontrolled trials in the Safety Update, the most commonly reported body systems for AE's were CNS, GI, and Psychiatric. Drowsiness, headache, infection viral and fatigue were commonly reported events in these trials. There were no new cases of hepatic failure, renal failure, Stevens Johnson syndrome, aplastic anemia, or rhabdomyolysis (Safety Update Review, pp. 9-10).

Current Submission

Overall Safety Population (3/16/97-6/30/07)

Ovation reported that 77% (1,651/2,146) of subjects in the safety update population experienced one or more adverse events (12/28/07 submission, p.39). The following events were reported by at least 5% of the study subjects: visual field defect (15.7%, 336), Upper respiratory tract infection (10.8%, 232), headache (9.8%, 210), convulsion (8.3%, 178), dizziness (8.3%, 177), somnolence (7.9%, 169), fatigue (7.7%, 165), weight increased (7.5%, 160), nasopharyngitis (7.2%, 154), otitis media (5.9%, 126), pyrexia (5.4%, 116), and insomnia (5.1%, 110) (12/28/07 submission, Table 10, p.41).

I reviewed Appendix 3 table 4.1.3 that included all AEs reported for the safety update population to look for less frequent events of potential concern. There were 18 (0.8%, 18/2146) anemia AEs, 9 (0.4%, 9/2146) neutropenia AEs, and six platelet count decreased AEs (0.3%, 6/2146), but no aplastic anemia or agranulocytosis AEs. There were 17 events (0.8%, 17/2146) coded as hypersensitivity. There were 3 events coded to the term swelling face and 2 events of face edema. There were 12 AEs coded as drug toxicity and 11 (0.5%, 11/2146) coded as adverse drug reaction for which no additional information was available. There were 2 events of acute renal failure, one of hepatic failure and one of hepatic necrosis. There was one event of skin exfoliation and one event of Stevens Johnson Syndrome.

Pediatric Subpopulation (non IS, age 3-<16)
Ovation reported that 76% (337/444) of pediatric patients in the Overall population experienced one or more adverse events. The percentage of pediatric subjects reporting AEs was similar to the percentage of subjects with AEs in the overall population (77%). Ovation provided Table 38, which summarized the AEs reported by at least 5% of pediatric subjects. The AEs in this table were generally similar to and occurred at a similar frequency as the AEs reported for at least 5% of the Overall population. There appeared to be an increased risk for the following three AEs among pediatric subjects: convulsion (peds 15.8%, 70/444, overall 8.3%, 178/2146), Headache (peds 14.4%, 64/444, overall 9.8%, 210/2146), and weight increase (peds 14.2%, 63/444, overall 7.5%, 160/2146). The following AEs were reported by at least 5% of pediatric subjects but not by at least 5% of subjects in the Overall group: influenza (7%, 31/444), viral infection (7%, 31/444), pharyngitis streptococcal (6.5%, 29/444), sinusitis (5.9%, 26/444), abnormal behavior (8.1%, 36/444), aggression (6.5%, 29/444), and vomiting (7.2%, 32/444) Insomnia was the only AE reported by at least 5% of subjects in the overall population but not for the pediatric subpopulation. (Source: 12/28/07 submission, pp.120-1).

IS Subpopulation
Ovation reported that 93% (208/223) of subjects from IS trials experienced one or more AEs. The AE risk was higher in the IS subpopulation than the Overall population or the Pediatric non-IS subjects subpopulation. The following table summarizes the AE risks occurring in at least 5% of the Overall population and for the IS subpopulation.

Adverse Event	IS Subpopulation (n=223) % (n)	Overall population (n=2148) % (n)
Infections and Infestations		
Upper Respiratory tract infection	47.5% (106)	11% (232)
Otitis media	36.3% (81)	5.9% (126)
Viral infection	19.7% (44)	4.3% (93)
Pneumonia	13% (29)	2.1% (44)
Ear infection	10.8% (24)	2.6% (55)
Sinusitis	7.2% (16)	3.7% (80)
Bronchitis	6.3% (14)	2.5% (54)
Candidiasis	5.4% (12)	0.7% (14)
Gastroenteritis viral	5.4% (12)	1.9% (41)
Urinary tract infection	5.4% (12)	2.1% (46)
Nasopharyngitis	3.1% (7)	7% (154)
Nervous System Disorders		
Sedation	17.9% (40)	3.0% (65)
Somnolence	17.0% (38)	7.9% (169)
Lethargy	6.7% (15)	2.2% (48)
Convulsion	6.3% (14)	8.3% (179)
Status epilepticus	5.8% (13)	1.3% (28)
Headache	0.5% (1)	9.8% (210)
Gastrointestinal Disorders		
Vomiting	16.6% (37)	4.9% (105)
Constipation	13% (29)	3.3% (71)
Diarrhea	12.6% (28)	4.7% (101)
General Disorders and Administration Site Conditions		

Pyrexia	24.2% (54)	5.4% (115)
Unevaluable event	5.4% (12)	2% (42)
Fatigue	0	7.7% (165)
Psychiatric disorders		
Irritability	19.7% (44)	9.0% (20)
Insomnia	11.2% (25)	5.8% (13)
Respiratory, Thoracic, and Mediastinal Disorders		
Nasal Congestion	8.5% (19)	1.7% (36)
Cough	5.4% (12)	1.8% 938)
Skin and Subcutaneous Tissue Disorders		
Rash	9.2% (21)	4.4% (95)
Metabolism and Nutritional Disorders		
Decreased appetite	7.6% (17)	1.4% (31)
Investigations		
Weight increased	0.5% (1)	7.5% (160)

Source 12/28/07 Submission, Table 56, pp. 161-162; Table 10, p.41.

The AEs reported by at least 5% generally occurred more frequently among the IS subjects compared to the Overall population subjects. The greatest differences between the IS and Overall populations were for infection related AEs. While the risks for convulsion were similar for the IS (6.3%) and Overall populations (8.3%), the risk for status epilepticus was notably higher among IS subjects (5.8%) compared to the Overall subjects (1.3%).

Integrated Data

Ovation reported that 96% (3,917/4,077) of the vigabatrin treated epilepsy subjects in the Integrated database reported one or more adverse events (12/28/07 submission, p.180). Ovation provided Table 64 which summarized the adverse events occurring in at least 5% of subjects and I reproduce that table below. Please note that the Prior data and Current data populations cannot be summed to arrive at the Combined population size because 733 subjects contributed data to both the prior and current columns, mostly during study 0098 (12/28/07 submission, p.179).

Table 64. Adverse Events Occurring in ≥5% of Vigabatrin-Treated Subjects- Prior, Current and Combined

Event Category Adverse Event	Prior Data (N=2662) % (n)	Current Data (N=2148) % (n)	Combined (N=4077) % (n)
Any Adverse Event	85.1% (2266)	76.9% (1651)	96.1% (3917)
Eye Disorders			
Vision blurred	6.6% (175)	3.7% (80)	6.3% (255)
Diplopia	6.8% (182)	3.2% (69)	6.2% (251)
Gastrointestinal Disorders			
Nausea	8.3% (222)	2.8% (61)	6.9% (283)
Diarrhea	6.5% (173)	4.7% (101)	6.7% (274)
Vomiting	5.4% (143)	4.9% (105)	6.1% (248)
Constipation	5.0% (132)	3.3% (71)	5.0% (203)
General Disorders and Administration Site Conditions			
Fatigue	19.0% (505)	7.7% (165)	16.4% (670)

Pyrexia	4.3% (114)	5.4% (115)	5.6% (229)
Infections and Infestations			
Nasopharyngitis	9.8% (262)	7.2% (154)	10.2% (416)
Upper respiratory tract infection	6.4% (171)	10.8% (232)	9.9% (403)
Influenza	5.9% (158)	4.0% (86)	6.0% (244)
Otitis media	0.9% (24)	5.9% (126)	3.7% (150)
Investigations			
Weight increased	9.6% (255)	7.5% (160)	10.2% (415)
Musculoskeletal and Connective Tissue Disorders			
Back pain	5.3% (141)	2.2% (47)	4.6% (188)
Nervous System Disorders			
Headache	20.1% (534)	9.8% (210)	18.3% (744)
Somnolence	19.8% (528)	7.9% (169)	17.1% (697)
Dizziness	16.7% (445)	8.2% (177)	15.3% (622)
Convulsion	10.2% (272)	8.3% (179)	11.1% (451)
Visual field defect	0.2% (4)	16.3% (349)	8.7% (353)
Tremor	7.8% (208)	3.8% (82)	7.1% (290)
Nystagmus	7.7% (205)	3.8% (81)	7.0% (286)
Memory impairment	7.5% (199)	3.4% (73)	6.7% (272)
Coordination abnormal	6.6% (175)	4.1% (88)	6.5% (263)
Psychiatric Disorders			
Depression	8.8% (234)	4.7% (100)	8.2% (334)
Insomnia	6.0% (160)	5.1% (110)	6.6% (270)
Irritability	6.2% (166)	4.8% (104)	6.6% (270)
Skin and Subcutaneous Tissue Disorders			
Rash	5.0% (133)	4.4% (95)	5.6% (228)

Ovation commented that with the exceptions of visual field defect, upper respiratory tract infection, otitis media, and pyrexia, the proportion of subjects reporting AEs was higher in the prior data compared to the current data (NDA Amendment, p.179). The Division asked Ovation to search for explanations for the differences in AE risk when comparing prior and current data. In a 4/15/08 response, Ovation provided results from analyses looking for explanatory factors. Ovation noted that study 4020, included among the current data, did not uniformly capture AEs. When Ovation excluded the AE risk data from study 4020, the differences between current and prior data were less marked but did not completely resolve. Ovation noted that a higher proportion of person time in the prior data set was at vigabatrin doses of >=4g/day (27.4%) compared to the current data (16.3%). Ovation found that the current data included a higher proportion of pediatric patients compared to the prior data but when the AE risks for adults and children were analyzed separately, the differences between prior and current data persisted. Similarly, after stratifying by study design (controlled vs. uncontrolled), study dosing (fixed dose vs. flexible dose) and country (US studies vs. non US studies) the differences in AE risks in the prior and current data persisted. Based on these results, Ovation felt the reasons for the higher AE risks in the prior data were mostly due to the use of higher vigabatrin doses in prior data studies and underreporting of AE risks in study 4020, which was included with the current data (Source, Ovation response to Division questions, 4/15/08, pp 6-22)

7.1.5.4 Common adverse event tables

Current Submission

In their proposed vigabatrin labeling, Ovation listed the AEs that occurred in at least 5% of vigabatrin subjects in the Integrated database (see combined column in Table 64 above). Ovation also identified depression and convulsion as the adverse events resulting in discontinuation of at least 1% of subjects treated with vigabatrin.

7.1.5.5 Identifying common and drug-related adverse events

Current Submission
In their proposed labeling, to illustrate treatment related adverse events from clinical trials, Ovation used a table of adverse events occurring in at least 5% of vigabatrin treated subjects from the 2 placebo controlled trials submitted in the original NDA (024 and 025). I reproduce that table below.

Table 1. Treatment-Related Adverse Events Occurring in ≥5% of Patients (Studies 024 and 025)

Body System Preferred Term	Vigabatrin [N=222] %	Placebo [N=135] %
General disorders and administration site conditions		
Fatigue	28.4	14.8
Irritability	9.5	5.9
Gait disturbance	5.4	3.0
Nervous system disorders		
Somnolence	24.3	10.4
Dizziness	19.4	13.3
Headache	14.4	11.9
Nystagmus	13.5	8.1
Tremor	10.8	5.9
Coordination abnormal	8.6	1.5
Amnesia	9.0	3.0
Eye Disorders		
Vision blurred	10.8	4.4
Diplopia	5.4	3.7
Investigations		
Weight increased	7.2	3.0
Psychiatric disorders		
Paraesthesia	6.3	1.5
Depression	6.3	3.0
Disorientation	5.4	0.74
Hypoaesthesia	5.0	1.5
Gastrointestinal Disorders		
Nausea	6.8	5.9

The Division asked Ovation to submit a pooled comparative analysis of AEs using the same 12 controlled trials that they used for the comparative mortality analysis, SAE analysis, and AE leading to dropout analysis (see above). In this pooled analysis, the incidence for any AE was 187.3/100PY (873/466 PY) for vigabatrin compared to 116.9/100 PY (194/166 PY) for carbamazepine, 114.7/100 PY (78/68 PY) for valproate, 470.6/100 PY (8/1.7 PY) for gabapentin, and 342.6/100 PY (346/101 PY) for placebo. I reviewed the results of this analysis and identified the AEs occurring in at least 1% (n=11) of vigabatrin subjects and more frequently when compared to placebo. I list those events below.

Adverse Event	Vigabatrin 466 PY (n=952) Rate/100PY (n)	Carbamazepine 166 PY (n=229) Rate/100PY (n)	Valproate 68 PY (n=113) Rate/100PY (n)	Gabapentin 1.7 PY (n=9) Rate/100PY (n)	Placebo 101 PY (n=393) Rate/100PY (n)
Depression	13.3 (62)	4.2 (7)	5.9 (4)	0	12.9 (13)
Memory impairment	12.2 (57)	9.6 (16)	1.5 (1)	0	11.9 (12)
Coordination abnormal	11.4 (53)	4.8 (8)	5.9 (4)	0	9.0 (9)
Confusional state	7.9 (37)	3.0 (5)	0	58.8 (1)	5.9 (6)
Disturbance in attention	7.3 (34)	6.0 (10)	0	58.8 (1)	6.9 (7)
Asthenia	6.9 (32)	4.2 (7)	2.9 (2)	0	5.9 (6)
Aggression	5.8 (27)	2.4 (4)	2.9 (2)	0	4.0 (4)
Vertigo	5.6 (26)	2.4 (4)	2.9 (2)	0	5.0 (5)
Parasthesia	5.2 (24)	2.4 (4)	1.5 (1)	0	5.0 (5)
Agitation	4.9 (23)	0.6 (1)	0	0	4.0 (4)
Bronchitis	4.7 (22)	2.4 (4)	0	0	4.0 (4)
Edema peripheral	4.1 (19)	0.6 (1)	0	0	3.0 (3)
Urinary tract infection	4.1 (19)	3.0 (5)	0	0	4.0 (4)
Myalgia	3.9 (18)	0.6 (1)	0	0	3.0 (3)
Sleep disorder	3.6 (17)	3.6 (6)	1.5 (1)	0	3.0 (3)
Pruritis	2.9 (13)	6.0 (10)	0	0	2.0 (2)
Hyporeflexia	2.6 (12)	0	0	0	1.0(1)
Eye disorder	2.6 (12)	0.6 (1)	0	0	0
Sedation	2.6 (12)	1.2 (2)	0	0	1.0 (1)
Dyspnea	2.4 (11)	0.6 (1)	0	0	2.0 (2)
Speech disorder	2.4 (11)	0	0	0	2.0 (2)

Source 3/14/08 Submission, Table 14.4; Person years data from p.83

The majority of events appearing above are from the Psychiatric disorder and Nervous system disorder event categories. The only suicide attempt (n=1) and completed suicide (n=1) AEs in these studies were reported for vigabatrin subjects. The incidence of convulsions in this analysis was 16.7/100 PY (78/466 PY) for vigabatrin treated subjects compared to 1.8/100 PY (3/166 PY) for carbamazepine subjects, 7.4/100 PY (5/68 PY) for valproate subjects, 0 (0/1.7PY) for gabapentin subjects and 42.6/100 PY (43/101 PY) for placebo subjects. The incidence of status epilepticus was 3.4/100 PY (16/466 PY) for vigabatrin treated subjects compared to 0 (0/166 PY) for carbamazepine subjects, 1.5/100 PY (1/68 PY) for valproate subjects, 0 (0/1.7 PY) for gabapentin subjects and 5/100 PY (5/101 PY) for placebo subjects. Anemia was reported for 6 vigabatin subjects (1.3/100PY, 6/466PY) 4 carbamazepine subjects (1.7/100PY, 4/229PY) and no valproate, gabapentin, or placebo subjects.

7.1.5.6 Additional analyses and explorations

Prior Submissions

NDA and NDA Amendment (Cutoff date 12/31/95)

Primary Data

Adverse Events by Sex
The NDA Amendment review noted that 76% of females and 68% of males in the primary data cohort reported one or more AEs. Females were more likely than males to report confusion, hypesthesia, tremor, depression, anxiety, emotional lability, and thinking abnormal. Males were more likely than females to report parathesias and aggressive reactions. Without placebo comparator data we cannot determine if the differences in risk by sex observed in these vigabatrin subjects reflect differences in the background risk for these events or are due to a drug sex interaction (Source Amendment Review, p.36).

Adverse Events by Age
The NDA Amendment Review noted that AE reporting among vigabatrin subjects increased with increasing age. Among 2-12 year old subjects the AE risk was 48% (60/125) compared to 95% (53/56) for subjects at least 65 years old. Drowsiness, dizziness, and confusion consistently increased with increasing age. Older patients seemed to be at greater risk for thinking abnormal. The risk for thinking abnormal was 11% among subjects at least 65 years of age (6/56) with the next closest age stratum 0.9% (6/676, age 16-<40). Again, without placebo comparator data we cannot determine if the differences in risk by age observed in these vigabatrin subjects reflect differences in the background risk for these events or are due to a drug age interaction (Source Amendment Review, p.36).

Safety Update (1/1/96-3/15/97)

Adverse Events by Sex
The sponsor identified the following adverse events where the percentage of individuals reporting an event was at least double when comparing vigabatrin treated males and females:

Adverse events by gender in vigabatrin patients

	Males	Females
Aggressive reaction	2.8% (24/861)	0.9% (8/901)
Alopecia	0.6% (5/861)	2.3% (21/901)
Neuropathy	0.9% (8/861)	2.1% (19/901)
Hypoesthesia	1.6% (14/861)	4.2% (38/901)

This analysis suffered from the same limitations noted above with respect to lack of comparator data.

Adverse Events by Age
In the Safety Update, the sponsor's presentation of AE's stratified by age groups used 6 categories for a relatively small number of patients and resulted in few subjects in the youngest and oldest categories, limiting the value of comparisons among strata. In addition, there was no presentation for a similar, unexposed (control) group (Source Final Safety Update Review, p.10).

Current Submission

Overall Safety Population (3/16/97-6/30/07)

Adverse Events by Sex
Ovation reported that the incidence of non-gender specific adverse events were similar for males and females (12/28/07 submission, p.59). I examined appendix 3 Table 4.1.8 to identify any adverse events occurring in at least 1% of male or female subjects and where the risk was at least double when comparing males and females. I provide those results below.

Adverse Events Occurring in >= 1% of Male or Female Subjects and Where the Risk Was at Least Double When Comparing Males and Females

Adverse Event	Risk in Males (n=1,074)	Risk in Females (n=1,061)
Urinary Tract infection	1.4% (15)	2.9% (31)
Affect lability	0.6% (6)	1.4% (15)
Nervousness	0.6% (6)	1.2% (13)
Pain	0.5% (5)	1.5% (16)
Gastroesophageal reflux disease	1.1% (12)	0.3% (3)
Injury	1.7% (18)	0.7% (7)
Anticonvulsant toxicity	1.5% (16)	0.6% (6)
Alopecia	0.6% (6)	2.5% (27)
Rhinorrhea	0.4% (4)	1.4% (15)
Sinus congestion	0.5% (5)	1.1% (12)
Arthralgia	1.2% (13)	2.5% (27)
Lymphadenopathy	0.2% (2)	1.3% (14)
Hypertension	1.4% (15)	0.6% (6)
Hot flush	0.4% (4)	1.0% (11)
Hypersensitivity	0.3% (3)	1.3% (14)

Excludes Reproductive System and Breast Disorders System Organ Class

This analysis suffered from the same limitations noted above with respect to lack of untreated comparator data.

Adverse Events by Age
In their analysis of adverse events by age, Ovation reported that vigabatrin treated subjects in the <2 year old group had the highest adverse event risk (94%, 205/219) in the Overall population followed by the >=65 year old group (86%, 19/22), the 40-<65 year old group (82%, 301/365), the 12-<16 year old group (79%, 140/177), the 16-<40 year old group (77%, 594/771), and the 2-12 year old group (74%, 199/268) (12/28/07 submission, p.57). Since the <2 year old group consists of IS patients, any observed differences from age stratified analyses could be due to

differences in the underlying populations, differences in age, combinations of these factors or other unconsidered factors.

Ovation reported that nasopharyngitis and depression were more commonly reported by adults than children and that children more commonly reported upper respiratory tract infections, pyrexia, abnormal behavior, otitis media, vomiting, influenza, viral infection, aggression, streptococcal pharyngitis and sinusitis.

I examined appendix 3 Table 4.1.7 to identify any common adverse events occurring in at least 5% of all subjects and where the risk was at least double for one age group when compared to the other age groups. I provide those results below.

Adverse Events Occurring in at least 5% of All Subjects, and at least Double for One Age Group when Compared to the Other Age Groups

Event	<2 yrs (n=219)	2-<12 yrs (n=268)	12-<16 yrs (n=177)	16-<40 yrs (n=771)	40-<65 yrs (N=365)	>=65 yrs (n=22)
Visual field defect	0	17% (45)	25% (45)	21% (165)	23% (83)	27% (6)
Headache	<1% (1)	15% (41)	14% (25)	11% (82)	9% (34)	9% (2)
Convulsion	6% (13)	14% (38)	19% (33)	7% (57)	8% (29)	0
Dizziness	0	4% (12)	10% (18)	10% (78)	12% (44)	18% (4)
Somnolence	17% (38)	6% (15)	6% (11)	7% (51)	8% (29)	13% (3)
Upper respiratory tract infection	48% (104)	17% (45)	13% (23)	5% (37)	3% (11)	0
Nasopharyngitis	3% (7)	14% (38)	11% (19)	6% (47)	6% (22)	5% (1)
Otitis media	36% (79)	10% (26)	5% (9)	<1% (6)	<1% (2)	0
Insomnia	11% (24)	1% (3)	2% (4)	5% (38)	6% (22)	5% (1)
Irritability	20% (42)	4% (11)	3% (6)	3% (22)	2% (9)	0
Depression	0	2% (5)	4% (7)	7% (52)	6% (22)	0
Fatigue	0	9% (23)	8% (15)	11% (81)	7% 925)	23% (5)
Pyrexia	24% (53)	11% (30)	5% (9)	1% (10)	1% (5)	5% (1)
Vomiting	16% (36)	9% (23)	5% (9)	3% (24)	1% (5)	5% (1)
Diarrhea	12% (27)	5% (13)	5% (8)	3% (26)	4% (14)	5% (1)
Weight increased	<1% (1)	13% (34)	17% (30)	7% (51)	5% (19)	0
Other events of interest (<5% of all subjects but demonstrating notable risk differences by age)						
Sedation	18% (40)	<1% (2)	1% (2)	2% (13)	1% (4)	0
Decreased appetite	8% (17)	<1% (2)	<1% (1)	1% (8)	<1% (1)	0

Dose Response

In response to a Division request for a dose response analysis, Ovation provided a table of treatment emergent adverse events. Using pooled data from 5 fixed-dose, randomized, placebo-controlled CPS trials, Ovation calculated person time exposure for the different dose groups and assigned adverse events to the dose category at which the event occurred. I reviewed the table to identify AEs occurring in at least 1% of vigabatrin subjects (n=4) and at least twice as frequent when compared to placebo. For any such events, I selected the events where the rate appeared to increase with increasing vigabatrin dose. I present those results below.

Dose Response for Select AEs from 5 Fixed Dose Randomized Placebo CPS Controlled Trials

Event	Vigabatrin Dose (g/day)					Placebo
	>0-2 g/day (34 PY) Rate (n)	2-<3 g/day (17 PY) Rate (n)	3-<4 g/day (62 PY) Rate (n)	4-<5 g/day (15 PY) Rate (n)	>=5 g/day (13 PY) Rate (n)	(141 PY) Rate (n)
Abdominal pain upper	0.06 (2)	0.12 (2)	0.10 (6)	0.07 (1)	0.16 (2)	0.02 (3)
Edema peripheral	0.06 (2)	0.12 (2)	0.11 (7)	0.13 (2)	0.23 (3)	0.01 (1)
Swelling	0	0.06 (1)	0.02 (1)	0	0.23 (3)	0.01 (1)
Weight increase	0.21 (7)	0.42 (7)	0.18 (11)	0.53 (8)	0.39 (5)	0.04 (6)
Back pain	0.15 (5)	0.18 (3)	0.11 (7)	0.33 (5)	0.16 (2)	0.05 (7)
Muscle twitching	0	0.06 (1)	0.03 (2)	0.13 (2)	0.31 (4)	0.01 (2)
Myalgia	0.06 (2)	0	0.06 (4)	0	0.16 (2)	0.02 (3)
Coordination abnormal	0.21 (7)	0.36 (6)	0.19 (12)	0.46 (7)	0.39 (5)	0.05 (7)
Hypoaesthesia	0.06 (2)	0.12 (2)	0.13 (8)	0.26 (4)	0	0.04 (6)
Hyporeflexia	0.06 (2)	0	0.10 (6)	0	0.16 (2)	0.01 (1)
Memory impairment	0.18 (6)	0.18 (3)	0.26 (16)	0.73 (11)	0.39 (5)	0.06 (8)
Abnormal dreams	0.03 (1)	0.12 (2)	0.03 (2)	0.07 (1)	0.16 (2)	0.01 (1)
Confusional state	0.06 (2)	0.18 (3)	0.18 (11)	0.20 (3)	0.47 (6)	0.02 (3)
Expressive language disorder	0.06 (2)	0.18 (3)	0.03 (2)	0.20 (3)	0.31 (4)	0.02 (3)

Source 5/1/08 Submission, Table 1.2

For most of the events listed above, the small number of outcomes precludes drawing firm conclusions about dose response.

Analyses of Specific Events

Depression and Suicide

Ovation provided a summary of safety data related to depression and suicide with vigabatrin (Source 12/28/07 Submission, pp.227-228). The summary included descriptions of results from clinical pharmacology studies, literature reports, adverse event risks in the development program clinical trials, comparisons of risks for vigabatrin and placebo subjects in controlled trials and a summary of spontaneous reports for depression and suicide in patients treated with vigabatrin.

Ovation noted that clinical pharmacology studies of the effects of vigabatrin on psychometric and psychomotor function showed no significant effects on concentration, attention, coordination, memory, or mood. Ovation referenced the 1994 NDA submission that included the results from these studies but did not provide details about these studies in the current amendment submission.

Ovation acknowledged literature reports of behavioral symptoms in patients treated with vigabatrin but said these adverse events were associated with confounding factors such as withdrawal, control of seizures, cerebral lesions, mental retardation, and overdose.

Ovation summarized an expert report presented in the NDA Amendment (5/31/97) that examined the risks for psychiatric AEs using a pool of three controlled trials. Ovation noted that the vigabatrin clinical trials were not specifically designed to study relationships between vigabatrin and psychiatric events. Using data from controlled trials 021, 024, and 025, a psychiatric expert examined the incidence of psychosis (hallucination, paranoid reaction, psychosis, and schizophrenic reaction), depression, agitation, aggression reaction, manic symptoms (manic reaction, euphoria, libido increased, and cyclothymic reaction), suicide attempt, emotional lability, and anxiety (anxiety and nervousness). This analysis found an increased risk for psychotic symptoms (2.5% vs. 0.3%, $p=0.028$) and depression (12.1% vs. 3.5%, $p<0.001$) among vigabatrin subjects. The NDA Amendment review of the psychiatric expert report noted that the 49 vigabatrin subjects who experienced depression in these 3 controlled trials had more serious outcomes (6/49 discontinued, 3/49 hospitalized, and 2/49 with psychotic depression) compared to the placebo subjects (0/11) who developed depression (Source NDA Amendment review, p.50). The expert felt that most of the subjects that developed psychosis had mild symptoms and noted that some cases resolved with discontinuation of vigabatrin, some with continuation of vigabatrin and some with neuroleptic treatment.

Ovation reported that during open label studies, agitation and aggression were the most commonly reported psychiatric AEs and that 2 of 38 subjects with a history of schizophrenia had exacerbations of their disease during vigabatrin treatment. In the open label trials, the rate of discontinuation for psychiatric AEs was 6.1% for subjects with a history of psychiatric illness compared to 5.2% for subjects with no such history.

Ovation also summarized psychiatric event data from the 1998 Response to the Approvable letter. In that submission, the sponsor reported that the discontinuation rates for select psychiatric AEs (depression and psychosis, psychomotor slowing, and drowsiness and fatigue) was low. The sponsor reported that 2.5% of subjects in all North American controlled trials discontinued, was hospitalized, or received medical treatment for depression. One and a half percent of subjects in North American trials discontinued, was hospitalized, or received medical treatment for psychosis. The sponsor also noted that 2 vigabatrin and no placebo subjects in North American trials attempted suicide.

There was 1 completed suicide among 4,855 subjects in epilepsy trials included in the Integrated database. In addition, there were 21 Depression SAEs (0.44%) 12 Suicidal ideation (0.25%) SAEs, 10 Suicide attempt (0.21%) SAEs, 2 (0.04%) Depression suicidal SAEs and 1 (0.02%) major depression SAE.

Using the data from 12 pooled controlled studies, one vigabatrin subject died as a result of suicide (0.2/100 PY, 1/446 PY) compared to no comparator subjects (placebo 101 PY, Carbamazepine 166 PY, Valproate 68 PY, Gabapentin 1.7 PY). The table below provides the non fatal depression related SAE risks for the pooled controlled trial data. These data suggest an

increased risk for depression and suicide related SAEs among vigabatrin subjects compared to the comparator subjects in these trials, although the number of SAEs is relatively small.

Depression Related SAEs for Pool of Phase II/III Studies with Vigabatrin

Event	Vigabatrin 446 PY Rate/100 PY	Carbamazepine 166 PY Rate/100 PY	Valproate 68 PY Rate/100 PY	Gabapentin 1.7 PY Rate/100 PY	Placebo 101 PY Rate/100 PY
Depression	2.2 (10)	0.6 (1)	0	0	0
Suicidal ideation	0.4 (2)	0	1.5 (1)	0	0
Suicide attempt	0.2 (1)	0	0	0	0
Depressed mood	0.2 (1)	0	0	0	0

Source 3/14/08 Submission, Table 14.2, pp.37-8

In the Integrated database Ovation reported that 71 subjects (1.5%, 71/4855) discontinued for depression AEs. In addition, Ovation reported that 10 subjects (0.2%) discontinued for suicidal ideation, 5 (0.1%) for suicide attempt, 2 (0.04%) for depressed mood, 2 (0.04%) for depression suicidal, 2 (0.04%) for major depression, and 1 (0.02%) for completed suicide.

The table below provides the discontinuation for AE risks for depression related AEs for the pooled controlled trial data. These data suggest an increased risk for depression AEs leading to discontinuation among vigabatrin subjects compared to the comparator subjects in these trials.

Depression Related AEs Leading to Discontinuation for Pool of Phase II/III Studies with Vigabatrin

Event	Vigabatrin 446 PY Rate/100 PY	Carbamazepine 166 PY Rate/100 PY	Valproate 68 PY Rate/100 PY	Gabapentin 1.7 PY Rate/100 PY	Placebo 101 PY Rate/100 PY
Depression	3.4 (15)	1.2 (2)	2.9 (2)	0	1.0 (1)
Suicidal ideation	0.4 (2)	0	0	0	1.0 (1)
Suicide attempt	0.2 (1)	0	0	0	0
Depressed mood	0.2 (1)	0	0	0	0
Major depression	0.2 (1)	0	0	0	0

Source 3/14/08 Submission, Table 14.3, pp.44-5.

In the Integrated database, 8.2% (334/4077) of subjects reported depression AEs, 1.0% (40/4077) reported depressed mood AEs, 0.6% (23/4077) reported suicidal ideation AEs 0.3% (13/4077) reported suicide attempt AEs, 0.1% (4/4077) reported depression suicidal AEs, and 0.07% (3/4077) reported major depression AEs and 1 subject committed suicide.

The table below provides the depression related AE risks for the pooled phase II/III controlled trial data. These data suggest similar risks for depression AEs for vigabatrin and placebo, and

increased risks for depression AEs among vigabatrin subjects compared to the active comparator subjects in these trials.

Depression Related AEs for Pool of Phase II/III Studies with Vigabatrin

Event	Vigabatrin 446 PY Rate/100 PY	Carbamazepine 166 PY Rate/100 PY	Valproate 68 PY Rate/100 PY	Gabapentin 1.7 PY Rate/100 PY	Placebo 101 PY Rate/100 PY
Depression	13.9 (62)	4.2 (7)	5.9 (4)	0	12.9 (13)
Suicidal ideation	1.1 (5)	0	0	0	1.0 (1)
Suicide attempt	0.2 (1)	0	0	0	0
Depressed mood	3.1 (14)	0.6 (1)	0	0	4.0 (4)
Major depression	0.2 (1)	0	0	0	0

Source 3/14/08 Submission, Table 14.4, pp.67-9.

There did not appear to be a clear dose response for depression related AEs in a pool of 5 randomized placebo controlled trials that included more than one dose of vigabatrin. I provide those results below.

Event	Vigabatrin Dose (g/day)					Placebo
	>0-2 g/day (34 PY) Rate (n)	2-<3 g/day (17 PY) Rate (n)	3-<4 g/day (62 PY) Rate (n)	4-<5 g/day (15 PY) Rate (n)	>=5 g/day (13 PY) Rate (n)	(141 PY) Rate (n)
Depression	0.18 (6)	0.77 (13)	0.26 (16)	0.40 (6)	0.47 (6)	0.05 (7)
Depressed mood	0.06 (2)	0.12 (2)	0.11 (7)	0	0	0.01 (2)
Suicidal ideation	0.03 (1)	0.06 (1)	0	0	0.08 (1)	0
Suicide attempt	0	0	0	0	0.08 (1)	0

Source 5/1/08 Submission, Table 1.2

Peripheral Neuropathy

Ovation summarized data related to peripheral neuropathy in individuals treated with vigabatrin. Ovation explained that as part of the 1997 response to the Approvable letter, the previous sponsor submitted an expert review of neuropathy related adverse events. The sponsor's expert reported that in North American controlled trials and their open label follow up studies, 2.4% (11/457) of vigabatrin subjects developed symptoms and or signs of a distal, large fiber, sensory, polyneuropathy. Manifestations of polyneuropathy included numbness or tingling in the toes or feet, reduced lower limb vibration or positional sensation, and progressive loss of reflexes, starting at the ankles. The sponsor's expert found no relationship between neuropathy and daily vigabatrin dose or cumulative dose. The sponsor reported that for cases with follow up, neuropathy was reversible upon discontinuation of vigabatrin. Ovation noted that the reviewed

studies were not designed to systematically evaluate peripheral neuropathy and did not include nerve conduction studies, quantitative sensory testing or skin or nerve biopsy.

In addition to summarizing the expert review, Ovation provided a review of post marketing reports of neurological events. Ovation reviewed reports received from 3/15/97 through 6/30/07. Ovation provided estimates of postmarketing exposure from 9/22/89 through 9/22/06 including an estimate of 821,969 person years and 1,600,000 patients exposed. Ovation commented that few postmarketing reports described events related to peripheral neuropathy. Ovation reported that the most common adverse event possibly associated with peripheral neuropathy was parasthesia (n=3). Ovation noted that one additional report described peripheral neuropathy. Ovation concluded that postmarketing reports describing peripheral neuropathy were rare; often include few details, in some cases described confounding factors.

Hepatic Injury
In the original NDA review, the medical officer summarized 12 cases of hepatic injury in subjects/patients treated with vigabatrin. The summary did not specify the source of the cases (clinical trials, spontaneous reports, compassionate use, etc.). The summary did note that 7 of the 12 cases resulted in death and that the range of exposure duration prior to these events was 4 days to 6 years (median 8.5 months). In addition, half of the cases occurred in individuals aged 10 years or younger (3 deaths, 2 survived, 1 unknown). The medical officer commented that the clinical laboratory liver function results were unremarkable except for the documented declines in SGPT.

In the 1997 Amendment to the NDA, the sponsor provided an expert review of hepatic injury cases with vigabatrin. The consultant, Dr. Zimmerman, wrote that "Vigabatrin appears to be associated with a very low risk of hepatotoxicity." The consultant recommended informing prescribers that ALT levels may be unreliable for detecting early hepatotoxicity (given that vigabatrin loweres these levels) and that attention to clinical manifestations of liver injury (jaundice, hepatomegaly, nausea) is necessary. The consultant also commented that "...the lack of production of active metabolites (1) leads to the inference that hepatic injury by this drug is unlikely. Nevertheless, the possibility that vigabatrin might produce hepatic injury by another mechanism cannot be excluded.

The consultant reviewed available information for all 21 hepatic serious adverse events and offered an opinion about the relationship to vigabatrin. The cases included 3 deaths and 3 non fatal hepatic AEs from vigabatrin clinical trials. The consultant ruled out vigabatrin as a cause in 2 of the fatal cases (one attributed to metastatic carcinoma and the other to clarithromycin). The consultant could not rule out vigabatrin as a cause of fulminant hepatitis death from a Japanese controlled trial (not part of the integrated safety database). The consultant concluded that 3 non-fatal hepatic SAEs from clinical trials were not related to vigabatrin (one viral, two due to concomitant medications). The consultant's summaries of the fatal clinical trials cases are included below.

Patient 202-06Y-06 (Protocol JGVG-CL-202)
A 34-year-old female from Japan taking vigabatrin 3 g/day for 251 days concomitantly with phenytoin and phenobarbital. The patient experienced fulminant hepatitis and was hospitalized. All medications were stopped abruptly after occurrence of the event. The patient eventually died. Autopsy findings showed fulminant hepatitis. Other drugs include phenytoin and phenobarbital. No way to distinguish between vigabatrin and other anticonvulsants.
Attribution to vigabatrin: Possible.

Patient 31730707 (VGST-MUMF-350)
A 39-year old male from Italy had been taking vigabatrin 3.5 g/day for approximately 6 years concomitantly with phenytoin, primidone, aspirin, clarithromycin, and dipyrone, when he experienced hyperpyrexia probably due to an infection. He was treated at home with aspirin, noraminopyridine, and clarithromycin. Subsequently, the patient was admitted to an intensive care unit where he died 2 days later. Hepatic insufficiency attributed to clarithromycin.
Attribution to vigabatrin: Unlikely.

Patient 30330028 (Protocol 097-306)
A 45-year-old male from Denmark had been taking vigabatrin in doses ranging from 4.5 to 6 g/day for just under 2 years when he died from metastatic brain carcinoma. Over the course of his therapy, this patient suffered increasing neurological symptoms from his cerebral tumor including depression, dementia memory loss, nausea and vomiting, nervousness, sleep disturbances, and dizziness. As his cancer metastasized to his colon and liver, he also suffered from abdominal pain, flu, hiccups and muscle atrophy. Increased liver enzymes, including AST were reported and attributed by the reporting physician to the hepatic tumors.
Attribution to vigabatrin: Unlikely.

The remaining 15 hepatic AEs were identified from spontaneous reports (estimated exposure was 125,000 patients). The consultant concluded that 3 deaths and one transplant case identified from spontaneous reports were probably or possibly related to vigabatrin, but did not feel vigabatrin was a contributing factor in 2 other deaths. For the remaining serious hepatic adverse events, the consultant felt that 8 were probably or possibly related to vigabatrin and one was not. The consultant noted the lack of information about the cases and stated that the duration of treatment argued against vigabatrin as the cause.

I provide the consultant's summaries and comments for the fatal/transplant post marketing cases that the consultant classified as probably/possibly related to vigabatrin.

Patient 94001440
A 34-year-old female from France had been taking vigabatrin 2 g/day for 789 days concomitantly with phenytoin, carbamazepine, and paracetamol when she developed hepatic disease and was hospitalized for the hepatorenal syndrome with necrotizing hepatitis, portalsystemic encephalopathy, and generalized seizures. She was considered a candidate for liver transplant; however, there was a sudden decrease in factor V with acidosis and the patient subsequently died. The reporting physicians assessed the events as being unrelated to vigabatrin therapy but possibly related to carbamazepine or phenytoin. Unable to rule out association with vigabatrin.
Attribution to vigabatrin: Possible.

Patient 94003033
A 10-year-old female from Germany had been taking vigabatrin 1.5g/day for 1 year concomitantly with carbamazepine and clonazepam, when she was hospitalized with a diagnosis of acute liver necrosis and subsequently died. A liver biopsy revealed subacute hepatodystrophy with hepatic necrosis and intrahepatic cholestasis that apparently attributed to a toxic hepatosis which may have been present for a long time. According to the reporting physicians, it was not possible to determine whether the hepatosis was due to an endogenous or exogenous toxin.

Attribution to vigabatrin: Possible.

Patient 94007742
A 26-year-old female from the U.K. had been taking vigabatrin 4 g/day for 137 days concomitantly with valproate and gabapentin when she experienced fulminant hepatic failure and hepatic coma. Subsequently she received a liver transplant. Reporting physicians were not certain whether the event was of post-viral etiology or drug induced. If drug induced, both vigabatrin and gabapentin was suspected. Patient survived.
Attribution to vigabatrin: Possible.

Patient 95001102
An 18-year-old male from France had been taking vigabatrin 5 g/day for 1,192 days when he developed hepatic disease. He had previously taken carbamazepine and primidone but was on vigabatrin alone for 13 months prior to the event. It should be noted that this patient also was potentially exposed to toxic chemicals in the workplace. His hepatic disease presented with gastroenteritis, then icterus, and he was hospitalized. The patient developed signs of hepatic encephalopathy with no fever or rash. He also developed massive acute hepatitis during hospitalization. Bilirubin continued to increase and the patient developed secondary renal impairment. The patient subsequently died due to intracranial hypertension secondary to cerebral edema.
Attribution to vigabatrin: Possible.

Among the 13 cases that the consultant classified as probably or possibly related to vigabatrin, 10 were taking other medications known or reported to cause hepatotoxicity. The consultant felt the reports provided insufficient information to support a definite causal relationship between vigabatrin and hepatotoxicity or to assess demographic risk factors.

When specifically asked what information to provide prescribers, the consultant responded, "**Information provided to prescribing** physicians should include reference to the reported hepatic adverse events and to the fact that the inhibitory effect of vigabatrin on transaminase levels may preclude the use of transaminase levels **to detect hepatotoxicity.**"

In the current submission, the sponsor reported a death due to hepatic failure from a clinical trial (described above with deaths). That case is confounded by the documented complicated post-operative clinical course (status epilepticus, presumed hypotension requiring pressor therapy, etc.) making it unclear as to whether vigabatrin contributed to hepatic failure in this subject. The sponsor did not identify any additional hepatic related adverse events from clinical trials in the current submission.

Based on the information available in 1997, the Division proposed labeling that referenced the cases of liver injury with vigabatrin and attempted to describe the risk in terms of the exposure and estimated underreporting. Ovation proposes no reference to hepatic injury in labeling. Ovation cites the minimal biotransformation of vigabatrin, use of concomitant medications in many cases, and the long duration of treatment prior to development of liver injury as arguments against a relationship between vigabatrin and hepatotoxicity.

To be able to calculate a reporting rate for hepatic failure resulting in death or transplant, the Division asked Ovation to provide reports for all serious hepatic post marketing cases not included in the expert review. Ovation provided 12 reports. The list included 3 deaths. One death was not likely related to vigabatrin because the patient had stopped vigabatrin 2 months prior and was being treated with phenytoin and carbamazepine at the time of the event. The second death

was a literature report of the clinical trial patient that was taking clarithromycin and was mentioned above. The third report was also literature report but appeared to be a previously unreported case with not obvious alternative explanation. A summary of that case is provided below.

A 3 year old male with a history of pre-term birth (30 weeks), perinatal cerebral hemorrhage, generalized leucomalacia, developmental delay, microcephaly, spastcity, and simple motor seizures beginning at age 14 months was treated with phenobarbital. Vigabatrin was added due to insufficient seizure control. Nine months later, the patient presented with fever, hypovolemia, hypoglycemia, coma, elevated AST (577 U/L), elevated ammonia, elevated BUN and creatinine. The patient was diagnosed with liver failure. The patient developed a severe coagulopathy, a GI bleed, and died. A post mortem liver biopsy revealed massive parenchymal necrosis, periportal fibrosis, central sclerosis of lobules, and no evidence of fatty deposits. The authors stated that that other causes, acute infectious disease, or other toxic events had been excluded. The authors did not provide the details of the evaluation for causes of liver failure in this patient.

I searched PubMed and found no additional published cases of hepatic injury with vigabatrin.

Clinical trial hepatic failure risk

Over the course of development program, the sponsors have reported 4 clinical trial deaths for hepatic related events. Three events are from prior submissions and one event is from the current submission. One death appeared to be due to metastatic cancer and another was likely due to concomitant medication (clarithromycin). The third death occurred in the setting of multiple organ failure that followed a hypotensive episode in a subject who developed status epilepticus. One additional hepatic related death occurred in a Japanese clinical trial that was not part of the integrated database. Thus there were no unexplained liver failure cases resulting in death or transplant in the clinical development program.

From post marketing reports, there were four hepatic related deaths and one transplant. In none of the cases was a likely alternative explanation documented but all were taking multiple medications at the time of the event. If one were to consider the five post marketing reports and the one Japanese study report, there were a total of 6 deaths or transplants with 856,000 person years of vigabatrin use. This yields a risk for liver failure resulting in death or transplant of 7.0/1,000,000PY. Excluding cases with exposure to vigabatrin for more than 1 year prior to developing liver injury leaves 3 cases of death/transplant and a reporting rate of 3.5/1,000,000PYs.

Discussion

According the Dr. Zimmerman, the sponsor's consultant, there was no preclinical evidence of vigabatrin related hepatotoxicity. There did not appear to be an increased risk of transaminase elevations among vigabatrin treated subjects in controlled trials, although vigabatrin does result in *decreases* in transaminases that could possible obscure these test result comparisons. Ovation found no "Hy's Law" cases (transaminase elevations >3x ULN and total bilirubin >2.0mg/dL) in the development program. The clinical trial database included 3 hepatic related deaths. All three cases were confounded (one metastatic cancer, one concomitant chlarithromycin, one in the setting of multiple organ failure following hypotension). There was a case from a Japanese study

that was not part of the sponsor's development program and therefore should not be counted among the clinical trial deaths.

In the post marketing period there have been 6 reports of hepatic injury resulting in death/transplant. The reporting rate for these events exceed the general population background rate we have used in the past to assess these events although this background rate may not accurately reflect the rate in patients with seizure disorder who are exposed to medications that are known to cause liver injury. I do not believe that available data are sufficient to allow the conclusion that vigabatrin causes liver injury but the data do merit close monitoring.

Cognition/Neuropsychiatric Function
Ovation commented that animal studies demonstrated anti-aggression and anti-depression effects of vigabatrin but not anxiolytic, antipsychotic, learning or memory effects.

In adult human healthy volunteers, Ovation reported that vigabatrin had no effect on cognition or other neuropsychiatric function in acute or sub chronic doses. Furthermore, Ovation reported that chronic vigabatrin doses in subjects with epilepsy did not have an effect on psychometric or psychomotor function. Ovation cited clinical pharmacology studies that reportedly did not find differences in learning, memory, reaction time, attention, or concentration when comparing normal volunteers exposed to vigabatrin to volunteers exposed to placebo.

Ovation cited data neuropsychiatric test data collected during vigabatrin clinical trials. In studies 024 and 025 (US controlled epilepsy trials), Ovation reported that comparing vigabatrin and placebo subjects, no differences were observed in verbal and non verbal memory, coordination, adjustment, and general intellect tests.

Ovation noted that study 024 found statistically significant differences in the change from baseline when comparing vigabatrin and placebo subjects for the Profile of Mood States for the following items: depression/dejection, fatigue/inertia, confusion/bewilderment and total mood disturbance. Ovation commented that the differences were due to small improvements in the placebo group. Study 025 did not replicate the findings for the Profile of Mood States but instead found a significant, dose dependent decrease in the Digit Cancellation Test score.

Ovation reported that they had little data available for examining the effects of vigabatrin on cognition and neuropsychological functions in children. Ovation noted that neurocognitive data from studies 071754PR0118, 071754PR0192, and 071754PR0221, and 071754PR0294 were not analyzed because of the small sample sizes. In addition neurocognitive data from study 071754PR0201, the open label follow up study for studies 071754PR0118, 071754PR0192 were not analyzed. Ovation reported that an independent study found that for 6 children (mean age, 5.5 years) with partial epilepsy treated with vigabatrin the DQ, a global measure of mental development, remained unchanged at the end of the follow-up period

Ovation reported results from developmental tests administered to IS patients during vigabatrin clinical trials. In study W019, Ovation noted that at baseline 3/40 subjects were noted as normal, 33/40 suspect and 4/40 untestable using the Denver Test of Psychomotor Development. At end

study, 23% were rated normal and 60% suspect. In study FR03, Ovation reported improvement in the Developmental Quotient in all subjects (statistical test not performed due to missing data). Ovation also reported results from longitudinal neuropsychological evaluations of a group of 7 children (mean age, 5.5 years) with infantile spasms due to tuberous sclerosis who were treated with vigabatrin. The development quotient was assessed at onset of initiation of vigabatrin and at the end of the follow-up (a mean of approximately 3 years). At baseline all children demonstrated moderate to severe mental retardation; five with autistic behavior. After disappearance of spasms, DQ increased by approximately 10 points in 6 of the subjects (p=0.03). In 4 subjects, the DQ rose by 20 points; one subject showed an increase by 30 points and another one increased by 40 points. One subject remained with severe mental retardation and autistic behavior. Ovation interpreted these results as suggesting that vigabatrin does not adversely affect mental function.

Ovation felt that the information presented supported that vigabatrin had little effect on neuropsychological function in adults and children with epilepsy. Ovation's conclusions are not consistent with the findings from phase II/III controlled trials where vigabatrin was associated with an increased risk for a number of CNS AEs including somnolence, sedation, coordination abnormalities and confusional state.

Edema related events
In the Integrated Database, Ovation identified 3% (124/4077) patients with AE of edema peripheral, 0.4% (16/4077) with edema, 0.1% (5/4077) with generalized edema, 0.1% (5/4077) with localized edema, 0.1% (4/4077) with facial edema, <0.1% (3/4077) with pitting edema <0.1% (3/4077) with gravitational edema. None of these events were SAEs, and only 5 edema peripheral events and 2 edema events led to d/c.

In the group of 12 phase II/III controlled trials there were slight increases in risk among vigabatrin subjects compared to control subjects for edema peripheral (vigabatrin 4.3/100PY, 19/446PY; placebo 3/100PY, 3/101PY), edema (vigabatrin 1.1/100PY, 5/446PY; placebo 0/101PY) generalized edema (vigabatrin 0.7/100PY, 3/446PY; placebo 0/101PY) One placebo and no vigabatrin subject had an AE of pitting edema. In these studies, none of the edema related AEs were SAEs. One vigabatrin (0.2/100PY, 1/446PY) and no placebo subjects (0/101PY) discontinued for an edema related AE (Source 3/15/08 Submission).

Dose response analyses of controlled trials data suggested an increasing risk of edema peripheral and generalized edema with increasing vigabatrin dose but not other edema related adverse events. The analysis is limited by the small number of edema related events. The results are provided below.

Dose Response for Edema AEs from 5 Fixed Dose Randomized Placebo CPS Controlled Trials

Event	Vigabatrin Dose (g/day)					Placebo
	>0-2 g/day (34 PY) Rate (n)	2-<3 g/day (17 PY) Rate (n)	3-<4 g/day (62 PY) Rate (n)	4-<5 g/day (15 PY) Rate (n)	>=5 g/day (13 PY) Rate (n)	(141 PY) Rate (n)
Edema peripheral	0.06 (2)	0.12 (2)	0.11 (7)	0.13 (2)	0.23 (3)	0.01 (1)

Generalized edema	0	0	0.03 (2)	0.07 (1)	0.08 (1)	0
Edema	0.03 (1)	0	0.02 (1)	0	0	0
Pitting edema	0	0	0	0	0	0.01(1)

Source 5/1/08 Submission, Table 1.2

The Division requested additional data to further explore the risk of edema AEs among vigabatrin subjects. We were specifically interested in events related to peripheral/generalized edema, face edema, and pulmonary edema. Ovation provided a data set that included adverse event information and lab data information for vigabatrin subjects that experienced an AE included in the Standardized MedDRA query (SMQ) of hemodynamic edema, effusions, and fluid overload and the SMQ of angioedema. Ovation identified 281 subjects with 361 AEs that met the SMQ search criteria. A number of these AEs did not appear to describe events related to **the Division's intended analysis. I excluded events describing localized/focal edema (ex. brain** edema, joint effusion, nasal edema, etc.) and events not directly related to the purpose of the analysis (wheezing, hypersensitivity). After exclusion of these events, there were 215 subjects with 273 edema related AEs. I list the edema AE preferred terms below.

Included Edema Event Preferred Terms from the Integrated Database

Included Edema Preferred Terms	N
Eyelid edema	2
Face edema	2
Fluid retention	25
Generalized edema	5
Gravitational edema	5
Edema	21
Edema peripheral	163
Periorbital edema	2
Pitting edema	4
Pulmonary edema	5
Swelling	30
Swelling Face	9

For the 215 subjects in this analysis, 140 were female, 72 were male and sex was not reported for 3 subjects. The average age of subjects with an edema AE was 38.2 years (median 38.5 years) and the range of ages was from 0.6 years to 72 years (age missing for 9 subjects). The median **time to onset for the subjects'** first edema AE was 77 days (mean 260 days, range 0-4456 days).

Two of the included 273 edema related AEs were SAEs (both pulmonary edema events). For these 2 subjects, (0101/13490007, 71754-W-002/078-051) pulmonary edema was the only edema related AE reported. Eight subjects discontinued for edema related AEs. The edema AEs leading to discontinuation were edema peripheral (n=4), edema (n=2), gravitational edema and pulmonary edema.

Of the 215 subjects with an edema AE, 50 also had a weight gain AE. Twenty three of these weight gain AEs were reported within 30 days of the edema AE. Fifteen weight gain AEs were

reported more than 30 days prior to the edema event and 9 were reported more than 30 days after the edema event was reported (relationship not known for 3 events).

Of the 215 subjects with an edema AE, 19 also had a cardiovascular AE. Six of these CV AEs (high blood pressure n=3, low blood pressure, pulmonary edema, and cardiac arrest), occurred within 30 days of the edema AE. Five CV AEs (isolated PVC, heart racing, heart palpitations, hypotension, hypertension) occurred more than 30 days before the edema AE and 5 occurred more than 30 days after (palpitations n=2, ventricular tachycardia, acute MI, poor blood circulation) (relationship not known for 3 events).

Of the 215 subjects with an edema AE, 12 also had a renal AE. Two of these renal AEs (passing urine less, incontinence), occurred within 30 days of the edema AE. Five renal AEs (difficulty in micturation, urinary problems, increased frequency of urination, difficulty initiating urination, and decreased albumin) occurred more than 30 days before the edema AE and 5 occurred more than 30 days after (excessive urination, increased nocturia, difficulties in micturition, dimished bladder strength, and urgency but voiding small amount).

Three of the 215 subjects with an edema AE also had an AE of proteinuria. Proteiuria was reported 5 days before the edema AE in 1 subject and 32 days after the edema AE in the second subject (relationship not know for the third subject).

Of the 215 subjects with edema AEs, 104 had a total of 114 serum albumin results within 30 days of the AE. Seven of the 114 serum albumin results were <3.5g/dL.

Of the 215 subjects with edema AEs, 109 had a total of 119 serum creatinine results within 30 days of the AE. Sixteen results were above 1.0mg/dL with the highest reported creatinine being 1.2mg/dL. Only one subject with an edema AE experienced an increase in creatinine from baseline of >0.3mg/dL. Subject 1A/269, a subject with a history of nephrotic syndrome, **experienced edema, proteinuria, hypertension, and worsening nephritic syndrome. This subject's** creatinine rose from 0.2mg/dL at baseline to 1.0mg/dL.

None of the subjects with an edema related AE also had a hepatic AE.

The data provided by Ovation identifies a number of subjects that developed edema during treatment with vigabatrin. These events were infrequently classified as SAEs and were not common causes of discontinuation from trials. These edema events in these subjects did not appear to be related to cardiovascular, renal or hepatic adverse events. Lab data did not suggest that these subjects were experiencing hypoalbuminemia, proteinuria, or increases in creatinine, although the lab data was incomplete.

SUDEP

In their proposed labeling, Ovation updated their SUDEP rate for vigabatrin using the data from the Integrated safety population. Ovation did not discuss SUDEP in their Amendment safety **presentation. Ovation's updated** SUDEP rate for vigabatrin (1.9/1,000 person years,

18/7091PYs) was similar to the rates presented in their previous submissions and continues to be in the range of SUDEP rates observed during the development programs for other AEDs.

Status Epilepticus
In their proposed labeling, Ovation provided risks for status epilepticus in 3 placebo controlled epilepsy trials and in the Integrated population. Ovation reports a risk of status epilepticus of 2.3% (5/222) among vigabatrin subjects and 2.2% (3/135) for placebo subjects in the pooled controlled trials. For the Integrated safety database, Ovation reports that the risk for status epilepticus was 2.6% (105/4077). Ovation did not discuss status epilepticus in their Amendment safety presentation.

7.1.6 Less Common Adverse Events

Included in an appendix to this review is a table that presents adverse events occurring at rates between 1/100 and 1/1000, and adverse events estimated to occur at rates less than 1/1000 for the overall safety population.

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

Prior Submissions

NDA and NDA Amendment

Primary Data
The analyses of lab data from US studies was presented in the original NDA and was not repeated in the NDA amendment. The sponsor reported that laboratory data from US studies were obtained at pre and post dose visits. The majority of subjects had liver transaminases tests, BUN, creatinine, electrolytes, and hematological (hemoglobin, hematocrit, WBC, differential, and platelets) tests. The NDA included comparisons of lab results by treatment from controlled studies as well as results for all vigabatrin treated subjects. The protocols for the US studies stated that clinically significant abnormal lab results would be followed up. The protocol did not require rechallenges for abnormal lab results and any unscheduled lab test results were not included in the lab data analyses. Studies 024 and 025 used central labs to analyze samples while studies 005 and 006 used local labs (Response to Division questions, 4/15/08, pp.85-6).

The majority of subjects in the NDA amendment presentation had liver transaminases tests, BUN, creatinine, electrolytes, and hematological (hemoglobin, hematocrit, WBC, differential, and platelets) tests. A smaller subset of subjects had urinalysis testing, coagulation testing, and AED blood levels. The sponsor noted that the laboratory site normal ranges were available for only 32 of the 87 protocols included in their analyses and for those protocols without laboratory site normal ranges, sponsor defined normal ranges were used to identify outliers (NDA

Amendment Sb-V2-P263). The protocols for the non-US primary studies did not require that clinically significant abnormal lab results to be followed up. The protocol did not require rechallenges for abnormal lab results and any unscheduled lab test results were not included in the lab data analyses. Ovation reported that the protocols did not mention if central or local labs were used to analyze samples (Response to Division questions, 4/15/08, p.86).

Safety Update (1/1/96-3/15/97)
The Safety Update did not include laboratory result analyses.

Current Submission

Overall Safety Population (3/16/97-6/30/07)

The studies summarized in the current submission required laboratory testing including liver transaminases tests, BUN, creatinine, electrolytes, and hematological (hemoglobin, hematocrit, WBC, differential, and platelets) tests. Ovation reported that none of the protocols for the studies in the current submission specifically addressed whether patients were followed until any abnormal results normalized or if patients were rechallenged following abnormal test results. Except for IS study 1A which used local labs, all studies that collected labs used central labs to analyze the samples. Unscheduled labs results were not used in the safety data analyses (Response to Division questions, 4/15/08, pp.86-7).

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

Prior Submissions

NDA and NDA Amendment (Cutoff date 12/31/95)
In the NDA, the sponsor presented comparative lab data for subjects participating in the US controlled epilepsy trials (024, 025). The NDA amendment presented pooled data from the study dosing periods for vigabatrin treated subjects from non-US, CRF supported studies (non US primary data and the Secondary data) (Source NDA Amendment review, p.36).

Current Submission
Ovation did not provide lab data analyses for the Overall population in their NDA amendment. Ovation did provide summaries of select lab data for the adult partial epilepsy subpopulation, the pediatric non-IS subpopulation and the IS subpopulation. For the adult partial epilepsy subpopulation, Ovation provided results taken directly from the study reports for studies 0101 (controlled adjunctive therapy), 0222 (controlled monotherapy), 0223 (controlled monotherapy), and 0242 (long term study) (Source: NDA Amendment 12/28/07 submission, p.111). For the pediatric non-IS subpopulation, Ovation summarized select lab results from controlled CPS studies 0118, 0221, and 0192, and from long term CPS studies 0201 and 0294 (Source: NDA Amendment 12/28/07 submission, pp.156-7). Ovation presented limited laboratory analyses for IS subjects from study 1A (Source: NDA Amendment 12/28/07 submission, p.172).

7.1.7.3 Standard analyses and explorations of laboratory data

Prior Submissions

NDA and NDA Amendment (Cutoff date 12/31/95)

Primary Data
The lab data for the US studies was presented in the original NDA and consisted of mean change analyses, outlier analyses, and review of lab related AEs. The NDA amendment included pooled analyses of lab data for the combined primary non-US studies and secondary studies. The sponsor did not provide comparative analyses from controlled trials in the NDA amendment. The **sponsor's NDA amendment lab analyses consisted** of outlier risk calculations for vigabatrin exposed subjects and presentation of lab related AEs. The sponsor did not provide mean change from baseline analyses in the NDA amendment because they said they lacked site normal ranges across protocols (Source: NDA Amendment, p. 286).

The following table lists the outlier criteria used for the primary studies (NDA and NDA amendment).

Lab Outlier Criteria for US and Primary Non US Studies

Analyte	Low Outlier	High Outlier
SGOT (U/L)	N/A	>=150 and increase 50
SGPT (U/L)	N/A	>=165 and increase 50
Alkaline phosphatase (U/L)	N/A	>=390 and increase 75
Total protein (g/dL)	<= 4.5 and decrease 1	>=10 and increase 2
Albumin (g/dL)	<=2.5 and decrease 0.5	>=5 and increase 1.5
Total bilirubin (mg/dL)	N/A	>=2 and increase 0.5
LDH (U/L)	N/A	>=750 and increase 75
GGTP (U/L)	N/A	>=300 and increase 100
Creatinine (mg/dL)	N/A	>=2 and increase 0.5
BUN (mg/dL)	N/A	>=30 and increase 10
RBC ($x10^6$/L)	<=3.5 and decrease 0.5	N/A
Hemoglobin (g/dL)	Males <=11.5 and decrease 1.1 Females <=9.5 and decrease 1.1	N/A
Hematocrit (%)	Males <=37 and decrease 5 Females <=32 and decrease 5	N/A
Platelet count ($x10^3$/L)	<=75 and decrease 20	>=700 and increase 100
WBC ($x10^3$/L)	<=2.8 and decrease 0.5	>=16 and increase 5
Neutrophils ($x10^3$/L)	<=1.2 and decrease 0.2	N/A
Lymphocytes ($x10^3$/L)	<=0.8 and decrease 0.2	>=5 and increase 3
Eosinophils ($x10^3$/L)	N/A	>=0.57 and increase 0.4
Sodium (meq/L)	<=126 and decrease 5	>=156 and increase 4
Potassium (meq/L)	<=3 and decrease 0.9	>=6 and increase 0.5
Chloride (meq/L)	<=90 and decrease 10	>=118 and increase 10
Calcium (mg/dL)	<=8.2 and decrease 0.7	>=12 and increase 0.8
Phosphorus (mg/dL)	<=1.7 and decrease 1.8	>=5.5 and increase 1.8
Glucose (mg/dL)	<=50 and decrease 20	>=175 and increase 89
Cholesterol (mg/dL)	N/A	>=600 and increase 100
Amylase (U/L)	N/A	>=220 and increase 50

Uric acid (mg/dL)	N/A	Males >=10.5 and increase 2 Females >=8.5 and increase 2

Source NDA amendment Table B-39.

7.1.7.3.1 Analyses focused on measures of central tendency

Prior Submissions

NDA and NDA Amendment (Cutoff date 12/31/95)

The NDA reviewer did not discuss analyses of lab data that focused on measures of central tendency. In the NDA amendment, the sponsor presented an analysis of mean change data to further examine changes in hematocrit and hemoglobin among vigabatrin treated subjects compared to placebo. The sponsor looked for a dose response using data from the 2 US controlled studies. The sponsor reported finding a dose response in their analyses and commented that the trends achieved statistical significance in the dataset for US controlled trial 71754-3-C-025 (Source: NDA Amendment, p.286). I present the results for the pooled US controlled trials dose response analysis below.

Hematocrit and Hemoglobin Change from Baseline to End of Study by Dose, Us Controlled Epilepsy Studies

		US Controlled Epilepsy Studies (024, 025)				
Parameter		Placebo	1g VGB	3g VGB	6g VGB	All VGB
Hematocrit	Change from baseline	0.53	0.58	-0.24	-1.39	-0.29
Hemoglobin	Change from baseline	0.02	-0.12	-0.44	-0.91	-0.46

Source: 5/31/97 Submission, table B-47

The sponsor also presented in the NDA amendment results from mean change lab analyses that demonstrated that vigabatrin was associated with reduction of transaminases in US trials and the sponsor identified a dose response for this finding. Those results are summarized below.

Mean Change from Baseline for AST and ALT, Studies 024 and 025

Parameter	Placebo (n=135)	VGB 1g/d (n=45)	VGB 3g/d (n=135)	VGB 6g/d (n=41)	All VGB (n=221)
AST	-0.18 ±4.34	-1.51 ±5.53	-3.65 ± 6.05	-3.88 ± 4.35	-3.26 ± 5.71
ALT	-0.07 ± 8.12	-11.82 ± 9.30	-16.23 ± 10.10	-19.12 ±12.88	-15.87± 10.72

Source: 5/31/97 Submission, table B-42, p.SB-V2-P273.

Current Submission

Adult Subpopulation

Ovation provided selected mean change results (those with statistically significant differences) from 3 of the 4 studies that comprise the adult subpopulation database (0101, 0222, and 0223).

Those results are summarized below. For the remaining adult study, 0242, Ovation reported that the observed mean changes for labs were small and not clinically significant and that one subject had an SAE of thrombocytopenia and one had an SAE of renal failure (both cases described above with SAEs).

Select Lab Test Mean Change from Baseline Results from Adult Vigabatrin Studies

Laboratory test	Treatment	Mean Change ± SD
Study 0101		
SGPT (ALT) (U/L)	Vigabatrin (n=110)	-13.87 ± 1.64
	Placebo (n=56)	0.17 ± 2.30
Creatinine (mg/dL)	Vigabatrin (n=110)	-0.04 ± 0.01
	Placebo (n=56)	0.00 ± 0.01
RBC (/mm^3)		
Females	Vigabatrin (n=59)	-0.18 ± 0.03
	Placebo (n=23)	0.06 ± 0.05
Males	Vigabatrin (n=47)	-0.11 ± 0.04
	Placebo (n=30)	0.06
Hemoglobin (g/dL)		
Females	Vigabatrin (n=59)	-0.44 ± 0.09
	Placebo (n=23)	-0.07 ± 0.15
Males	Vigabatrin (n=47)	-0.27 ± 0.11
	Placebo (n=30)	0.02 ± 0.14
Study 0222		
SGPT (ALT) (U/L)	Vigabatrin (n=7)	-25.29 ± 14.10
	Gabapentin (n=8)	0.88 ± 10.79
Creatinine (mg/dL)	Vigabatrin (n=7)	-0.09 ± 0.11
	Gabapentin (n=8)	0.05 ± 0.08
Sodium (mEq/L)	Vigabatrin (n=7)	2.57 ± 3.26
	Gabapentin (n=8)	-1.88 ± 3.98
Study 0223		
SGPT (ALT) (U/L)	Vigabatrin 1g/day (n=17)	-13.76 ± 13.09
	Vigabatrin 3g/day (n=15)	-17.47 ± 12.42
	Vigabatrin 4g/day (n=17)	-16.59 ± 13.01
	Vigabatrin 6g/day (n=18)	-15.56 ± 10.11

Source: 12/28/07 Submission, pp.111-112.

The information provided by Ovation for study 0101 is consistent with previously submitted data demonstrating declines in ALT, hemoglobin, and RBCs in vigabatrin treated subjects.

I reviewed all lab mean change results listed in the study reports for the adult vigabatrin studies in the current submission. While the hematocrit mean change comparison between vigabatrin and placebo in study 0101 had a p value>.05, the difference was in the same direction as for hemoglobin with larger mean declines among vigabatrin subjects. I provide those results below.

Hematocrit Mean Change from Baseline Results from Study 0101

Laboratory test	Treatment	Mean Change ± SD
Study 0101		
Hematocrit (%)		

Females	Vigabatrin (n=59)	-1.70 ± 0.42
	Placebo (n=23)	-0.98 ± 0.67
Males	Vigabatrin (n=47)	-1.99 ± 0.44
	Placebo (n=30)	-1.28 ± 0.56

Source: Study report for 0101

Subjects in study 0223 experienced declines in hemoglobin and hematocrit but there did not appear to be a clear dose response relationship in this study. I provide those results below.

Hemoglobin and Hematocrit Mean Change from Baseline Results from Study 0223

Study 0223		
Hemoglobin (g/dL)	Vigabatrin 1g/day (n=17)	-0.14 ± 0.67
	Vigabatrin 3g/day (n=18)	-0.01 ± 0.80
	Vigabatrin 4g/day (n=17)	-0.10 ± 0.77
	Vigabatrin 6g/day (n=18)	-0.09 ± 0.71
Hematocrit (%)	Vigabatrin 1g/day (n=17)	-0.58 ± 2.50
	Vigabatrin 3g/day (n=18)	-0.54 ± 2.21
	Vigabatrin 4g/day (n=17)	-0.34 ± 2.71
	Vigabatrin 6g/day (n=18)	-0.43 ± 2.76

Source: Study report for 0223

Mean change from baseline for alkaline phosphatase did not appear to be consistent across studies. In study 0101, the mean change from baseline for alkaline phosphatase among vigabatrin subjects was -0.76 compared to 5.24 for placebo but in study 0222, the mean change from baseline for alkaline phosphatase was similar for vigabatrin subjects (4.29) and placebo subjects (5.24). In study 0223 the mean change from baseline for alkaline phosphatase for the vigabatrin 1g/day group was -44.29, for the 3g/day group was -19.13, for the 4g/day group was -18.88 and for the 6g/day group was -7.83.

Pediatric non-IS Subpopulation
Ovation provided selected mean change results (those with statistically significant differences) from the 3 controlled studies that comprise the pediatric non-IS subpopulation database (0118, 0221, 0192). Those results are summarized below. For the long term studies 0201 and 0294, Ovation only reported that the mean changes from baseline for all parameters were not clinically relevant (12/28/07 Submission, p.157).

Mean Change from Baseline Results from Pediatric non-IS Controlled Trials (0118, 0221, and 0192)

Laboratory test	Treatment	Mean Change ± SD
Study 0118		
SGPT (ALT) (U/L)	Vigabatrin (n=90)	-22.19 ± 18.14
	Placebo (n=27)	-3.12 ± 5.57
SGOT (AST) (U/L)	Vigabatrin (n=90)	-10.13 ± 13.88
	Placebo (n=27)	0.54 ± 5.60
RBC (x $10^3/\mu L$)	Vigabatrin (n=87)	-0.22 ± 0.29
	Placebo (n=29)	0.13 ± 0.61
Hemoglobin (g/dL)	Vigabatrin (n=87)	-0.35 ± 0.74
	Placebo (n=29)	0.56 ± 1.57

Hematocrit (%)	Vigabatrin (n=87)	-1.04 ± 2.34
Study 0221		
SGPT (ALT) (U/L)	Vigabatrin (n=40)	-12.40 ± 7.40
	Placebo (n=40)	1.90 ± 8.12
SGOT (AST) (U/L)	Vigabatrin (n=40)	-5.59 ± 7.67
	Placebo (n=40)	0.97 ± 9.35
Alkaline phosphatase (U/L)	Vigabatrin (n=40)	15.03 ± 68.79
	Placebo (n=40)	-11.46 ± 31.02
Creatinine (mg/dL)	Vigabatrin (n=40)	-0.07 ± 0.07
	Placebo (n=40)	0.01 ± 0.08
Hemoglobin (g/dL)	Vigabatrin (n=39)	-0.39 ± 0.65
	Placebo (n=40)	0.19 ± 0.71
Hematocrit (%)	Vigabatrin (n=39)	-1.13 ± 2.26
	Placebo (n=40)	0.62 ± 2.35
Platelets (x $10^3/\mu L$)	Vigabatrin (n=38)	16.72 ± 39.96
	Placebo (n=40)	-15.83 ± 82.57
Study 0192		
SGPT (ALT) (U/L)	Vigabatrin (n=20)	-11.45 ± 10.71
	Placebo (n=21)	-3.33 ± 4.03

Source: 12/28/07 Submission, pp.156-7.

As the table above illustrates, the changes in transaminases, and hemoglobin seen in the adult population were also observed in the pediatric non-IS population.

I reviewed all lab mean change results listed in the original study reports for the pediatric non-IS vigabatrin studies. Study 0118 randomized subjects to three different vigabatrin doses (20mg/kg/day, 60mg/kg/day, and 100mg/kg/day) and therefore provides information about dose response. The study 0118 lab results suggest dose response for transaminase decline and hemoglobin, hematocrit and RBC declines. I provide those results below.

Transaminase, Hemoglobin, Hematocrit, and RBC Mean Change from Baseline Results from Study 0118

Study 0118		
SGPT (ALT) (U/L)	Placebo (n=27)	-3.12 ± 5.57
	Vigabatrin 20mg/kg/day (n=29)	-13.52 ± 8.30
	Vigabatrin 60mg/kg/day (n=29)	-22.19 ± 18.14
	Vigabatrin 100mg/kg/day (n=32)	-19.53 ± 11.48
SGOT (AST) (U/L)	Placebo (n=27)	0.54 ± 5.60
	Vigabatrin 20mg/kg/day (n=29)	-5.41 ± 11.59
	Vigabatrin 60mg/kg/day (n=29)	-6.93 ± 9.19
	Vigabatrin 100mg/kg/day (n=32)	-10.13 ± 13.88
Hemoglobin (g/dL)	Placebo (n=29)	0.56 ± 1.57
	Vigabatrin 20mg/kg/day (n=28)	0.02 ± 0.59
	Vigabatrin 60mg/kg/day (n=31)	-0.20 ± 0.72
	Vigabatrin 100mg/kg/day (n=28)	-0.35 ± 0.74
Hematocrit (%)	Placebo (n=29)	1.84 ± 5.20
	Vigabatrin 20mg/kg/day (n=28)	-0.41 ± 2.01
	Vigabatrin 60mg/kg/day (n=31)	-0.30 ± 2.20
	Vigabatrin 100mg/kg/day (n=28)	-1.04 ± 2.34

RBC (x $10^3/\mu L$)	Placebo (n=29)	0.13 ± 0.61
	Vigabatrin 20mg/kg/day (n=28)	-0.10 ± 0.20
	Vigabatrin 60mg/kg/day (n=31)	-0.15 ± 0.22
	Vigabatrin 100mg/kg/day (n=28)	-0.22 ± 0.29

Source Study report for 0118, Table 34.

In study 0192, the mean change from baseline for alkaline phosphatase among vigabatrin subjects was 20.18 compare to -2.50 for placebo. Similarly, in study 0221, the mean change from baseline for alkaline phosphatase for vigabatrin subjects was 15.03 compared to -2.50 for placebo. The remaining mean change lab results from study 0192 and from study 0221 were unremarkable.

The mean changes from baseline lab results from long term open label studies 0201 and 0204 were generally in the same direction as the changes observed in vigabatrin subjects in the controlled trials.

IS subpopulation
Ovation did not provide mean change analyses for the lab data from study 1A in the Current submission. The Division requested mean change analyses for study 1A. Ovation noted that lab values were not collected during the blinded phase of the trial, when subjects were randomized to low or high dose vigabatrin. Lab data are available only for the open label phase of the trial, which allowed flexible dosing. When Ovation presented the results from the open label phase, the results were grouped by high dose and low dose, reflecting the original randomization, and for all subjects combined. Since the classification by dose does not necessarily reflect the dosing that the subject received at the time of the lab test, I present the combined data below.

Subjects in study 1A experienced declines in AST and ALT. At month 1, the mean change from baseline for AST was -10.2 and for ALT was -17.7. There did not appear to be marked additional decline during months 3-30 (Source 5/16/08 Response to Questions, pp.23-25).

At month 1, subjects in study 1A experienced a mean decline in hematocrit of -0.65 and hemoglobin of -0.33. For the remaining months of the study the surviving subjects experienced mean increases and deceases in hematocrit and hemoglobin compared to baseline (Source 5/16/08 Response to Questions, pp.41-44). For platelets, study subjects consistently experienced mean decreases for all study months with the largest mean decline compared to baseline at month 24 (-56.7 x10^3, n=39) (Source 5/16/08 Response to Questions, pp.52-53).

7.1.7.3.2 Analyses focused on outliers or shifts from normal to abnormal

Prior Submissions

NDA and NDA Amendment (Cutoff date 12/31/95)

Primary Data

The following table summarizes select lab outlier risks for the US epilepsy controlled trials in the original NDA.

Select Lab Outlier Results, US Controlled Epilepsy Studies 024, 025

Analyte	Vigabatrin	Placebo
High SGOT	0.4% (1/222)	0.7% (1/135)
Low Sodium	4% (8/221)	4% (5/135)
Low Calcium	20% (45/221)	30% (40/135)
Low glucose	4% (8/221)	4% (5/135)
High Amylase	5.2% (3/58)	3.8% (2/53)
Low Hematocrit	13% (28/221)	6% (8/135)
Low Hemoglobin	0.9% (2/221)	(0/135)
Low WBC	10% (23/221)	5% (7/135)
Low neutrophils	7% (16/221)	4% (6/135)
Low lymphocytes	15.4% (68/442)	6.7% (9/135)

No vigabatrin or placebo subjects in US epilepsy controlled trials had lab results that met outlier criteria for SGPT, bilirubin, alkaline phosphatase, BUN, or creatinine (Source Amendment Review, pp.38-41, NDA Amendment p.Sb-V2-P286).

Safety Update (1/1/96-3/15/97)

The safety update review included reviews of responses to Division questions that were part of the Approvable letter. One of the Division's questions asked the sponsor to characterize transaminase test low outliers. In response, the sponsor noted that in the North American controlled trials, 94% (263/280) of subjects had a 60-100% maximum decrease in their ALT compared to baseline. Furthermore, 4% (11/280) had an ALT result of 0. In the placebo subjects from these trials, 78% had a 0%-40% maximum decrease in their ALT compared to baseline. In the vigabatrin subjects, the decrease in ALT appeared to be dose related. In looking at the time course, the sponsor noted that 94% had their first abnormal ALT (defined as a 20% drop from baseline) during the first 3 weeks of therapy. The sponsor noted that 47% reached their maximum decrease within 4-8 weeks of staring vigabatrin. AST was also decreased in vigabatrin exposed subjects but less so than the ALT. The sponsor reported that 93% of subjects in the North American controlled trials had a 0-60% maximum decrease in their AST from baseline with 54% experiencing maximum decreases in the 20-40% range. No vigabatrin exposed subjects had an AST result of 0. The drop in AST also appeared to be dose related. The time to onset for the first abnormal AST was 4-8 weeks after starting vigabatrin and 40% reached their maximum decrease during this period of time (Source Safety Update review, p.20).

In addition to requests about transaminase results, the Division requested additional information regarding anemia related events in vigabatrin subjects. The sponsor confirmed the finding of an excess of anemia adverse events (4) and clinically significant outliers for anemia (12) in the vigabatrin treated group (5.7%; 16/280) compared to the placebo group (1.6%, 3/188) in the North American controlled trials. The sponsor reported that none of the 16 vigabatrin subjects with an anemia adverse event or outlier result required hospitalization, transfusion, or discontinuation from the study for this event. The Division requested information about the work up of these events and the sponsor reported that no other relevant lab tests (Coombs, ferritin, reticulocyte count etc.) were reported for these patients. For the 4 patients with anemia recorded

as an adverse event, the sponsor noted that they had underlying medical conditions associated with anemia (PUD, ulcerative colitis) or a history of anemia. They stated that 3 of these individuals were treated (2 with iron, 1 with folate) and improved (Source Safety Update review, p.20).

Current Submission

Adult Subpopulation

I reviewed the lab outlier analyses in the study reports for controlled trials 0101, 0222, and 0223. None of these studies included low transaminase outlier criteria. For the lab test outliers examined in these studies, the frequency of outliers was low and there was little difference in risk between vigabatrin and control groups or among different vigabatrin dose groups. In study 0101, 1 vigabatrin (0.5%, 1/190) and no placebo (0/100) subjects had a low outlier for RBC, hematocrit, and hemoglobin (Source Study report 0101, p.113). In study 0222, 1 vigabatrin (10%, 1/10) subject had a low hemoglobin outlier compared to no gabapentin subjects (0/10) and 2 vigabatrin subjects (20%, 1/10) had low hematocrit outliers compared to no gabapentin subjects (Source Study report 0222, p.88). The results from study 0223 were similar to the results for the other Adult epilepsy studies. I provide the low outlier results for hemoglobin and hematocrit from study 0223 in the table below.

Treatment	Outlier at any time % (n)
Low Hemoglobin (females <=9.5g/dL, males <=11.5g/dL)	
Vigabatrin 1g/day	0/17
Vigabatrin 3g/day	0/18
Vigabatrin 4g/day	5.3% (1/19)
Vigabatrin 6g/dL	4.8% (1/21)
Low Hematocrit (females <=32%, males <=37%)	
Vigabatrin 1g/day	5.3% (1/17)
Vigabatrin 3g/day	0/18
Vigabatrin 4g/day	5.3% (1/19)
Vigabatrin 6g/dL	9.5% (2/21)

Source: Study report for 0223, pp.111-112

Pediatric non IS Subpopulation

I reviewed the lab outlier analyses in the study reports for controlled trials 0118, 0221, and 0192. None of these studies included low transaminase outlier criteria. In study 0118, the risks for low hemoglobin and hematocrit outliers were similar across the three vigabatrin dose levels and for placebo (Source Study report 0118, pp.138-9). In study 0221, 9.3% (4/43) of vigabatrin subjects and 2.3% (1/43) of placebo subjects had a low hemoglobin outlier while 33% (14/43) of vigabatrin subjects and 14% (6/43) of placebo subjects experienced low hematocrit outliers (Source Study report 0221, p. 110). In study 0192, no vigabatrin or placebo subjects experienced low hemoglobin outliers and 18% (5/28) of vigabatrin subjects and 11% (3/27) of placebo subjects experienced low hematocrit outliers (Source Study report 0192, p.94).

IS Subpopulation

The study report for 1A noted that of the 145 subjects with normal hemoglobin at baseline, 18 (12.4%) had a low outlier result after 1 month of vigabatrin treatment and of the 147 subjects

with a normal hematocrit at baseline, 8 (5.4%) had a low result after 1 month of vigabatrin treatment (source Study report 1A, p.368).

7.1.7.3.3 Marked outliers and dropouts for laboratory abnormalities

Prior Submissions

NDA and NDA Amendment (Cutoff date 12/31/95)

The NDA review noted that there were no reports of deaths or withdrawal for hematology test results (NDA review p.76). The NDA amendment review identified one primary non US study subject that discontinued for a hypochromic anemia that improved with iron replacement (NDA amendment review, p.41).

Current Submission

Overall Safety Population (3/16/97-6/30/07)

Ovation provided a table summarizing the lab related SAEs. Ovation identified 2 SAEs of renal failure acute, 2 of anemia and one of DIC (Amendment Submission, Table 20, p.80). In addition, there was one subject that died from acute hepatic failure that was not included in the table. These events were discussed above with the SAEs. Ovation reported that one subject discontinued for low platelets (discussed above with SAEs) and one for increased ALP (Amendment Submission, Table 4.1.6.1, p.7340).

Given the findings of mean decreases and increased risk for low outliers in hemoglobin and hematocrit in subjects treated with vigabatrin, the Division asked Ovation to look for clinically important anemia events. Specifically, the Division asked Ovation to identify all study subjects with a hemoglobin result below 8g/dL and or a hematocrit result below 24%.

Ovation identified 8 cases of treatment emergent anemia meeting the search criteria, but 4 of the cases did not appear to be actual anemia events. Subject 057-013 had a hematocrit result of 13% at the time her hemoglobin was 12.5g/dL and Ovation noted that all of her other hematological test results were normal. Subject 25405 had a hemoglobin of 7g/dL at the time her hematocrit was 53%. This subject's remaining hematocrit values during the study were above 47%. Subjects 013-007 and 089-013 had low hemoglobin and hematocrit results but repeat testing within 3 days were normal, suggesting that the abnormal results were spurious.

Two subjects with lab results that met the anemia search criteria had apparent explanations for their results. Subject 26324 had a history of microcytic anemia and had a hemoglobin of 8.4g/dL with a hematocrit of 31% at baseline. The subject's lowest recorded hemoglobin was 7.8g/dL (Hct 27%). Subject 0269, a 26 month old with IS, developed renal disease (glomerulonephritis) and required treatment with erythropoietin and transfusions. This subject's lowest recorded hemoglobin was 5.6g/dL (Hct 18.3%) and he remained anemic throughout the study.

Ovation provided no clear explanatory factors for the treatment emergent anemia in the remaining 2 cases. Subject 0308, a 13 month old male with IS, had a baseline hemoglobin of 11.7g/dL (Hct 35.2%). During the study, his hemoglobin dropped to 7.9g/dL (Hct 24.5%) and Ovation commented that this occurred when the subject stopped taking iron supplements. The subject's hemoglobin improved to 11.2g/dL (Hct 33.8%) by the end of the study, but Ovation was not able to determine if the subject received treatment for the anemia. Subject 0174, a 5 month old with IS had a baseline hemoglobin of 13.1g/dL (Hct 40.1%). By visit 4, the subject's hemoglobin had declined to 5.3g/dL (Hct 13.1%). The subject withdrew from the study for lack of efficacy and Ovation did not provide follow up information. Anemia was not reported as an adverse event for this subject. (Source 5/16/08 Submission, pp. 6-8).

7.1.7.4 Additional analyses and explorations

7.1.7.5 Special assessments

Hepatic Injury
The Division asked Ovation to identify the number of vigabatrin clinical trial subjects with evidence of hepatic injury as defined by elevation of AST or ALT to 3 X ULN AND elevation of total bilirubin to 2 X ULN. Ovation identified 64 studies that captured at least one baseline and one on treatment transaminase result and total bilirubin result. Ovation manually reviewed lab result data listings for the studies included in prior submissions, for which electronic data sets do not exist, and queried lab result electronic datasets for the studies included in the current submission. Ovation reported that no vigabatrin subjects in the development program studies had elevation of AST or ALT to 3 X ULN AND elevation of total bilirubin to 2 X ULN (Source 5/2/08 Submission).

The Division also asked Ovation to provide an analysis of pooled controlled trial data that summarized the risk for transaminase and total bilirubin high outliers for vigabatrin and comparator treatments. The results of that analysis are provided in the following table (Source 5/2/08 submission).

Table 3. Liver Function Data

	Vigabatrin (N=952) n / N (%)[a]	Carbamazepine (N=229) n(%)[a]	Valproate (N=113) n(%)[a]	Gabapentin (N=9) n(%)[a]	Placebo (N=393) n(%)[a]	Total (N=1696) n(%)[a]
ALT (SGPT) (U/L)[a]						
>1.5x ULN	4 / 892 (0.45)	4 / 226 (1.77)	2 / 110 (1.82)	1 / 7 (14.29)	1 / 354 (0.28)	12 / 1589 (0.76)
>3x ULN	1 / 892 (0.11)	1 / 226 (0.44)	1 / 110 (0.91)	0 / 7 (0.00)	0 / 354 (0.00)	3 / 1589 (0.19)
>5x ULN	0 / 892 (0.00)	0 / 226 (0.00)	0 / 110 (0.00)	0 / 7 (0.00)	0 / 354 (0.00)	0 / 1589 (0.00)
>10x ULN	0 / 892 (0.00)	0 / 226 (0.00)	0 / 110 (0.00)	0 / 7 (0.00)	0 / 354 (0.00)	0 / 1589 (0.00)
>20x ULN	0 / 892 (0.00)	0 / 226 (0.00)	0 / 110 (0.00)	0 / 7 (0.00)	0 / 354 (0.00)	0 / 1589 (0.00)
AST (SGOT) (U/L)[a]						
>1.5x ULN	2 / 778 (0.26)	3 / 226 (1.33)	1 / 111 (0.90)	0 / 9 (0.00)	0 / 343 (0.00)	6 / 1577 (0.38)
>3x ULN	2 / 778 (0.26)	0 / 226 (0.00)	1 / 111 (0.90)	0 / 9 (0.00)	0 / 343 (0.00)	3 / 1577 (0.19)
>5x ULN	1 / 778 (0.13)	0 / 226 (0.00)	0 / 111 (0.00)	0 / 9 (0.00)	0 / 343 (0.00)	1 / 1577 (0.06)
>10x ULN	0 / 778 (0.00)	0 / 226 (0.00)	0 / 111 (0.00)	0 / 9 (0.00)	0 / 343 (0.00)	0 / 1577 (0.00)
>20x ULN	0 / 778 (0.00)	0 / 226 (0.00)	0 / 111 (0.00)	0 / 9 (0.00)	0 / 343 (0.00)	0 / 1577 (0.00)
Total Bilirubin (mg/dL)[b]						
>1.5x ULN	1 / 927 (0.11)	0 / 223 (0.00)	0 / 112 (0.00)	0 / 6 (0.00)	0 / 374 (0.00)	1 / 1642 (0.06)
>2x ULN	0 / 927 (0.00)	0 / 223 (0.00)	0 / 112 (0.00)	0 / 6 (0.00)	0 / 374 (0.00)	0 / 1642 (0.00)
Either AST or ALT > 3x ULN with Total Bilirubin > 1.5x ULN	0 / 916 (0.00)	0 / 229 (0.00)	0 / 113 (0.00)	0 / 6 (0.00)	0 / 367 (0.00)	0 / 1631 (0.00)

n= number of subjects with specified abnormality / N=number of subjects normal (i.e. ≤ ULN) at baseline. Percentages are calculated based on the number of subjects normal at baseline.
[a] ULN=Upper limit of normal, defined as 40 U/L.
[b] ULN=Upper limit of normal, defined as 1.2 mg/dl..

These results suggest that transaminase and total bilirubin high outlier results were uncommon among the subjects enrolled in the pool of vigabatrin controlled trials. One must interpret the transaminase elevation outlier results in light of the evidence presented above that suggests vigabatrin causes dose dependent declines in transaminase results.

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

Prior Submissions

NDA and NDA Amendment (Cutoff date 12/31/95)

The NDA review did not document the extent of vital sign testing in the vigabatrin studies. The NDA review included a summary of outlier risks for systolic and diastolic blood pressure, pulse, and weight observed in the US epilepsy controlled trials 024 and 025. The NDA amendment review noted that the sponsor provided a summary of vital sign mean changes from study 025 but included no summary of vital sign data from non US studies (NDA Amendment review, pp.44-45).

Safety Update (1/1/96-3/15/97)
The Safety update did not provide a summary of vital sign data.

Current Submission

Overall Safety Population (3/16/97-6/30/07)

The studies included in the current NDA amendment submission collected vital signs including pulse, systolic and diastolic blood pressure, respiration, and in some cases weight.

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

Prior Submissions

NDA and NDA Amendment (Cutoff date 12/31/95)
In the NDA review, comparative vital sign data were presented for subjects participating in the US controlled epilepsy trials (024, 025). In the NDA Amendment the sponsor provided a dose response analysis for vital signs in study 025, but no comparative vital sign analyses for non US studies.

Current Submission
In the current NDA Amendment submission, Ovation provided comparative vital sign data from individual controlled trials. The results from each controlled trial were presented separately and no pooled analyses were performed.

7.1.8.3 Standard analyses and explorations of vital signs data

7.1.8.3.1 Analyses focused on measures of central tendencies

Prior Submissions

NDA and NDA Amendment (Cutoff date 12/31/95)
The NDA Amendment review included a table that summarized mean change from baseline results for vitals signs from US controlled epilepsy study 025. Aside from small mean increases in respiration that appeared to show evidence of dose response, there did not appear to be a relationship between vigabatrin and vital sign changes. I provide a summary of the vital sign results below.

Parameter/ Treatment	N	Mean change from Baseline	P value*
Pulse (bpm)			
Placebo	45	-1.8	.1692
Vigabatrin 1g/day	45	0.4	
Vigabatrin 3g/day	43	1.7	
Vigabatrin 6g/day	41	1.2	
Respirations (rpm)			
Placebo	45	-0.7	.0182

Vigabatrin 1g/day	45	0.1	
Vigabatrin 3g/day	43	0.4	
Vigabatrin 6g/day	41	0.6	
Systolic BP (mmHg)			
Placebo	45	-5.1	.1284
Vigabatrin 1g/day	45	1.0	
Vigabatrin 3g/day	43	3.4	
Vigabatrin 6g/day	41	0.0	
Diastolic BP (mmHg)			
Placebo	45	-1.4	.1284
Vigabatrin 1g/day	45	1.3	
Vigabatrin 3g/day	43	0.7	
Vigabatrin 6g/day	41	-1.3	

*Linear trend test across 4 treatment groups from an analysis of covariance model adjusting for baseline
Source NDA Amendment, Appendix A, Table 6, p. Sa-V1-P297

Current Submission

For the Adult and Pediatric non IS subpopulations, Ovation commented only that weight gain has been observed in studies and that there were no clinically relevant effects of vigabatrin on vital signs in the adult studies. Ovation provided no comment about vital sign data from study 1A.

Adult Subpopulation

I reviewed the study reports for controlled trials 0101, 0222, and 0223 to look for evidence of vigabatrin related changes in vital sign parameters. I found no analysis of vital sign data in study 0101. For study 0222, the investigators provided a mean change from baseline to final visit analysis. Vigabatrin subjects experienced larger drops in mean diastolic and systolic blood pressure and larger mean increases in weight compared to gabapentin subjects. I provide those results below.

Vital sign parameter	Treatment	Mean change from baseline to final
Diastolic Blood Pressure (mmHg)	Vigabatrin (n=9)	-10.00
	Gabapentin (n=9)	-2.67
Systolic Blood pressure (mmHg)	Vigabatrin (n=9)	-10.00
	Gabapentin (n=9)	-7.11
Heart Rate (bpm)	Vigabatrin (n=9)	-0.67
	Gabapentin (n=9)	-1.11
Weight (lbs)	Vigabatrin (n=8)	5.63
	Gabapentin (n=9)	-1.00

Source Study report 0222, pp.1764-1766.

Mean change from baseline to final vital sign results for systolic blood pressure, diastolic blood pressure and pulse did not appear to demonstrate dose response in study 0223. For weight, subjects exposed to vigabatrin 1g/day gained an average of 2.5 pounds compared to 3.2 pounds for the 3g/day group, 3.2 pounds for the 4g/day group and 3.8 pounds for the 6g/day group (Source Study report 0223, p.1359).

Pediatric non-IS Subpopulation

For the pediatric non-IS controlled studies 0118, 0221, and 0192 the investigators stratified the mean vital sign changes from baseline into 3 age categories (3-<6yrs, >=6-<12 yrs, and >=12 yrs), resulting in few subjects in each category. For diastolic BP, systolic BP, heart rate and respirations there did not appear to be any consistent differences between vigabatrin and placebo (stratified by age) in any of these 3 studies. There did appear to be evidence of vigabatrin associated weight gain. In study 0118 (treatment phase up to 14 weeks), in the youngest age group (3-<6yrs old) there was little difference in mean weight change when comparing the different vigabatrin doses to placebo but for the older age groups, vigabatrin subjects gained more weight than placebo subjects and there was a suggestion of a dose response in the oldest age group (>=12 yrs). I provide those weight results below.

Mean Weight change (lbs) from baseline to Visit 9, by Age group, study 0118

Age Group	Placebo (n)	Vigabatrin 20mg/kg/day	Vigabatrin 60mg/kg/day	Vigabatrin 100mg/kg/day
3-<6 years	2.3 (7)	1.8 (5)	4.0 (1)	2.3 (8)
>=6-<12 yrs	1.5 (14)	4.1 (7)	6.0 (12)	5.5 (11)
>=12 yrs	-1.9 (10)	7.3 (17)	9.1 (18)	9.7 (11)

Source Study report 0118, Table 16.2, p.3421

In study 0221 (treatement phase up to 17 weeks), there was little difference between the vigabatrin and placebo groups for the two youngest age strata (3-<6 yrs, >=6yrs-1<12 yrs) for mean weight change. For the >=12 yrs age group the mean change in weight from baseline to maintenance visit was 3.1 pounds for vigabatrin (n=20) and 1.5 pounds for placebo (n=14) (Source Study report 0221, p.2788). In study 0192, there was little difference between vigabatrin and placebo subjects in the 3-<6 yrs age category for mean weight change. In the >=6-<12yrs category, vigabatrin subjects (n=10) gained 2.5 pounds compared to 1.1 pounds for placebo subjects (n=14). In the >=12 yrs age category, vigabatrin subjects (n=15) gained an average of 3.3 pounds compared to 1.2 pounds for placebo subjects (n=12) (Source Study report 0192, p.98).

IS Subpopulation

Since neither the Amendment submission nor the study report included vital sign analyses for study 1A, the Division asked Ovation to provide this information. Ovation provided their response in a 4/23/08 submission. In the first 2 weeks of study 1A, subjects were randomized to low dose or high dose vigabatrin. After those 2 weeks, subjects continued in the flexible dose open label phase. During the first two weeks, there did not appear to be notable differences when comparing the low and high dose groups for vital signs mean changes from baseline. I provide the vital sign mean changes from baseline at week 2 for the low dose and high dose groups.

Study 1A Vital Sign Mean Changes from Baseline at Week 2, by Dose Group

Vital sign parameter	Treatment	Mean change from baseline to week 2
Diastolic Blood Pressure (mmHg)	Low dose (n=90)	-0.4
	High dose (n=74)	-0.5
Systolic Blood pressure (mmHg)	Low dose (n=102)	-0.6

	High dose (n=94)	2.9
Heart Rate (bpm)	Low dose (n=108)	-0.7
	High dose (n=98)	0.4
Respiratory rate	Low dose (n=86)	-0.6
	High dose (n=80)	0.5

Source Tables 5.2-5.4, 4/23/08 submission

7.1.8.3.2 Analyses focused on outliers or shifts from normal to abnormal

Prior Submissions

NDA and NDA Amendment (Cutoff date 12/31/95)

The NDA review included a table of vital sign outliers (normal at baseline and then exceeded outlier criteria at some time during treatment) from the US epilepsy controlled trials. I include information from that presentation below.

Vital Sign Parameter	Outlier criteria	Vigabatrin N=221	Placebo N=135
Systolic BP low	< 90mm Hg	1.4% (3)	0.8% (1)
Systolic BP high	>180mm Hg	0	0
Diastolic BP low	<50 mm Hg	0	0
Diastolic BP high	>120mm Hg	0	0
Pulse low	<50 bpm	0.5% (1)	0
Pulse high	>120 bpm	2.7% (6)	3% (4)
Weight decrease	>15%	0	0
Weight increase	>15%	0.5% (1)	0
Weight increase	7-15%	47.3% (62)	15.8% (21)

Source NDA review p.77

The NDA Amendment review did not include vital sign outlier data.

Current Submission
Adult Subpopulation
The study reports for controlled studies 0101, 0222, and 0223 did not provide summaries of subjects with outliers for vital signs.

Pediatric non-IS Subpopulation
The outlier analyses for the Pediatric non IS controlled trials were limited. All three studies used the same criteria to identify end study vital sign outliers. I provide those criteria below.

Vital Sign Parameter	Low Outlier Criteria	High Outlier Criteria
Pulse (bpm)	<50 and a drop >=15 from baseline	>140 and an increase of >=15 from baseline
Systolic BP (mmHg)	<80 and a drop of >=20 from baseline	>140 and an increase of >=20 from baseline
Diastolic BP	<50 and a drop of >=15 from baseline	>90 and an increase of >=15 from baseline

In study 0118, investigators reported that no subjects experienced an end study outlier result (low or high) for heart rate or systolic BP measurement and no subjects experienced a high outlier diastolic BP. One placebo subject and three vigabatrin 20mg/kg/day subjects (but no vigabatrin 60 or 100mg/kg/day subjects) experienced low end study diastolic BP measurements (Source Study report 0118, p.141). In study 0221 no subjects had an end study outlier for pulse (high or low) or low systolic BP or high diastolic BP. One vigabatrin and one placebo subject had an end study outlier for high systolic BP and one vigabatrin and one placebo subject had an end study outlier for low diastolic BP (Source Study report 0221, p.113). The only end study vital sign outliers from study 0192 occurred in placebo subjects (one low SBP, two low DBP) (Source Study Report 0192, p.99).

IS Population (Study 1A)
In their 4/23/08 submission, Ovation provided an outlier vital sign analysis for Study 1A that defined outlier values as those >2 SD from the mean. The Division requested additional vital sign outlier analyses for Study 1A that used specific cutoff values. Those cutoff values are listed below.

Pulse

Age	Low	High
1-12 months	<100	>160
>12 months	<80	>110

Systolic Blood Pressure

Age	Low	High
1-12 months	<70	>110
>12 months	<74	>110

Diastolic Blood Pressure

Age	Low	High
1-12 months	<50	>70
>12 months	<55	>75

Respirations

Age	Low	High
1-12 months	<30	>60
>12 months	<24	>40

Ovation provided the results of their analyses in their 5/16/08 submission. Week 2 results from those analyses are summarized below. Week 2 includes data from subjects receiving randomized low or high dose vigabatrin. The remainder of the study allowed flexible dosing and so they lack comparative value.

Vital Sign Outlier Results, Study 1A, Week 2			
	High Dose	Low Dose	Combined
Pulse (BPM)			

N	82	85	167
Low outlier	1.2% (1)	4.7% (4)	3.0% (5)
High Outlier	2.4% (2)	9.4% (8)	6.0% (10)
Systolic Blood Pressure (mm Hg)			
N	66	81	147
Low outlier	3.0% (2)	8.6% (7)	6.1% (9)
High Outlier	19.7% (13)	12.3% (10)	15.6% (23)
Diastolic Blood Pressure (mm Hg)			
N	37	49	86
Low outlier	24.3% (9)	24.5% (12)	24.4% (21)
High Outlier	16.2% (6)	16.3% (8)	16.3% (14)
Respirations (resp/min)			
N	46	55	101
Low outlier	17.4% (8)	21.8% (12)	19.8% (20)
High Outlier	(0)	4.1% (2)	3.5% (3)

In general, outlier risks were either similar for the two vigabatrin dose groups or higher among the low dose group. There was a slight increase high outlier risk for systolic blood pressure for the vigabatrin high dose group compared to the low dose group.

7.1.8.3.3 Marked outliers and dropouts for vital sign abnormalities

Prior Submissions

NDA and NDA Amendment (Cutoff date 12/31/95)

Neither the NDA review nor the NDA Amendment review discussed marked vital sign outliers or dropouts for vital sign outliers.

Current Submission
Ovation did not provide an analysis of marked vital sign outliers. For the Integrated population, the only vital sign related SAEs were hypertension (0.04%, 2/4,739). Thirty-one vigabatrin subjects (0.64%, 31/4,855) discontinued from trials included in the Integrated Population for weight increased and one subject (0.02%, 1/4,855) discontinued for weight decreased. One subject from the Integrated Population discontinued for blood pressure increased (0.02%, 1/4,855)

7.1.8.4 Additional analyses and explorations

Given the evidence supporting a relationship between weight gain and vigabatrin, the Division requested additional analyses to clarify this relationship. Using weight data from studies included in the Integrated analysis, Ovation provided summary data about weight gain in vigabatrin treated subjects. After excluding data from IS studies and from infants in non IS studies, and excluding studies that did not include at least one baseline and one post baseline weight measurement, Ovation examined weight gain in 1843 vigabatrin subjects. Ovation reported that 26.3% (484/1843) vigabatrin subjects gained >= 7% weight compared to baseline.

Ovation also provided a comparative analysis. Using data from 9 controlled trials, Ovation found that 17.4% (77/443) of vigabatrin subjects gained >=7% of baseline body weight during treatment compared to 8% (22/275) of placebo subjects, 19% (4/21) of valproate subjects and no (0/8) gabapentin subjects. The mean weight change from baseline was highest for vigabatrin (3.5kg) followed by valproate (2.7kg), and placebo (1.6kg). Gabapentin subjects experienced a mean change in weight of -0.63kg.

Ovation provided analyses that stratified by sex and age to look for differences in weight gain by demographic factors. As demonstrated below, females appeared to have a greater risk of gaining at least 7% of baseline body weight and had a higher mean increase in body weight compared to placebo.

Weight change by sex, from 9 randomized controlled vigabatrin trials

% of Subjects that gained >=7% compared to baseline			
Sex	Vigabatrin	Placebo	RR
Male	17.1% (38/215)	8.5% (11/130)	2.0
Female	17.1% (39/228)	7.6% (11/145)	2.3
Mean weight change from baseline (kg)			
	Vigabatrin	Placebo	Vigabatrin-Placebo
Male	3.0	1.8	1.2
Female	3.9	1.5	2.4

Source 5/23/08 submission, Tables 3.3, 3.4, p.11

Ovation provided weight change analyses that stratified subjects into the following 3 age groups: <18 years, 18-45 years, and 46-64 years. The relative risk for weight gain of >=7% of baseline body weight was highest among the 18-45 year old age group. The mean weight gain relative to placebo was similar in all three age groups. Those results are provided below.

% of Subjects that gained >=7% compared to baseline			
Age group	Vigabatrin	Placebo	RR
<18 years	36.7% (51/139)	19.3% (17/88)	1.9
18-45 years	8.9% (23/258)	3.1% (5/162)	2.9
46-64 years	6.5% (3/46)	0	-
Mean weight change from baseline (kg)			
	Vigabatrin	Placebo	Vigabatrin-Placebo
<18 years	6.0	3.6	2.4
18-45 years	2.4	0.8	1.6
46-64 years	2.0	-0.1	2.1

Source 5/23/08 submission, Tables 3.5, 3.6, and 3.7 pp.11-12

Ovation also attempted to analyze weight change by dose using data pooled from 5 studies. Given the differences in trial durations, and different dosing regimens in each of the included trials, the differences attributed to dose are likely greatly influenced by the different durations of treatment.

7.1.9 Electrocardiograms (ECGs)

7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results

Ovation acknowledged that the non-clinical and clinical studies conducted during the vigabatrin development program preceded the recent FDA and ICH guidelines recommending that drugs be evaluated for QT interval prolongation. Ovation summarized cardiovascular-related results from previously submitted studies as well as results from newly completed pre-clinical studies designed to assess the effect of vigabatrin on cardiac repolarization.

Among the preclinical findings cited by Ovation was the lack of effect in raising the electrical stimulation threshold or the ventricular fibrillation threshold in perfused rabbit heart preparations, transient dose dependent elevation in blood pressure in rats when vigabatrin was injected into the nucleus tract solitarius, and slight increase in blood pressure in intravenously injected rats. Ovation also reported no increases in blood pressure, heart rate, interventricular pressure, dP/dt, cardiac output, calculated peripheral resistance, stroke volume or atrial pressures following intravenous or subacute oral administration in dogs. In addition, Ovation reported that a long term toxicity study in dogs that included ECGs found **"no drug effect throughout the one year dosing period."**

In 2006, Ovation hired ChanTest Inc. to conduct **studies of vigabatrin's effect on the hERG** channel current. Vigabatrin was exposed to cells at 100 and 300μg/mL concentrations (highest dose corresponds to approximately 4 times the maximum plasma concentration). Vigabatrin did not significantly inhibit hERG currents (0.4% and 0.8%) while terfenadine, the positive control, inhibited hERG currents by 75%.

In follow up tests in isolated rabbit Purkinje fibers there was no significant difference in when comparing the effect of vigabatrin and vehicle on action potential duration. The positive control, sotalol, caused significant prolongation of action potential duration.

7.1.9.2 Selection of studies and analyses for overall drug-control comparisons

In a report included in the October 10, 2006 NDA Amendment submission, Ovation reviewed the vigabatrin cardiovascular safety data. Ovation summarized cardiovascular safety data from the previously conducted clinical trials. The summaries did not provide details about the number of ECGs conducted, or mention if the ECGs were recorded at the time of estimated peak or trough drug or metabolite levels. Examples of the types of information in these summaries are that there were no significant changes observed or that ECG data were not collected or that no adverse events of QT prolongation or torsades were observed. There were no quantitative assessments of intervals provided in these summaries.

Ovation referenced an evaluation of cardiovascular safety data that was performed by a consultant cardiologist, Craig Pratt MD and was submitted as part of the 1997 NDA Amendment. Dr. Pratt reviewed selected abnormal ECGs from studies 097-005 and 097-006 (the reported QT intervals and heart rate data for subjects who reported cardiovascular AEs or had changes in ECGs). In addition, Dr. Pratt reviewed all cardiovascular deaths and AEs that had occurred on vigabatrin. Ovation reported that this review included a total of 2,516 vigabatrin and 1,219 placebo subjects from US and non US studies, as well as vigabatrin spontaneous cardiovascular reports through 31 December 1995." Ovation reported that Dr. Pratt found no meaningful effects of vigabatrin on PR, QRS, or QT intervals and no signal of cardiovascular AEs related to vigabatrin (Source 10/10/06 Amendment Submission, Analysis of Vigabatrin Effect on QTc, p.10).

Ovation also referenced cardiovascular safety data from clinical trials that was presented in the Safety Update for 3/15/97 through 6/17/05. Ovation noted that there were 21 cardiovascular AEs reported in this Safety Update including heart rate increased, hypertension, hypotension, orthostatic hypotension, tachycardia, bradycardia, and palpitations. Four study subjects withdrew from clinical trials for cardiovascular AEs. The cardiovascular AEs leading to discontinuation were hypertension (n=2), infarction NOS, and AV block second degree. Ovation did not summarize all serious cardiovascular AEs or all cardiovascular AEs resulting in death. Ovation did note that there were 3 fatal events coded to the term myocardial infarction. Ovation provided narratives for these events. One death occurred in a 54 year old male with no history of cardiovascular disease. This subject's was found dead in bed and a post mortem examination was not performed. The two remaining deaths occurred in subjects with histories of cardiovascular disease and the narratives provided no information to support the reported cause of death (Source 10/10/06 Amendment Submission, Analysis of Vigabatrin Effect on QTc, pp.10-12).

Ovation referenced a second source of cardiovascular risk data, postmarketing reports collected by Aventis. Ovation identified cardiovascular 6 postmarketing reports during the period of 3/97 through 6/05. The events reported were AV block complete, cardiac failure, cardiomyopathy, palpitations, pulmonary valve stenosis, and tachycardia.

In their report on vigabatrin's effect on QTc, Ovation reanalyzed ECG data from a controlled trial (005) and its open label extension (006). These trials were conducted between 1982 and 1983. Study 005 was an add-on trial with a flexible dose design allowing titration to the maximum tolerated dose. Ovation's new analyses used heart rate, PR, QRS, and QT interval data contained in electronic files. The ECG intervals were not re-measured using current standards and the original ECGs are not available for review or re-measurement (p.22). These analyses were based on data for 76 subjects from study 005 and 71 subjects from study 006. The analyses provided the mean change from baseline among vigabatrin treated subjects and there were no control data for comparison.

7.1.9.3 Standard analyses and explorations of ECG data

7.1.9.3.1 Analyses focused on measures of central tendency

Study 005

Ovation presented analyses of the mean change from baseline at week 3 and week 15 in study 005. Week 3 was the week of maximum tolerated dose and week 15 was the end of the maintenance period. In addition to slight declines in heart rate, Ovation found increases from baseline in mean QT, QTcB, and QTcF that were greater at week 3 than at week 15. The results for their ECG interval data analyses from study 005 are presented in the following table.

Mean Change from Baseline for Heart Rate, PR interval, QRS interval, QT interval, QTcB, and QTcF, Study 005

ECG Parameter	Week 3 Change from Baseline	Week 15 Change from Baseline
Heart rate (bpm)	-0.6 (n=72)	-2.7 (n=72)
PR (ms)	0.3 (n=72)	2.2 (N=72)
QRS (ms)	0.1 (n=72)	3.0 (n=72)
QT	11.6 (n=69)*	8.6 (n=71)
QTcB	10.2 (n=69)*	1.7 (n=71)
QTcF	10.7 (n=69)*	4.1 (n=71)

Data from Appendices 1-7

*These change from baseline statistics include data for a subject with a recorded QT of 870msec which Ovation feels is likely an error but this hypothesis cannot be evaluated because the ECGs from this study are not available.

In addition to the mean change analyses presented above, Ovation also presented results that were stratified by sex. This study included 76 males and 14 females. Ovation reported finding a difference in mean heart rate change from baseline by sex. At week 15, among males the mean heart rate change from baseline was -3.4 bpm compared to an increase of 0.8 bpm for females. Females had smaller mean increases from baseline for QTcB and QTcF compared to males at week 3 and longer increases at week 15. Given the small number of female subjects in this trial, and limitations related to methodology, any conclusions based on these results are questionable. The results are provided below.

Mean Change from Baseline by Sex for Heart Rate, PR interval, QRS interval, QT interval, QTcB, and QTcF, Study 005

ECG Parameter	Sex	Week 3 Change from Baseline	Week 15 Change from Baseline
Heart rate (bpm)	Male	-0.1 (n=60)	-3.4 (n=60)
	Female	-2.9 (n=12)	0.8 (n=12)
PR (ms)	Male	-0.3 (n=60)	3.7 (N=60)
	Female	3.3 (n=12)	-5.0 (n=12)
QRS (ms)	Male	0.0 (n=60)	3.4 (n=60)
	Female	0.8 (n=12)	0.8 (n=12)
QT	Male	11.9 (n=58)*	8.8 (n=60)
	Female	10.0 (n=11)	7.6 (n=11)
QTcB	Male	12.0 (n=58)*	-0.5 (n=60)
	Female	1.2 (n=11)	14.0 (n=11)
QTcF	Male	11.9 (n=58)*	2.7 (n=60)
	Female	4.2 (n=11)	11.8 (n=11)

Data from Appendices 8-21

*These change from baseline statistics include data for a subject with a recorded QT of 870msec which Ovation feels is likely an error but this hypothesis cannot be evaluated because the ECGs from this study are not available.

Ovation felt that the ECG results from these studies did not show clinically important changes in any conduction interval.

Extension 006
Ovation presented mean ECG interval changes from baseline data from the open label extension 006. These analyses included results from months 3, 6, 9, 12, 18, 24, 30, and 36. The study included 52 subjects at month 3, but by month 36 the study size had dropped to 24 subjects. The mean heart rate change from baseline was negative in each month that was analyzed (range -0.6bpm at month 3 to -4.8bpm at month 30). For each of the 8 months analyzed, the mean QTcB change from baseline was negative (range -0.8 at month 36 to -12.9 at month 18). The range of mean QTcF changes from baseline was -9.1 at month 18, to 3.2 at month 6 (Source Appendices 1-7).

7.1.9.3.2 Analyses focused on outliers or shifts from normal to abnormal

Study 005
Using cutoffs of increase from baseline of >30ms and >60ms, Ovation identified the percentage of vigabatrin treated subjects with increases in QT, QTcB, and QTcF. Those results are provided below.

Study 005: Percentage of subjects with increases of >30msec and >60msec from baseline for QT, QTcB, and QTcF

ECG Parameter	>30ms increase	>60ms increase
Week 3		
QT	13% (n=9)	1.4% (n=1)
QTcB	18.8% (n=13)	4.3% (n=3)
QTcF	15.9% (n=11)	1.4% (n=1)
Week 15		
QT	18.3% (n=13)	5.6% (n=4)
QTcB	18.3% (n=13)	5.6% (n=4)
QTcF	15.5% (n=11)	2.8% (n=2)

Source Appendices 1-7

Ovation also identified the percentage of subjects with absolute QT, QTcB, and QTcF intervals that exceeded 450ms, 480ms, and 500ms. Those results are provided below.

Outliers, Absolute values for QT interval, QTcB, and QTcF

ECG Parameter	>450ms	>480ms	>500ms
Week 3			
QT	1.3% (1)	1.3% (1)	1.3% (1)
QTcB	2.7% (2)	1.3% (1)	1.3% (1)
QTcF	1.3% (1)	1.3% (1)	1.3% (1)
Week 15			
QT	0	0	0
QTcB	3.9% (3)	2.6% (2)	0
QTcF	2.6% (2)	0	0

Extension 006
In study 006, the percentage of subjects with increases in QTcB of more than 30ms ranged from 9.1% (3/33, month 18) to 24.5% (12/49, month 3). The percentage of subjects with increases in QTcB of more than 60ms ranged from 0% (months 12, 18, 30, and 36) to 10.3% (3/29, month 24). The percentage of subjects with increases in QTcF of more than 30ms ranged from 4.3% (1/23, month 36) to 20.4% (10/49, month 3). The percentage of subjects with increases in QTcF of more than 60ms ranged from 0% (months 12, 18, 30, and 36) to 8.2% (4/49, month 3) (Appendices 6 and 7).

In study 006, 4 subjects experienced an absolute QTcB >480ms (all at month 3) and 3 subjects experienced an absolute QTcB>500msec (all at month 3). Three subjects experienced a QTcF >480msec (2 at month 3 and 1 at month 6) and no subjects had an absolute QTcF>500ms (Appendices 6 and 7).

Given the methodological limitations of the data analyses and without comparator data it is difficult to interpret the significance of the outlier risks from studies 005 and 006.

7.1.9.3.3 Marked outliers and dropouts for ECG abnormalities

No vigabatrin subjects from the Overall population or the Integrated population discontinued from a clinical trial for QT prolongation.

7.1.9.4 Additional analyses and explorations

Post-Marketing Experience
Ovation searched their Oracle AERS post marketing database and the medical literature for cases of cardiovascular AEs associated with vigabatrin. The Ovation post marketing report search used the following preferred terms: cardiac death, sudden cardiac death, sudden death, syncope, coronary artery reocclusion, acute pulmonary edema, pulmonary congestion, and pulmonary edema. Ovation stated that their search strategy would also capture torsades de pointes, ventricular tachycardia, and ventricular fibrillation.

Ovation reported that they identified 41 events with one or more of the listed search terms. Ovation excluded 5 reports from further consideration because 2 were clinical trial reports, 2 described congenital heart defects, and one described elevated CPK levels in a febrile child. For the remaining 36 reports, Ovation provided tables that included demographic data and brief narrative summaries of the events.

Ovation identified nine reports as having insufficient information to allow analysis. The event terms for these reports were cardiomyopathy (2), bradycardia (2), arrhythmia, palpitation, creatine phosphokinase increased, CK increased, and cyanosis/irregular heartbeat. Ovation felt that another five reports suggested etiologies other than vigabatrin for the reported events. The AE terms for these reports were cardiorespiratory failure, tachycardia, cardiac arrest, syncope

and palpitations. One of these events occurred prior to vigabatrin treatment and the alternative etiologies identified for the remaining events were pneumonia/sepsis, obstructive apnea, fulminant hepatic failure, and hypoglycemia. Ovation's assessment of these reports appeared reasonable.

Ovation felt that 13 reports had complicating factors for the described events. There appeared to be overlap for some of the events included in this category and the category described above (identified etiologies other than vigabatrin). The cardiac adverse events included in this group were bradycardia (n=3), sudden death (n=2), palpitation (n=2), palpitation/sick sinus syndrome, tachycardia, syncope, cardiac failure, third degree heart block, and first degree AV block. Ovation identified the following complicating factors: improbable temporal relationship (symptoms predated treatment), overdose, allergic reaction, cerebral hemorrhage, acute liver failure, concomitant carbamazepine, seizure, event continued after vigabatrin discontinued and normal ECG at the time of the event.

Ovation felt that the remaining 9 cardiovascular events did not have clear alternative etiologies or complicating factors. These events were tachycardia (n=2), sudden death (n=2), sudden death unexplained, faint, bradycardia, angina, arrhythmia/PACs.

Ovation felt that most reports had either documented alternative etiologies or complicating factors. For events without those explanations, Ovation felt there was limited information and that the sudden deaths might represent background cases of SUDEP. Ovation noted that there were no cases of torsades de pointes, ventricular tachycardia, or ventricular fibrillation.

7.1.10 Immunogenicity

7.1.11 Human Carcinogenicity

The NDA Amendment did not include a discussion of human carcinogenicity with vigabatrin. The Division requested analyses comparing the number of treatment emergent cancers in the vigabatrin development program to the expected number of cancers based on SEER data. In their 4/23/08 response to a Division request, Ovation provided a listing of 86 subjects/patients with malignancies. Ovation included 2 patients from Japanese studies, 4 from compassionate use programs, and 6 from spontaneous reports. The remaining 74 subjects were from clinical trials included in the Integrated database. Ovation calculated expected numbers of cancers based on the sex and age distribution and the duration of treatment of the clinical trial population. Ovation reported excesses of breast cancer, brain cancers and pancreatic cancers among vigabatrin treated patients. Ovation did not discuss these findings.

The Division asked Ovation for their interpretation of these findings. In a submission dated 5/7/08, Ovation noted that in their 4/23/08 submission they included not only treatment emergent cancer diagnoses but also included prevalent cases. In addition, they included cases that were not confirmed malignancies. Lastly Ovation included cases from outside the development program.

The inclusions of these cases resulted in an erroneously inflated estimate of cancer risk because these cases counted in the numerator of the risk calculations did not contribute exposure data to the denominator. Ovation repeated their analysis using only clinical trial, incident, confirmed cancer diagnoses in the numerator. Using these criteria, Ovation identified 33 subjects with an incident cancer diagnosis in the vigabatrin development program studies. A table of cancer diagnoses is provided below.

Table 1.2. Tumors by Site from the Integrated Safety Database* (N=4855) - Revised

Site	No of Patients	Patient (protocol) numbers
Breast (infiltrating ductal carcinoma right breast, malignant breast tumor, breast cancer, , breast lump removed,)	7	1237-0018(98), 061-002(71754-3-C-028), 26626(097-266LT), 1206-0008(98), 1231-0005(98), 1258-0004(98), 1195-0002(98)
Brain (cerebral tumor, astrocytoma, low grade glioma, left frontal cerebral glioma, neuroblastoma, oligodendroglioma, retinal	10	34031911(097-345), 34031915(097-345), W-108-002(71754-3-W-007), W-101-032(71754-3-W-007), VGB-175(1A), 1193-0004(98), 1204-0019(98), 009-011(097- 005)
Site unspecified and ill defined (excision of an occipital hole tumor)	1	40733203(097-332)
Skin- basal cell (basal cell carcinoma)	5	1255-0001(98),1259-0001(98), 1198-0031(98), 1204-0013(98), 1260-0010(98)
Lung (lung cancer, lung tumor with metastasis, lung neoplasm malignant)	4	1228-0001(98), 1198-0017(98), 21202(097- 306), 1230-0010(98)
Pancreas (pancreatic carcinoma)	1	1237-0012(98)
Cervix (cervical carcinoma, cervix carcinoma)	2	1192-0014(98),1195-0002(98)
Adenocarcinoma	1	VGB-15400001(242)
Angiosarcoma	1	VGB-475(1A)
Colon (colon tumor)	1	30330028(097-306)
Leukemia (chronic myelogenous leukemia)	1	1268-0007(98)
Liver (liver tumor)	1	30330028(097-306)
Ovary (ovarian cancer)	1	068-068(097-335)
Total No. of Patients with Cancer Reports Through the December 2007 Safety Update = 33		
* Excludes patients from Japanese studies, Compassionate Use studies, and spontaneous reports.		

Source 5/7/08 Submission, p.7

Ovation found an increased ratio of observed to expected cancer diagnoses (all malignances) in the vigabatrin development program (O:E 1.45, 95% CI 1.0-2.04). For site specific diagnoses, the biggest increase when comparing observed to expected diagnoses was for brain cancers. The observed to expected ratio for brain cancers was 31.25 (95% CI 14.99-57.47). As Ovation points out, this disparity is likely due to the differences between the vigabatrin clinical trial population (patients with epilepsy) and the general population from which SEER data is derived. Ovation cited publications from Shirts et al, Forsgren et al and Olsen et al and others that found increased risks for brain tumors among patients with intractable or refractory epilepsy. In the publication by Shirts et al, the most relevant of the publications, the investigators described the results of a population based cohort of seizure patients (n=959) in Rochester, MN, between 1935 and 1979.

The investigators found an SMR for all cancers of 1.4. The increase was driven by an increase in primary brain tumors (SMR 22). I provide a table summarizing the results of this study.

TABLE 1.—*SMR for total and site-specific cancer incidence, both sexes*

Site	Observed No. of cancers	Expected No. of cancers	SMR	95% CI
Digestive system	10	15.4	0.8	0.4, 1.4
Respiratory system	9	3.3	2.7	1.2, 5.2
Breast	10	4.9	2.0	0.98, 3.8
Urinary system	6	4.1	1.5	0.5, 3.2
Female genital system	2	3.2	0.6	0.1, 2.3
Male genital system	1	4.0	0.3	0.01, 1.4
Lymphatic-hematopoietic system	7	2.4	2.9	0.97, 5.0
Brain	17	0.7	24.3	14.2, 38.8
Other sites	3	7.7	0.4	0.1, 1.1
Total	65	45.7	1.4	1.1, 1.8

Shirts et al also found a downward trend in the SMR for brain cancer with time since the diagnosis of seizures. The investigators interpreted this finding as supporting that the brain tumors were leading to seizures rather than anticonvulsant medications leading to the development of brain tumors.

In relation to the brain cancers in the vigabatrin development program, a number of subjects had relatively short vigabatrin exposure durations prior to the cancer diagnoses. For the 9 subjects with exposure information, 4 subjects were exposed to vigabatrin for less than 9 months prior to diagnosis (18 days, 4.1 months, 7.5 months and 8.5 months), 2 were exposed for between 1 and 2 years (13.9 months, 23.1 months) and 3 were exposed for over 2 years (28.6 months, 28.7 months and 51 months). The short exposure duration raises questions about whether vigabatrin was causally involved with these events.

In addition to brain cancer, Ovation also found an excess of breast cancer diagnoses in the vigabatrin clinical trial database. Ovation identified 7 breast cancers when 3.33 would have been expected based on SEER data (O:E 2.1, 95% CI 0.85-4.33). This result is similar to result presented above by Shirts et al for their cohort study. Ovation did note that one breast cancer was diagnosed after only 1.9 months of vigabatrin and another after 6.1 months. The duration of vigabatrin treatment for the remaining cases was 32.1 months, 33.8 months and 47.7 months (duration not specified in 2 cases). Ovation noted that vigabatrin has no known interaction with steroidal hormones, and that carcinogenicity studies in vitro and in vivo have been negative. Ovation did not find any reported cases of breast cancer in association with vigabatrin treatment in the worldwide published literature.

7.1.12 Special Safety Studies

Safety studies examining visual field changes in vigabatrin treated patients are reviewed by Dr. Ronald Farkas and data related to IME are being reviewed by Dr. Phillip Sheridan, both of the Division of Neurology Products.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

Prior Submissions

NDA and NDA Amendment (Cutoff date 12/31/95)

The NDA reviewer noted that withdrawal seizures were documented in animal models using acute single dosing with vigabatrin. In addition, the reviewer noted that withdrawal seizures, including status epilepticus, were seen during discontinuation of vigabatrin in clinical trials. The reviewer discussed results from 10 clinical trials with follow up that would allow assessment of withdrawal seizures. The incidence of withdrawal seizures ranged from 0-15.7% and the incidence of status epilepticus during withdrawal was 1.3%. (Withdrawal seizures were defined by a twofold or greater increase in weekly seizures compared to the maximum seizure rate noted during baseline or active therapy within 4 weeks after vigabatrin was discontinued or after tapering was begun, or documented status epilepticus not present during baseline and occurring within 4 weeks after vigabatrin was discontinued or after tapering was begun). (Source NDA Review, pp. 98-99). The NDA Amendment did not present analyses of withdrawal phenomena.

Current Submission
In the 12/28/07 Amendment submission, Ovation provided a summary addressing abuse potential of vigabatrin. Ovation concluded that vigabatrin does not have significant activity at abuse related CNS targets. Ovation noted that in pre-clinical studies, vigabatrin did not produce significant reinforcement in a primate self administration study, did not substitute for phenobarbital, partially substituted for muscimol and did not produce suppression of morphine withdrawal. Ovation noted that a controlled human abuse liability study has not been performed. Ovation reported that there are no reports of recreational vigabatrin use or substitution with vigabatrin in methamphetamine or cocaine dependent subjects in abuse treatment trials. Ovation felt that abuse related events were infrequent in vigabatrin treated study subjects and that there is a lack of evidence of diversion. Ovation also felt that post marketing data show no evidence of abuse potential. Ovation did not comment on withdrawal phenomena. The formal FDA review of these data has not been completed at the time of this review.

7.1.14 Human Reproduction and Pregnancy Data

Prior Submissions

NDA and NDA Amendment (Cutoff date 12/31/95)

In the NDA Amendment, the sponsor identified 139 pregnancies in women exposed to vigabatrin (through 12/31/95). The sponsor reported that 13% (18/139) of the pregnancies resulted in major or minor malformations. The sponsor reported the following major and minor malformations: congenital dislocation of hip (n=2); unspecified musculoskeletal problems; conjoined twins (therapeutic abortion); squint requiring surgery; bilateral cleft palate; agenesis of cardiac septum, microcepahly, pulmonary artery atresia, spina bifida (therapeutic abortion); choanal atresia,

congenital nystagmus, craniosynostosis; ventricular septal defect; congenital diaphragmatic hernia (death within 24 hours of birth); left hemisphere atrophy, decreased right arm motor function, seizures; undescended testicle; club feet; shuddering when handled; facial palsy, tachypnea; eye roving, low hairline, low set ears, poor muscle tone, torticollis; hypospadia, bilateral clinodactyly of the fourth toes, capitonated deep palmar flexion creases, diastasis recti abdominis, multiple facial anomalies, wide internipple distance; and plagiocephaly, orbital asymmetry, hyperextensible interphalangeal joints, fifth finger clinodactyly. The sponsor also reported that 12% (16/139) of the pregnancies ended in spontaneous abortion and 7% (10/139) ended in therapeutic abortion, including the two mentioned above (Source Amendment review, pp 45-46).

Current Submission
Ovation summarized the post marketing adverse event reports in the Aventis Drug Exposure Via Mother database. Ovation first summarized reports through 8/31/2000, followed by reports from 9/1/2000 through 9/1/2006.

Through 8/31/2000, there were 268 reports of pregnancy exposures in the events pregnancy registry plus 6 reports from a UK PEM study. This total includes the 139 pregnancies that were identified in the 5/31/97 NDA Amendment and described above (Source: Response to Division Questions, 4/23/08). Of these reports, 219 included outcome information (127 normal, 53 abnormal). The abnormal outcomes included 23 major malformations, 22 minor malformations, 5 perinatal complications, and 2 developmental disorders. Ovation also identified 21 spontaneous abortions and 18 therapeutic abortions. Ovation reported that for the 23 major malformation reports, 9 mothers were taking 2 concomitant AEDs, 9 were taking 1 concomitant AED and 4 were either taking no concomitant AED or the status of concomitant AEDs was unknown. For the 22 minor malformation reports, 7 mothers were taking at least 2 concomitant AEDs, 9 were taking 1 concomitant AED, and 6 were either taking no concomitant AEDs or the status of concomitant AEDs was unknown (Source NDA Amendment, pp.233-4).

From 9/2000 through 9/2006 the Drug Exposure Via Mother Database received 26 reports of pregnancies with vigabatrin exposure including 19 reports that provided outcomes. These reports include 8 abnormal outcomes with 1 report of major malformations, 5 reports of minor malformations and dysmorphic abnormalities, 2 reports of perinatal complications, and 1 report of developmental disorder. Ovation reported 1 spontaneous abortion and no therapeutic abortions during this interval (Source NDA Amendment, pp.234-5).

7.1.15 Assessment of Effect on Growth

Ovation provided no discussion of the effect of vigabatrin on growth in their current submission. The Division asked Ovation to summarize data that would allow an assessment of growth in vigabatrin treated children.

In their 5/16/08 response to Division questions, Ovation identified pediatric studies that captured height and weight data. Ovation noted that CPS studies 0118, 0192, 0221, and 0294 and IS

studies W019, FR03, and 1A recorded baseline and final height and weight. The protocols for these studies did not specify the methodology for measuring these parameters.
Ovation provided a table summarizing the weight and height changes in the CPS placebo controlled trials (duration 14-17 weeks). Ovation stratified the results by sex and by age (2-<12, 12-16). The results are included in the table below.

Weight and Height Mean Changes from Baseline in the CPS Placebo Controlled Trials

Sex	Vigabatrin		Placebo	
	Weight	Height	Weight	Height
2-<12 year olds				
Male n	42	6	28	7
Mean change from baseline	3.4kg	2.6cm	1.5kg	3cm
Female n	42	6	39	8
Mean change from baseline	4.1kg	2.1cm	2kg	1.1cm
>12-16 year olds				
Male n	80	10	46	12
Mean change from baseline	4.5kg	2.4cm	1.9kg	2.4cm
Female n	87	15	57	14
Mean change from baseline	4.3kg	1.9cm	1.8kg	2.4cm

The data suggest consistently greater mean increases in weight for pediatric CPS subjects exposed to vigabatrin compared to placebo. The increases in height were similar for vigabatrin and placebo subjects although these results are based on very small numbers of treated individuals. In addition, the lack of protocol specified methodology requiring careful height measurement would be expected to lead to notable inaccuracy and decrease the ability to detect drug related differences, if present.

As Ovation noted, the short duration for controlled phases of the IS studies precludes any meaningful comparative analyses of height and weight data. Ovation felt the mean weight gain for the entire treatment period (including open label) was within the range predicted by growth charts. (Source 5/16/08 Submission, pp.8-13).

7.1.16 Overdose Experience

Prior Submissions

NDA and NDA Amendment (Cutoff date 12/31/95)

In the NDA amendment, the sponsor identified 33 overdose events in 31 individuals. These reports were identified from clinical trials, spontaneous reports and from the medical literature.

For 18 of the overdose events, vigabatrin was the only drug reported as used in the overdose. For those overdosing on vigabatrin only, the symptoms included in more than 1 report were coma/semi comatose (n=5), drowsy/sleepy (n=2), vertigo (n=2) seizure (n=2), and psychosis (n=2). The highest reported overdose was 50g taken by an 18 year old female. This individual

experienced coma and bradycardia and required intubation but the event resolved without sequelae.

Among patients overdosing on multiple drugs, the highest reported vigabatrin dose was 150mg. In addition to overdosing on vigabatrin this patient also ingested 30-50 primidone tablets and 30-50 valproic acid tablets. The sponsor did not include information about the clinical course for this patient but did report that the patient recovered.

Safety Update (1/1/96-3/15/97)
The sponsor updated the vigabatrin overdose experience in the Safety Update. Through the update cutoff there were 38 vigabatrin overdose events in 36 individuals (includes the events noted above). Fifteen events were suicide attempts, 7 were accidental, and the reason for overdose in the remaining 16 events was unknown. No deaths were reported but outcome information was missing for 7 events. The reported symptoms were coma/unconsciousness (12), drowsiness/somnolence (4), apnea/irregular breathing (3), bradycardia (3), vomiting (3), confusion (3), vertigo (2), agitation (2), and increased seizure activity or status epilepticus (2). Ataxia, semi comatose, delirium, concentration impaired, abnormal behavior, speech disorder, auditory hallucinations, psychosis, hypotension, hypothermia, headache, slowed thinking, irritability, tremor, oliguria, pupillary hippus, withdrawn, syncope, dehydration, and pulmonary infiltrates were reported for one patient each (Source Safety Update review, pp.7-8).

Current Submission

Overall Safety Population (3/16/97-6/30/07)
Ovation identified 2 subjects in the Overall Safety Population with SAEs of overdose and one subject with an SAE of accidental overdose. Subject 0201 13870001, a 4 year old female (body weight 15.4 kgs) ingested 6g of vigabatrin (usual daily dose 0.9g/day). She was taken to an emergency department and underwent gastric lavage and was discharged home after 6 hours of observation. The narrative included no information about overdose related symptoms for this subject. Subject 0201 14100003, a 9 year old female (weight 152 pounds) ingested 12g/day for one month (usual daily dose 6g/day) due to the parents misreading the medication bottle. The narrative provided no details about symptoms but stated that the subject recovered and continued in the study. Subject 0201 13970001, a 4 year old female (body weight 15.4 kgs) ingested 30-40 500mg vigabatrin tablets (usual dose 1g/day). She was taken to an emergency department and underwent gastric lavage and was given charcoal. She was hospitalized overnight for observation. She experienced mild ataxia that resolved after several days. She continued in the study. No additional serious spontaneous reports of overdose were included in Ovation's review of postmarketing reports.

Ovation's proposed labeling for overdose identified many of the overdose symptoms listed above. Ovation notes that there is no antidote for vigabatrin, and that measures to remove unabsorbed drug, including emesis or gastric lavage should be used in cases of overdose. Ovation that charcoal does not significantly adsorb vigabatrin and that the effectiveness of hemodialysis in the treatment of vigabatrin overdose is unknown.

7.1.17 Postmarketing Experience

Post marketing events are discussed in the relevant sections above.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

Prior Submissions

NDA and NDA Amendment (Cutoff date 12/31/95)

The safety data from the prior submissions included in this review comes from several sources. For prior submissions, including the original NDA (8/29/94), NDA amendment (5/31/97), safety updates (7/31/97, 1/20/98), and response to the approvable letter (4/28/98), information cited in this review comes from the FDA Amendment review (10/28/97), and the FDA Final Safety Update and Response to the Approvable letter review (8/21/98). In addition, Ovation references material from prior submissions when presenting their Integrated Data analyses in the Amendment.

Current Submission

Overall Safety Population (3/16/97-6/30/07)

Ovation's 12/23/05, 10/10/06, and 3/1/07 NDA Amendment submissions included Safety Updates that the Division found incomplete and therefore refused to file. **Ovation's 12/28/07** submission is the most recent submission and is the focus of this review. The 12/28/07 submission presents new (not previously reviewed) pooled clinical study data for all indications for the period from 3/16/97 to 6/30/07. Ovation refers to the subjects that provide the new data as the Overall Safety Population. The Overall Safety Population is comprised of the subjects that participated in 5 studies in adults with epilepsy, 5 studies in pediatric subjects with complex partial seizures, 4 studies assessing visual field defects, and one study in infants with infantile spasms (IS) (12/28/07 submission, p.16). Ovation pooled data from 14 of the 15 newly completed clinical studies for the overall safety population analyses (data for subjects from study 4103 were not pooled since only SAEs and not all AEs were collected in this study, SAEs from this study were presented separately, 12/28/07 submission, p.16). In addition to the overall pooled presentation, Ovation also separately presented the safety data from the studies identified above for adult subjects, pediatric (non IS) subjects and IS subjects.

Integrated Data

Section 6 of Ovation's 12/28/07 submission provides an integrated presentation of safety data from the original NDA filing through 3/15/97 (previously submitted data), from 3/16/97 through

6/30/07 (overall safety population data), and an updated integrated summary (previously submitted data + overall safety population data) that is cumulative through 6/30/07.

Clinical Data Sources
Ovation received clinical data for the vigabatrin trials from the previous sponsor in the form of data sets, data listings, case report forms, and study reports. For any data obtained from the previous sponsor that was not in the form of electronic data sets, Ovation hired a CRO to create electronic data sets by extracting the information from case report data listings or CRFs. (Source ISS, pp.32-33). In addition to their Integrated Summary of Safety presentation, Ovation submitted study reports, case report forms and narratives for deaths, SAEs, and AEs leading to withdrawal, and selected datasets for the overall safety population data in their submission.

7.2.1.1 Study type and design/patient enumeration

Prior Submissions

NDA and NDA Amendment (Cutoff date 12/31/95)

The data in the following table summarizes the exposure by data group and was taken from Table B-8 which was submitted with the NDA amendment (5/97).

Summary of Number of Exposed Subjects in US and Primary non-US Vigabatrin Trials

Data Group	Placebo	Vigabatrin	Other[1]	Total
US Studies	135	537	52	592
Non-US CRF Studies	682	1189	31	1290
Total Primary Data	*817*	*1726*	*83*	*1882*
Non US Secondary Studies	421	968	12	986
Non-CRF Studies[2]	-	-	-	925
Total unique number of patients[3]	-	-	-	***3561***

[1] Active control or no treatment
[2]Exposure in these studies is not known
[3]Patient subtotal cannot be summed since some patients participated in more than one study

The US studies subjects were exposed to vigabatrin during 6 clinical pharmacology studies, 2 placebo controlled epilepsy studies (vigabatrin n=222, placebo n=135), and 4 uncontrolled epilepsy studies (vigabatrin n=414). The sponsor reported that 443 unique subjects were exposed to vigabatrin in US epilepsy studies (controlled + uncontrolled) (Source: Amendment review 10/28/97, p.11 and attachment p.20).

The non-US primary studies subjects were exposed to vigabatrin during 14 clinical pharmacology studies (vigabatrin n=178), 9 controlled epilepsy studies (vigabatrin n=335, placebo n=284), 17 uncontrolled epilepsy studies (vigabatrin n=430) and 25 studies for other indications (vigabatrin n=246). The sponsor reported that 765 unique subjects were exposed to vigabatrin in the primary non-US epilepsy studies included in the NDA amendment (Source: Amendment review 10/28/97, p.11 and attachment table B-19).

Safety Update (Cutoff Date 3/15/97)

The sponsor reported an additional 1,773 subjects were exposed to vigabatrin for the period of 1/1/96 through 3/15/97. Thirty-three subjects were exposed in clinical pharmacology trials, 338 in epilepsy controlled trials, 1329 in epilepsy uncontrolled trials, and 73 in trials for other indications (infantile spasms, weight loss) (Source: Final Safety Update Review, p.2).

Current Submission

Overall Safety Population (3/16/97-6/30/07)

Ovation reported that 2,148 unique subjects were exposed to vigabatrin in the 14 studies included in the overall safety population data in the 12/28/07 submission. The appendix to this review includes brief summaries of the 15 studies that contribute new safety data. The sponsor presented safety analyses for 3 subpopulations of the overall population. Two of these groupings are age based; the adult subpopulation (age >=16 years, n=1,177), and the pediatric (non-IS) subpopulation (age <16 years, n=444). The third subpopulation, the IS subpopulation (n=223), is based on indication of use. Nineteen subjects were counted in both the adult and pediatric subgroups due to participation in multiple studies and their ages at enrollment. Due to incomplete data capture there were 326 subjects from the overall population with unknown age that could not be classified into one of the age-stratified subpopulations. An additional 3 infants from the IS subpopulation did not have their ages recorded. (Source 12/28/07 submission, pp. 27-8) The following table details the safety subpopulations.