mucosa of the mouth, dysphagia, and fever. Trileptal was discontinued, divalproex sodium started and a corticosteroid and antihistaminic administered. The patient recovered within 12 days.

A 19-year-old male patient on Trileptal 600mg/day for 3 days and co-medication with sucralfate, amikacin, and fosfomycin was reported with toxic epidermal necrolysis. The reaction resolved on discontinuation of oxcarbazepine and continued co-medication. The antibiotics were administered because of fever and leucocytosis. Outcome was reported as condition improving.

Using the 2 cases of SJS and the exposure estimate provided above, the sponsor calculated an incidence rate of 10/1,000,000 person years. They calculated an incidence rate for TEN of 5/1,000,000 person years.

The sponsor concluded that "as would be expected for other medications, the incidence of SJS and TEN in oxcarbazepine treated patients appears slightly higher than the incidence in the general population. To address this, the sponsor proposes that the labeling include the following statement under Post-marketing and other experience "Erythema multiforme and variants including Stevens-Johnson syndrome".

Discussion
Although not observed in their primary database, the sponsor did identify a case of SJS in their Named patient program and 2 cases of SJS, and a case of TEN from post marketing reports. The sponsor concluded that the overall rates of serious rash, TEN, and SJS for patients treated with oxcarbazepine compares favorably with other antiepileptic medication. The drug has a rate of SJS from the Named patient program and from post marketing use that exceeds the expected background rate. This may deserve more attention in labeling than what the sponsor has proposed.

9.0 Hematologic risk
In the NDA safety databases, there were two patients identified with events of "pancytopenia" with minimal or no information about their bone marrow. In addition there were several reports of cytopenias in the spontaneous report database that were suspicious for serious hematologic events (particularly aplastic anemia). In the approveable letter, the division asked the sponsor for a risk assessment of this issue.

In the sponsor's response, they provided additional information for the 2 cases from the NDA databases. For the Pre-GCP case, the sponsor stated that the subject had bone marrow biopsy results that demonstrated normoblastic erythropoiesis, normal megakaryocytes, and "overweight" granulopoiesis. For the case from the Named Patient Program, the sponsor reported that the patient did have a bone marrow biopsy. I reviewed the lab data and narrative provided by the sponsor. This patient was started on oxcarbazepine on October 25, 1989. Hematological lab values for this patient were normal until October 28, 1990 when the patient was diagnosed with pancytopenia (lab values for that day not provided). Oxcarbazepine was discontinued on October 30, 1990. The first lab values for the patient were from November 9, 1990 and at that time, the patient had a Hgb of 10g/dL, a WBC count of $3.0x10^9$/L (12% neutrophils, ANC=360) and a platelet count of $<40x10^9$/L. All three cell lines continued to decline and the lowest recorded values were on December 11,1990 when the Hgb was 7.6g/dL, the WBC count was $2.2x10^9$/L (17% neutrophils, ANC=374) and the platelet count was $22x10^9$/L. The reticulocyte count was 1.4%, which is inappropriately low considering the degree of anemia. It is not possible to tell when the bone marrow aspirate/biopsy was performed in relation to these lab values. In any event, the sponsor reported that the aspirate demonstrated hypoplastic myelopoiesis and normal

megakaryoblastosis. The sponsor considered this case complex and difficult to interpret but not completely consistent with aplastic anemia or with pancytopenia.

The sponsor also resubmitted information for the 4 cases of hematological dyscrasias affecting more than 1 cell line identified from the spontaneous reporting database. There was little new information included. One case was described as pancytopenia but lacked bone marrow information. The remaining 3 cases were anemia with thrombocytopenia, leucopenia with thrombocytopenia purpura, and granulocytopenia with thrombocytopenia.

Discussion
The bone marrow and the additional clinical information provided by the sponsor for the hematological event from the pre-GCP database are not consistent with a diagnosis of aplastic anemia. Although not completely consistent with aplastic anemia as described by the sponsor, the case from the named patient program is suspicious for such an event. There was little additional information provided for the spontaneously reported cases, limiting our ability to determine if there were cases of aplastic anemia from this source. The sponsor's suggestion to leave aplastic anemia out of the label, with no certain cases identified at this time, appears appropriate.

10.0 Jaundice
During the NDA safety Review, using the adverse event listings, I identified 2 patients who had events of jaundice but no lab data to support an elevated bilirubin. We asked the sponsor to provide additional information about these cases. The sponsor used source documentation to determine that in both cases, the patients appeared to be jaundiced to the investigators but that total bilirubin was not elevated in either case.

11.0 Uremia
During the NDA safety review, I came across an adverse event coded as uremia but with no lab data to support the diagnosis. We requested additional information from the sponsor about this case. Uremia was the preferred term for an event reported by the investigator as possible renal failure. This patient was a 14 year old female with a history of cerebral palsy contractures, and PEG tube placement who had normal BUN and creatinine during the first 6 months of treatment. She developed fever, nausea, vomiting, and diarrhea and was admitted to a hospital. She was diagnosed with hypovolemia and had a BUN of 36mg/dL and a creatinine of 2.6mg/dL. The hospital course was complicated by ARDS requiring mechanical ventilation and continued hypotension requiring pressors. During the hospitalizations she was also diagnosed with a myocarditis ("probably viral"). Four days after admission, she had a BUN of 18mg/dL and a creatinine of 0.7mg/dL. Her condition improved and she was discharged with normal renal function.

12.0 Status events
The sponsor did not report status epilepticus rates in the NDA submission and we requested information about status in the approveable letter. In their response, the sponsor calculated incidence rates by treatment for the controlled trials. In the adjunctive/monotherapy substitution trials, the incidence of status in oxacarbazepine subjects was 1.09/100PY compared to 1.73/100PY in placebo subjects and 0 in carbamazepine and phenobarbital subjects. In the initiation of monotherapy trials, the incidence of status among oxcarbazepine exposed subjects was 0.29/100PY compared to 0.5/100PY for phenytoin and 0 for placebo and valproic acid.

13.0 ECG clarification
In their NDA, the sponsor reported that ECGs from 3 studies were forwarded to a central laboratory for additional analyses of intervals. We asked the sponsor why these 3 studies were the

only ones that had additional analyses. They responded that for the remaining studies, ECGs were done as part of the protocol but the investigator was only required to note whether the ECG was normal and if abnormal to record the abnormality. As concern about drug influence on QT interval increased over recent years, the sponsor decided to include interval analysis of ECGs for these later studies.

14.0 Loss to Follow Up

The sponsor reported high loss to follow up percentages for oxcarbazepine trials. They were asked to explain this finding. They responded that 3.4% (76/2,224) of oxcarbazepine epilepsy patients were lost to follow up in the Primary database. Most (65/76) were lost to follow up from trials conducted outside of the United States. Of the 65 loss to follow up patients from outside of the US, 49 were lost from 3 active control comparative trials conducted in newly diagnosed patients. The sponsor suggested that newly diagnosed patients with epilepsy are more likely to have difficulty following treatment regimens and examination schedules leading to higher dropout rates.

15.0 Creatinine increases

There appeared to be an increased risk of elevated creatinine in oxcarbazepine subjects compared to placebo. The sponsor was asked to evaluate this issue. The sponsor identified 4 oxcarbazepine and 0 placebo subjects with increases in creatinine. For 2 oxcarbazepine subjects, the creatinine value abnormalities were due to data entry errors. For the remaining 2 subjects, the increase was described as isolated and transient.

16.0 Pre-Approval Safety Update

In addition to their responses to questions raised in the Approveable letter, the sponsor's 11/16/99 submission included a safety update (Pre-approval Safety Update). This safety update includes information from 4 studies not included in prior submissions as well as additional information from ongoing studies. The sponsor also provides updated information from the named patient program and post marketing experience. The cutoff date for this safety update is May 31, 1999.

16.1 Exposure

For the primary database, the sponsor reported that an additional 262 epilepsy patients were exposed to oxcarbazepine in clinical trials and that an additional 18 healthy volunteers were exposed in a clinical pharmacology trial (034). In the following table, I summarize the exposure (patients) for the 120-day safety update and the pre-approval safety update.

Treatment population	120 day Safety Update	Pre-Approval Safety Update
Overall OXC exposed	2,390	2,670
Epilepsy	2,224	2,486
Healthy volunteers	114	132
Other indications	52	52

The sponsor reported that 23 additional patients were treated with oxcarbazepine in the named patient program. They also provided an updated estimate of post marketing exposure of 200,000PY (increased from 156,000PY in the 120-day safety update).

16.1.1 Exposure by dose and duration

The sponsor documented the increases in the number of subjects exposed for 6 months (now 1,519), 12 months (now 1,176), and 24 months (now 637) in the various epilepsy trials. In addition, they updated the number exposed to various dosages. They report that 1,095 subjects have been exposed to a mean daily dose of >600-1,200mg/day, 459 have been exposed to

>1,200-1,800mg/day and that 617 subjects have been exposed to >1,800mg/day. The sponsor included a table that provided exposure by duration and maximum daily dose for subjects exposed to maximum dosages greater than 1,800mg/day. In this table, they note that 509 subjects have been exposed to maximum daily dosages >1,800-2,400mg/day (224 for at least 1 year), 253 have been exposed to >2,300-3,600mg/day (164 for at least 1 year) and 30 have been exposed to >3,600mg/day.

16.2 Adverse Events
The sponsor states that oxcarbazepine's adverse event profile in the Pre-approval safety update is similar to the profile in the 120 day safety update. They reported that they did not observe an increase in the incidence of adverse events reported in the Pre-approval safety update.

The sponsor provided a table that listed the most common AEs (occurring in at least 10% of exposed subjects) for the Pre-approval safety update and the 120 day safety update. There were no notable differences in risk when comparing the two tables.

16.3 Deaths
The sponsor reported 7 deaths in the Pre-approval safety update that had not yet been reported in the 120-day safety update.

Primary Database
The Pre-approval safety database included information about 1 death from the primary database that was not previously reported. Subject 026E/USA/M8706P/11(601), a 40-year-old male, had been treated with oxcarbazepine for almost 3 years prior to dying suddenly. An autopsy report noted bite marks on the tongue of the subject and his death was attributed to seizure disorder.

The sponsor updated the death rate in the Pre-approval safety update to 7.5/1,000PY (compared to 8/1,000PY for the 120-day safety update).

Secondary Database
Named Patient Program
The sponsor reported 3 deaths from the named patient program in the Pre-approval safety update that were not previously reported. All three patients were elderly (youngest 75 years old) and all were being treated with oxcarbazepine for trigeminal neuralgia. Two of the deaths were attributed to pneumonia and one to pulmonary edema.

Post-marketing
The sponsor reported 3 deaths from post marketing sources that were not previously reported. Two of the deaths occurred in patients who were noted to have hyponatremia at the time of death and were described in the NDA review (p.49) because they had been identified by the sponsor through a search of the medical literature.

For the remaining death, the report noted that the patient was mistakenly given another patient's medications (clomipramine and clozapine). He awoke, was agitated, and was then given the medications he was supposed to be taking. The next morning he suffered a cardiac arrest, was initially resuscitated but later died. The report noted that the patient's prescribed medications were oxazepam, haloperidol, sulpiride, valproate, oxcarbazepine, lamictal, felodipine, and corodil.

16.4 Serious Adverse Events
Primary database

The sponsor did not describe a notable difference in risk when comparing the overall population in the 120-day safety update to the Pre-approval safety update. There were no changes in the most commonly reported serious adverse events. The sponsor provided narratives for the serious adverse events reported in the Pre-approval safety update. I read the narratives and most described seizure-related events. There did not appear to be any new/previously unrecognized events. There were no reports of hepatic failure, renal failure, hematological abnormalities, rhabdomyolysis, or serious skin events.

Named Patient Program
The Pre-approval safety update contains 5 new reports of serious adverse events from the Named Patient Program. The sponsor provided a listing of these events with little additional information. The events were balance/coordination disorder, convulsive disorder, intracranial and spinal cord disorder (trigeminal neuralgia), pulmonary edema, and pain.

Post-marketing
The sponsor noted that they have received 124 spontaneous reports of serious adverse events through 5/31/99 (compared to 100 reports in the safety update). The sponsor provided information about the 24 new serious cases in line listings. Those events are reviewed in the following paragraphs.

Skin
One report (98SF-10008) described a 42-year-old male taking oxcarbazepine for 1-½ months and then developing a rash on his hands and legs and sores in his mouth. The report noted that this patient recovered. Another report (99SF-10007) described an 8-year-old male who developed rash, swelling of the ears and oral mucosal ulcerations that resolved after discontinuation of oxcarbazepine. A 61-year-old male patient developed a lupus like rash approximately 2 years after starting oxcarbazepine. A 71-year-old male patient developed an itchy, dry, exanthema that most affected the limbs, face and scalp. A 63-year-old female developed urticaria after 1 year of oxcarbazepine treatment. An 11-year-old female developed urticaria and arthralgias after 2 weeks of oxcarbazepine therapy and these events recurred upon re-challenge.

Vasculitis
An 11-year-old female was diagnosed with Henoch Schoenlein Purpura, following 2 years of treatment with oxcarbazepine.

Collagen
An 11-year-old male developed lupus while being treated with oxcarbazepine (5 years), phenytoin, and phenobarbital. Symptoms included rash, fever, weight loss, and malaise. Pertinent lab results included "significant increases" in antinuclear antibodies, double stranded DNA, and anti-histone antibodies.

CNS
The sponsor noted 1 report of atonic seizures. They also reported that a 17 year old male treated with oxcarbazepine and gabapentin developed auditory hallucinations and his condition was listed as unchanged following discontinuation of oxcarbazepine.

GI disorders
A 14-year-old female treated with oxcarbazepine and valproate developed pancreatitis, which resolved upon discontinuation of both drugs.

Hyponatremia

The sponsor reported 8 serious hyponatremia events, although 2 of these events had been previously identified from a published report and were presented in a previous submission (see post-marketing deaths above). For the remaining 6 serious spontaneous hyponatremia reports 3 were associated with seizures or increased seizure frequency. The lowest sodium reported was 110mmol/L in a 66-year-old female who was also taking a diuretic at the time of the event.

Thrombocytopenia
A 47-year-old female treated with atrovent, serevent, flixotide (corticosteroid), valproate and oxcarbazepine developed thrombocytopenia ($32,000x10^9$/L). Oxcarbazepine was discontinued and the outcome was complete recovery although no other platelet counts were noted.

Hypersensitivity events
The sponsor provided information about a 21-year-old female treated with valproate for years and oxcarbazepine for a few months, who developed rash. Oxcarbazepine was stopped and carbamazepine treatment was initiated. She subsequently experienced progressive worsening of the rash, fever, lymph node reaction, and fulminant hepatitis. Liver biopsy found necrosis and presence of eosinophils.

A 40-year-old female developed fever, erythematous rash, petechiae, edema and urticaria 2 days after initiating oxcarbazepine treatment. This patient had a similar reaction when taking carbamazepine.

Fatigue due to infection
A 16-year-old mentally retarded female developed slowness and loss of ability to carry out daily routines. These events were attributed to an infection.

16.5 Discontinuations Due to Adverse Events
The sponsor updated information about discontinuations due to adverse events. After updating the safety data, there were no notable changes in the risks for events leading to discontinuation and the sponsor noted that the most common treatment emergent adverse events during oxcarbazepine therapy were also the ones that most frequently caused premature discontinuation. The sponsor reported 17 discontinuations for adverse events but the listing provided by the sponsor identified only 15 subjects. The sponsor provided narratives for the subjects identified in the listing. I read through those narratives. Discontinuations were attributed to nausea, vomiting, dizziness, diplopia, increased seizures and lethargy but the narratives did not include information about the subjects' serum sodium level at the time of the event. There were 2 discontinuations due to AEs and 1 discontinuation for lab abnormality that were attributed to hyponatremia. There was a discontinuation for nausea but the narrative also documented hyponatremia. Those hyponatremia related discontinuations are summarized below.

04E/USA/M8456A/116(513) This 46 year old female developed hyponatremia (Na 126mEq/L) approximately 3 years after beginning treatment with oxcarbazepine. The sponsor also noted that the subject experienced weight gain and hypertension. The sponsor reported that this subject was taking Tegretol XR, Neurontin, and was on a high salt diet at the time of the event.

025E/USA/M0214X/105(569) This 55 year old female discontinued for a serum sodium of 122mEq/L that occurred 2 years after starting treatment with oxcarbazepine. The sponsor did not report any other symptoms. The sponsor noted that the subject was taking Maalox, Advil, Claritin, and Prilosec at the time of the event.

032/CDN/31/425(425) This 31 year old male discontinued for nausea but the narrative included information about hyponatremia. This trial was a pre-surgical design that used intravenous MHD

(monohydroxy derivative of oxcarbazepine- the main metabolite in humans). The sponsor reported that 2 days after randomization this subject had a serum sodium of 122mmol/L. There were no subsequent sodium measurements. The subject entered the extension phase and experienced nausea, blurred vision, and an outbreak of herpes zoster. The investigator reduced the oxcarbazepine dose and added topiramate and carbamazepine. The patient discontinued oxcarbazepine, reportedly for nausea.

032/AUS/11/402(402) A 51-year-old male enrolled in the pre-surgical MHD trial described above experienced dizziness and ataxia one day after randomization and the next day, blurred vision and increased seizure frequency (entered the open label oxcarbazepine extension). His serum sodium on the second day of the trial was 121mmol/L. On the third day, he discontinued for increased seizure frequency. Subsequent serum sodium levels were 115mmol/L and 110mmol/L. The sponsor described the subject as drowsy and noted that he continued to experience seizures. Oxcarbazepine was stopped and the subject had his water intake restricted. Within 5-6 days, his serum sodium had increased to 134mmol/L.

16.6 Pregnancy

The sponsor noted that there have been three additional pregnancies in women enrolled in trials included in the primary safety database. One was terminated by therapeutic abortion (no mention of fetal anomalies), and two were proceeding at the time of the submission. In the Named Patient Program, there was one pregnancy reported and it ended in a miscarriage at 6 weeks. The sponsor also received 3 spontaneous reports of pregnancies identified from post marketing use. All three pregnancies reportedly resulted in normal babies.

16.7 Review of Literature

The sponsor presented the results of a review of the scientific literature for oxcarbazepine. They identified a total of 19 new literature reports. They did not identify any new, previously unreported adverse events. Several of the case reports were for events that the sponsor had previously submitted because they had been received as spontaneous reports.

16.8 Discussion of Data Presented in the Safety Update

The sponsor presented additional information for patients exposed to oxcarbazepine in the development program. Most of the additional exposure is from patients continuing treatment in extension studies. The sponsor did not identify any new, previously unrecognized events. There were no cases of fulminant hepatic failure, renal failure, aplastic anemia, serious skin events, or rhabdomyolysis described from the primary database. Based on this safety update, there is no meaningful change in the safety profile for oxcarbazepine.

/S/

Gerard Boehm, MD, MPH

cc: NDA 21-014, Katz, Burkhart, Hershkowitz, Boehm

APPEARS THIS WAY
ON ORIGINAL

1/3/00

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- **Psychiatric symptoms:** acute stress reaction, aggressive reaction, agitation, anxiety, apathy, crying abnormal, delusion, depression, depression aggravated, emotional lability, euphoria, hallucination, illusion, impulse control impaired, insomnia, manic reaction, nervousness, paranoid reaction, personality disorder, psychic disorder, psychosis, suicide, suicide attempt;
- **Cognitive symptoms:** amnesia, aphasia, cognitive disturbances, concentration impaired, confusion, delirium, encephalopathy, feeling drunk, learning difficulties nos, mental deficiency, psychoneurologic disorder, speech disorder, stupor, thinking abnormal;
- **Somnolence symptoms:** including depressed level of consciousness and fatigue. Investigator terms included are: hypersomnia, diurnal drowsiness, drowsiness intermittent, drowsiness mild, drowsiness/sedation, drowsy, drowsy intermittent, heavy drowsiness, mild drowsiness, somnolencia, somnolenza daily, sedacion, sedate, sedated, sedation, sedation (daily), sedation (mild), sedation (very mild), sedation increased, sedation intermittent, very mild sedation, diurnal sleepiness, increased sleepiness, mild sleepiness, occasional episodes of sleepiness, sleepiness increased, sleepiness intermittent, sleepiness minimal excessive, sleepy, tired (sleepy), very sleepy, excessive somnolence, intermittent somnolence, groggy, grogginess, somnolence (Le Soir), somnolence apres midi et soir, somnolence de difficulte de concentration, somnolence diurne, somnolence l'apres midi, somnolence le soir, somnolence nocturne, somnolence soir, somnolence transitional, somnolentia, somnolenza dopo cena, somnolenza pomeridiana marcata, sensacion de embotamiento, torpidity, torpor.

  The independent preferred terms of fatigue and somnolence to which investigator terms could be coded, were reviewed. Investigator terms were linked exclusively to fatigue or to somnolence but not to both. When the incidence of somnolence and fatigue were analyzed separately, a similar conclusion was observed as to when the terms were pooled under somnolence symptoms. It is also difficult to distinguish between symptoms of somnolence from symptoms of fatigue in the investigator terms, particularly when translated from foreign languages. Consequently, in the discussion and analysis that follows, all symptoms listed above were included under somnolence symptoms.

The incidence of mental status changes in oxcarbazepine-treated patients was compared with placebo-treated and active comparators (PHT, CBZ, VPA, PB). Due to different treatment exposures, the incidence of mental status changes was normalized for the rate per 100-patient years in a separate analysis (Exhibit W2-1).

Exhibit W1-5. Incidence of selected adverse events occurring within ± 7 days of reaching a sodium value <125 mmol/L, sodium value <130mmol/L or reaching a lowest sodium value ≥ 130 mmol/L (all patients with epilepsy)

Mental Status Changes		OXC						Placebo	
		Na < 125 mmol/L (N=60)		Na 125-129 mmol/L (N=160)		Na ≥130 mmol/L (N=1787)		Na ≥130 mmol/L (N=399)	
	Preferred term	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Psychiatric symptoms	**TOTAL**	**3**	**5.0**	**9**	**5.6**	**88**	**4.9**	**17**	**4.3**
	Depression	2	3.3	1	0.6	14	0.8	4	1.0
	Insomnia	1	1.7	4	2.5	16	0.9	3	0.8
Cognitive symptoms	**TOTAL**	**1**	**1.7**	**7**	**4.4**	**48**	**2.7**	**11**	**2.8**
	Thinking abnormal	1	1.7	0	0.0	8	0.4	1	0.3
Somnolence	**TOTAL**	**2**	**3.3**	**14**	**8.8**	**135**	**7.6**	**30**	**7.5**
	Somnolence	2	3.3	3	1.9	83	4.6	20	5.0
	Fatigue	1	1.7	11	6.9	64	3.6	11	2.8
General Symptoms	**TOTAL**	**16**	**26.7**	**50**	**31.3**	**326**	**18.2**	**69**	**17.3**
	Dizziness	5	8.3	19	11.9	106	5.9	22	5.5
	Headache	5	8.3	14	8.8	149	8.3	33	8.3
	Vision abnormal	5	8.3	11	6.9	33	1.8	2	0.5
	Nausea	4	6.7	17	10.6	55	3.1	12	3.0
	Diplopia	3	5.0	19	11.9	73	4.1	10	2.5
	Convulsions	1	1.7	0	0.0	5	0.3	2	0.5
	Convul. aggravated	1	1.7	0	0.0	5	0.3	1	0.3
	Vomiting	1	1.7	16	10.0	71	4.0	20	5.0

Source: Appendix Table W1.2-1, Table W1.2-5, and Tabie W1.2-7.

Review of Clinical Data for the Oxcarbazepine NDA
Safety Review

NDA:	**21-014**
Drug Name:	**Generic: Oxcarbazepine** **Proposed trade name: Trileptal™**
Sponsor:	**Novartis**
Drug Characteristics:	**Proposed indications: monotherapy or adjunctive therapy in the treatment of partial seizures (which include the subtypes [redacted] partial seizures [redacted] in adults and children with epilepsy)** **Dosage forms: 150mg, 300mg, and 600mg film coated tablets** **Therapy should be initiated with a dose of 600mg/day (8-10mg/kg/day) given in two divided doses. If clinically indicated, the dose may be increased by a maximum increment of 600mg/day at approximately weekly intervals from the starting dose to achieve the desired clinical response. In controlled hospital settings, dose increases up to 2400mg/day have been achieved over 48 hours. When establishing Trileptal monotherapy in patients currently receiving other AEDs, the dose of other AEDs should be gradually reduced. The maximum recommended dose in children is 46mg/kg/day.**
Reviewer:	**Gerard Boehm, MD, MPH**
Completed:	**7/23/1999**

1.0 Materials Used in the Review

This review was conducted using the electronic versions of the Integrated Safety Summary (ISS), safety data sets, case report forms and study reports, which were submitted on CD-ROMs as part of the Oxcarbazepine New Drug Application (NDA) on 9/25/98. The electronic Safety Update, submitted on 2/5/99 was also reviewed. During the course of the review, additional information was requested from the sponsor and their responses were provided on paper.

2.0 Background

2.1 Background and Regulatory History

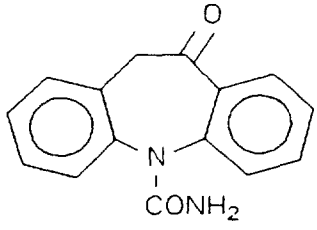
Oxcarbazepine (10,11-dihydro-10 oxo-5H-dibenz[b,f]azepine-5carboxamide) is an anticonvulsant intended to be administered as monotherapy and as adjunctive therapy in adults and children with partial epilepsy. The sponsor reported that in animal models, oxcarbazepine demonstrated anticonvulsant activity with minimal systemic toxicity. In humans, the drug is rapidly and almost completely reduced to an active 10-monohydroxy derivative (MHD) without epoxide formation. The sponsor claims that oxcarbazepine has a decreased propensity to induce oxidative enzymes.

Clinical development of oxcarbazepine began in Europe in the 1970's and the sponsor explained that many of the early trials that were conducted did not meet the current Good Clinical Practice Guidelines (vol. 1, sec C., p.3). In 1988 Ciba-Geigy compiled a registration dossier using data from these early trials and submitted it in numerous countries (notable exceptions were Canada, Ireland, the United Kingdom, and the United States). Oxcarbazepine was approved in over 50 countries including Denmark, Netherlands, and Switzerland and was first marketed in Denmark in 1990. The reviewing bodies in Australia, Sweden, France, and Germany identified safety concerns based on the original dossier, which led to withdrawal of the application. Criticisms included limited safety data, insufficient assessment of hyponatremia, limited information on patients intolerant to carbamazepine regarding allergic skin reactions and insufficient toxicological data. In 1991, a new development program was initiated to obtain worldwide registration. NDA 21-014 is based on the data collected from the recent development program.

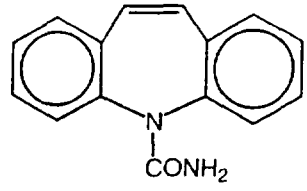
2.2 Information from Related Agents

Although they are metabolized differently (carbamazepine-epoxide formation, oxcarbazepine-reduction) as illustrated below, oxcarbazepine and carbamazepine have similar chemical structures.

Oxcarbazepine



Carbamazepine



The carbamazepine labeling includes a boxed warning for aplastic anemia and agranulocytosis (5-8x greater risk than in the general population). In addition, there are warnings about toxic epidermal necrolysis, Stevens-Johnson syndrome, use in those with increased intraocular pressure (anticholinergic), potential for activation of latent psychosis, and confusion in the elderly. Labeling mentions association with congenital defects including spina bifida. The carbamazepine labeling recommends baseline and periodic evaluations of liver function particularly in patients with a history of liver disease. Other recommended tests include baseline and periodic eye examinations and baseline and periodic urinalysis and BUN determinations. Lab changes observed with carbamazepine that are mentioned in the labeling include hyponatremia, decreases in thyroid function tests, and interference with some pregnancy tests.

2.3 Proposed Oxcarbazepine Labeling with Respect to Safety

The sponsor states that oxcarbazepine is indicated for use as monotherapy or adjunctive therapy in the treatment of partial seizures (which include the subtypes of simple, complex, and partial seizures evolving to secondarily generalized seizures) in adults and children with epilepsy;

seizures evolving to secondarily generalized seizures) in adults and children with epilepsy; including newly diagnosed patients. They state for adults and the elderly, for both monotherapy and adjunctive therapy, that oxcarbazepine should be initiated at 600mg/day in 2 divided doses and that good therapeutic effects are seen at doses between 600-2,400mg/day. For children, they recommend a starting dose of 8-10mg/kg/day in 2 divided doses and they suggest a maximum dose of 46mg/kg/day.

The sponsor lists "hypersensitivity to Trileptal or to any of its components" as the only contraindication to use.

In the ***Warning*** section of proposed labeling, the sponsor states that oxcarbazepine should be withdrawn gradually to minimize the potential of increased seizure frequency.

In the ***Precaution*** section, the sponsor states that patients who have exhibited hypersensitivity reactions to carbamazepine should be informed that approximately 25-30% of these patients might experience hypersensitivity reactions with oxcarbazepine and mentions severe skin reactions as an example. They suggest that oxcarbazepine be withdrawn immediately if this occurs. The sponsor also mentions that concurrent use of oxcarbazepine with hormonal contraceptives may render this type of contraceptive less effective. The sponsor mentions that using alcohol and oxcarbazepine in combination could result in an additive sedative effect. Lastly, the sponsor states that oxcarbazepine may cause dizziness and somnolence and therefore patients should not drive or operate machinery until they have gained sufficient experience on oxcarbazepine.

Under the Laboratory tests section, the sponsor states that serum sodium levels <125mmol have been observed in 2.7% of oxcarbazepine treated patients. The sponsor recommends monitoring serum sodium levels in patients with pre-existing renal conditions requiring high fluid intake, patients with pre-existing low sodium levels, and in patients treated with diuretics.

The sponsor proposes to include a table summarizing AED interactions (Carbamazepine, Phenobarbital, Phenytoin, and Valproic acid) with oxcarbazepine. In addition, they intend to include paragraphs discussing interactions with hormonal contraceptives (decrease in mean AUC by [redacted] for EE, LNG) and calcium antagonists (decrease in AUC for felodipine, decrease plasma levels of MHD of 20% when given with verapamil).

The sponsor states that there does not appear to be any difference between children (≥3yrs old) and adults with respect to safety and noted that the maximum plasma concentration and AUC of MHD were higher [redacted] in elderly volunteers compared to younger volunteers. This finding was attributed to differences in creatinine clearance.

In the sponsor's adverse event tables, they divide the controlled trial data into the following two categories: initiation of monotherapy trials, and adjunctive therapy and monotherapy substitution trials. They propose listing the AEs occurring in ≥ 3%. Table 4 from the proposed labeling is reproduced below.

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Table 4: Incidence (%) of Adverse Events (AEs) ≥ 3% in initiation of monotherapy trials

Body System and Preferred Term	Oxcarbazepine (N=440)	Placebo (N=66)
Body as a whole		
Fatigue	8.6	12.1
Fever	6.4	3.0
Weight Increase	4.3	1.5
Digestive System		
Nausea	13.2	12.1
Vomiting	6.6	6.1
Diarrhea	5.9	1.5
Dyspepsia	3.9	3.0
Gastrointestinal Disorder	3.2	0
Anorexia	3.0	1.5
Infections and Infestations		
Infection viral	14.5	10.6
Musculoskeletal System		
Arthralgia	3.6	1.5
Back pain	3.0	1.5
Nervous System		
Headache	37.5	12.1
Somnolence	21.6	6.1
Dizziness	19.5	4.5
Apathy	5.5	1.5
Nervousness	5.0	4.5
Depression	4.3	3.0
Anxiety	3.6	3.0
Tremor	3.4	0
Respiratory System		
Tonsillitis	3.9	3.0
URTI	3.9	1.5
Pharyngitis	3.4	1.5
Skin and Appendages		
Rash	6.8	4.5
Acne	3.4	0
Alopecia	3.2	0
Special Senses		
Vision Abnormal	3.2	0

In addition to the above table the sponsor proposes to include Table 5 for the adjunctive and monotherapy substitution trials using the same criteria (≥3%). Many of the same AEs appear in both tables. Table 5 includes the following AEs that were not listed in Table 4: Asthenia (3.9 v 2.8), Constipation (3.0 v 2.8), Ataxia (11.4 v 4.2), Nystagmus (8.4 v 2.8), Gait abnormal (5.8 v 2.4), Insomnia (4.2 v 2.3), Rhinitis (3.7 v 5.4), Coughing (3.0 v 4.0), Diplopia (17.2 v 2.5), and Vertigo (6.6 v 1.4).

The sponsor states that the abuse potential of oxcarbazepine has not been evaluated in humans but that a study in monkeys demonstrated no signs of physical dependence.

The sponsor states that isolated cases of overdose with oxcarbazepine have been reported and that the maximum dose taken was 24,000mg. Symptoms of overdose include somnolence, dizziness, hyponatremia, ataxia, and nystagmus. There is no known antidote for the treatment of overdose with oxcarbazepine and the sponsor suggests that gastric lavage and activated charcoal should be considered.

2.4 Animal/ Pre-Clinical Studies
In the animal studies section of the ISS (p.231), the sponsor describes how both oxcarbazepine and its active metabolite in man have been evaluated in single and repeated dose schedules in rodents and dogs over periods of 10 days to 2 years. The sponsor concluded that both oxcarbazepine and its metabolite were of a low order of single dose toxicity. Hepatocellular hypertrophy was observed and the sponsor attributed this finding to induction of liver enzymes in mice and rats. The sponsor reported that additional compound related findings included neuropathia, changes in the GI tract, heart, lymphatic system, blood and the endocrine system. Carcinogenicity studies found dose dependent formation of benign liver cell tumors in mice and rats and hepatocellular carcinomas in female rats. With the metabolite, the sponsor observed a marginal increase in the incidence of benign interstitial cell tumors of the testes at ≥250mg/kg in rodents. In addition, increases in the incidence of granular cell aggregates or tumors in the cervix and vagina were noted at≥75mg/kg. Thyroid follicular hypertrophy/hyperplasia was observed at 600mg/kg.

3.0 Approach to Safety Review/Methods
Using the electronic version of the NDA (primarily the ISS) and the Safety Update, I reviewed treatment emergent events identified from the oxcarbazepine development program. To verify the accuracy of the primary data for the deaths and serious adverse events summarized by the sponsor, I cross checked the data from the sponsor's listings, case report forms (CRFs), narrative summaries, and data tabulations (electronic data sets). To evaluate the adverse event (AE) coding procedures, I compared investigator verbatim terms with the corresponding preferred terms assigned by the sponsor. For selected events (ex. liver related abnormalities, rashes, hematological abnormalities), I reviewed the coding procedure in more detail by examining the CRF, data tabulations, narrative summaries, and listings to determine if the coded terms accurately reflected the described events. I reviewed the death narratives, CRFs and tabulations for oxcarbazepine exposed subjects who died and summarized each death that occurred within 30 days of last exposure. In addition, I reviewed the CRFs, narrative summaries, and tabulations for a sample of serious adverse events (SAEs), selected AEs leading to discontinuation from a study, and any AE preferred terms suggestive of events of interest such as Stevens Johnson Syndrome, agranulocytosis, aplastic anemia, hepatic failure, renal failure, and rhabdomyolysis. When events of interest were identified from listings for the secondary databases, I requested additional supporting information in the form of narratives to describe the events.

I reviewed the sponsor's ISS and Safety Update mortality summaries. I compared narrative summaries, CRFs, tabulations, and summary tables to assess consistency between sources. In the Safety Update, the sponsor provided mortality rates using person time exposure for the overall database as well as by treatment group for the controlled trials. I calculated a mortality rate for extension trials using exposure estimates provided by the sponsor.

SAEs, events leading to discontinuation and treatment emergent AEs were reviewed using information presented in the ISS and Safety Update. To assess the data for evidence of risk differences by age, I requested additional safety tables from the sponsor depicting AE risk by age group and treatment group for the controlled trials. Gender differences were examined using sex stratified AE tables from a large adjunctive therapy controlled trial. The sponsor's lab and vital sign data analyses were reviewed. Because of concerns about the validity of the results of pooled analyses, additional analyses of lab mean change from baseline data and outlier data were performed on the data sets from a single large adjunctive therapy controlled trial. An additional analysis of blood pressure data was also conducted.

4.0 Review Findings

4.1 Description of Data Sources

Because of the developmental history of this agent, the sponsor has safety data from several sources. The primary database includes the data that were collected during the most recently conducted trials, which were carried out in accordance with Good Clinical Practices. In addition, the sponsor has secondary data, which includes information from trials conducted prior to the institution of Good Clinical Practices (Pre-GCP), and information collected from patients who received oxcarbazepine through compassionate use (Named Patient Program). The drug has been marketed in foreign countries since 1990 and the sponsor has a database of spontaneous AE reports from post-marketing use.

4.1.1 Description of the Primary Database

The sponsor included safety data from 32 trials in their primary database (Safety Update, p.11). During these trials 2,390 subjects were exposed to oxcarbazepine. The sponsor reported that 234 subjects were exposed in clinical pharmacology studies (94 with epilepsy, 114 healthy volunteers, 26 hepatic impairment), 1,712 were exposed in controlled epilepsy trials, 26 patients were exposed in a mania trial, 293 subjects received their first exposure during epilepsy extension trials, and 125 were exposed during open label trials. Tables summarizing these trials are included as appendices to this review.

The ISS cutoff date for the primary database was March 31, 1997 but the sponsor included additional information about deaths and SAEs through 2/27/98 (ISS, p.32). The cutoff date for the Safety Update was 3/31/98 and the sponsor included additional information about deaths, and SAEs from completed and ongoing studies through 8/31/98 (Safety Update, p.11).

4.1.1.1 Demographics for Primary Database

In the sponsor's summary of demographic and baseline characteristics on p.30 of the Safety Update, they state that 50.2% (1,116/2,224) of the evaluated subjects were male. Forty-six percent of the subjects were white (no race information for 45.8%) and the mean age was 29.4 years (range 2-88).

4.1.1.2 Extent of Exposure for the Primary Database

The number of subjects exposed to each of the different treatments used in the primary database is included in the following table:

Number exposed by treatment in the Oxcarbazepine primary database

Oxcarbazepine	Placebo	Phenytoin	Carbamazepine	Valproate	Phenobarbital
2,390	503	252	134	121	52

Source Exhibit 2.4.1.-1, p.24 Safety Update

Exposure, primary database during epilepsy RCTs

The sponsor reported that a total of 1,712 subjects were exposed to oxcarbazepine in controlled epilepsy trials (1,272 in 8 double blind adjunctive and monotherapy substitution trials and 440 in 6 double blind monotherapy initiation trials).

Exposure, primary database during open label trials and extensions

The sponsor reported on p. 35 of the ISS that 125 subjects were exposed to oxcarbazepine during the open label trials 001 (n=13) and FTRI02 (n=112). Two hundred thirty nine subjects received their first exposure to oxcarbazepine during open label extension trials.

4.1.1.3 Exposure by duration, epilepsy patients in the primary database

For the 2,224 individuals exposed in the epilepsy trials, the mean duration of exposure was 14.1 months, with a range of .03 months to 83.1 months (Safety Update, p.33). The following table provides the number exposed by duration:

Exposure by Duration for Epilepsy Exposed Oxcarbazepine Subjects in the Primary Database

Number exposed	Duration
361	≤1month
212	>1-3months
195	>3-6months
360	>6-12months
627	>12-24months
336	>24-36months
77	>36-48months
56	>48months

Source Safety Update Table 4.2.-5.

The sponsor reported in the Safety Update that there were a total of 1,456 subjects exposed to oxcarbazepine for more than 6 months and that 1,096 were exposed for at least 1 year (Safety Update p.36).

4.1.1.4 Exposure by dose and duration in the primary database

The sponsor included the following chart on p.36 of the safety update, which summarized exposure by dose and duration for the primary database.

120-day Exhibit 4.2.2.-1. Duration of exposure[1] to OXC by duration and mean daily dose (all OXC-treated patients with epilepsy)

Duration of Exposure (months)	≤ 600 mg/day		>600 - 1200 mg/day		>1200 - 1800 mg/day		>1800 mg/day		All doses	
	n	%	n	%	n	%	n	%	n	%
≤ 1	72	25 4	150	14.9	37	8.8	102	20.0	361	16.2
>1 - 3	43	15 1	100	9.9	38	9.1	31	6 1	212	9 5
>3 - 6	36	12.7	79	7.8	33	7.9	47	9 2	195	8 8
>6 - 12	68	23 9	155	15.3	55	13 1	82	16 0	360	16.2
>12 - 24	28	9 9	276	27.3	178	42.5	145	28 4	627	28 2
>24 - 36	27	9.5	166	16.4	60	14.3	83	16 2	336	15.1
>36 - 48	7	2 5	45	4 5	9	2 1	16	3 1	77	3 5
>48	3	1.1	39	3.9	9	2.1	5	1.0	56	2 5
Total	284	100	1010	100	419	100	511	100	2224	100

Source 120-day Table 4.2.-2

[1] Includes oxcarbazepine exposure during all Open-label Extension Phases through March 31, 1998

4.1.1.5 Person time Exposure in the primary database

In the safety update, the sponsor calculated a total of 2,581 patient years exposure to oxcarbazepine in epilepsy subjects (Safety Update, p.33). This was estimated by multiplying the total number exposed by the mean duration of exposure. I used information from the above chart to calculate person time exposure in a slightly different manner in order to verify the estimate provided by the sponsor. For subjects surviving each time interval (ex 3-6 mos.), I attributed the full amount of time for that interval. For subjects discontinuing during an interval, I attributed half of the amount of time for that interval. I then summed the time for the intervals to arrive at a total exposure estimate. Using this method I calculated a person time estimate (2,668 PY) that was similar to the estimate provided by the sponsor. In addition, I used the method described above to estimate person time exposure by dose. Those results are included in the following table.

Person time exposure to Oxcarbazepine by dose for epilepsy patients in the primary database

≤600mg/day	>600-1,200mg/day	>1,200-1,800mg/day	>1,800mg/day	All doses
221 PY	1,311 PY	546 PY	590 PY	2,668 PY

This table demonstrates that the >600-1,200mg/day dose range had the most person time exposure in the primary database.

The sponsor did not report any changes in exposure for the controlled trials in the Safety Update. Using the sponsor's estimates for the controlled trials (pp.77, 82 Safety Update) there were a total of 891 person years exposure to oxcarbazepine (548PY in adjunctive therapy/monotherapy substitution trials, 343PY in initiation of monotherapy trials). Subtracting the person time provided by the sponsor for the controlled trials (891PY) from the overall exposure (2,581PY) leaves approximately 1,690 person years for the open label and extension trials*.

4.1.1.6 Exposure by age, primary database

On p. 34 of the Safety Update, the sponsor reports a total of 581 children (ages <6-17 years old) were exposed to oxcarbazepine. For the lowest age group, <6 years old, a total of 81 children were exposed. The sponsor reported that 21 children <6 years old were exposed in epilepsy controlled trials. Of the 581 children exposed to oxcarbazepine, 319 were treated for >12months. The sponsor reported that there have been 52 subjects ≥65 years old exposed to oxcarbazepine in the primary database and that 17 were exposed for at least 1 year (Safety Update p.34).

4.1.2 Description of the Secondary Databases

4.1.2.1 Pre-GCP database

The sponsor reported that oxcarbazepine had been evaluated in 62 trials that were conducted prior to the implementation of good clinical practice (ISS, p.263). Fourteen trials were in epilepsy patients, 20 in healthy volunteers, and 28 were clinical pharmacology studies in epilepsy or studies in other indications including mania, trigeminal neuralgia, and affective/schizoaffective psychoses. There were approximately 1,500 subjects exposed to oxcarbazepine in these trials. The reason that these trials were not included with the primary safety database is that the CRFs did not meet current safety data collection standards. The sponsor mentioned that only events considered related to trial drug were captured. Obviously there are serious doubts that all events of interest were identified from these studies. An example illustrating this concern is that the sponsor identified a total of 1 death, and 1 serious adverse event from these 62 studies.

4.1.2.2 Named Patient Program

The Named Patient Program (NPP) summarizes safety data for patients who received oxcarbazepine through compassionate use. The sponsor has data for almost 3,000 patients exposed to oxcarbazepine in the NPP. Some of the data were collected during retrospective surveys, and some were collected prospectively using standardized CRFs. In addition some local clinical trials that were prematurely discontinued for slow enrollment were converted to NPP CRFs and entered into the database (ISS, p.271). Typically, the NPP CRF captured information about demographics, diagnostic information, medical history/concomitant diseases, concomitant medications, reason for discontinuation, treatment emergent events, serious AEs, and deaths.

*This likely slightly overestimates open label and extension study exposure since this total also includes the exposure in epilepsy subjects participating in CP/PK trials.

4.1.3 Spontaneous Post-marketing reports

As mentioned above, oxcarbazepine is approved in over 50 countries and the sponsor has provided summary data (listings) for spontaneous AE reports. Through 8/31/98, the sponsor has received a total of 337 reports for oxcarbazepine. The sponsor estimated, based upon worldwide sales volume in kilograms, and assuming a daily dose of 1,200mg, that there have been approximately 156,000 person years of exposure to oxcarbazepine in the post-marketing setting through 8/31/98 (Safety update p.123).

4.2 Review of the sponsor's AE surveillance, coding of AEs, and approach to evaluating the safety of oxcarbazepine

On p. 103 of the ISS, the sponsor defined a treatment emergent adverse event as an event that was absent during the baseline phase and first occurred during the treatment phase or an adverse event that was present during the baseline phase and increased in severity during the treatment phase. A review of the provided CRFs demonstrated that patients were questioned, in a general fashion, about AEs and that checklists were not used. Investigators captured information about onset, duration, severity, and provided opinions about relationship to study drug. Investigator verbatim terms for AEs were coded to preferred terms using the International Medical Nomenclature/ International Therapy Dictionary (IMN/ITD).

For the sponsor's presentations in the ISS and Safety Update they divided the primary database safety data into the following groupings:

- All oxcarbazepine treated patients with epilepsy (n=2,224) which includes safety data from the controlled trials, open label extensions, open label trials, and clinical pharmacology trials in epilepsy patients.
- Double blind adjunctive therapy and monotherapy substitution trials in epilepsy patients (n=1,272)
- Double blind initiation of monotherapy in patients with epilepsy (n=440)
- Clinical Pharmacology in Healthy Volunteers (n=126)
- Clinical Pharmacology in hepatic impaired individuals (n=26)
- Mania trial (n=26)

There was no separate presentation of data for clinical pharmacology patients with epilepsy or for data collected during extension trials. Safety information collected from these trials appears in the All oxcarbazepine treated analyses and is not easily isolated. The sponsor pooled safety data from the adjunctive therapy and monotherapy substitution trials because these trials had similar populations (refractory patients, with previous or current exposure to at least 1 AED) and had similar AE profiles when viewed separately (ISS, p.36). Data from the controlled initiation of monotherapy trials were presented separately because of the differences in populations (recent onset/diagnosis, on monotherapy) and the lower risk for adverse events observed when comparing these trials with the controlled adjunctive therapy and monotherapy substitution trials. Analyses that include data from the adjunctive therapy controlled trials portray the comparison of risk on oxcarbazepine to placebo or another active comparator. It is important to consider that the risk represents that of oxcarbazepine or comparator added to a regimen of AED(s) and not simply

the risk observed for oxcarbazepine v. placebo or another agent. The designs of the controlled trials and exclusion criteria are summarized in an appendix to this review.

The sponsor's presentation of event risk provided the observed risk by body system and event for all oxcarbazepine exposed epilepsy subjects. Additional analyses stratifying risk by parameters such as age and gender were provided but were difficult to interpret without comparator data. The sponsor presented event risk for the controlled trials (pooled adjunctive therapy/monotherapy substitution trials, pooled initiation of monotherapy trials). Comparisons of event risk among treatments was possible using these tables. In addition to the crude event risks, the sponsor provided analyses stratified by mean and maximum daily dose. Generally, event risks were lower in the initiation of monotherapy trials but it is unclear if this is due to different populations (refractory v. new onset) not using concomitant anti-epileptic medications or the lower doses of oxcarbazepine studied in the initiation of monotherapy trials.

In general, the trials included in the primary database used local labs to analyze specimens. Testing varied from trial to trial with respect to schedule and analytes evaluated. The sponsor provided analyses of lab data focusing on both mean changes from baseline and outliers. The data were presented for the all oxcarbazepine exposed grouping, the adjunctive/monotherapy substitution grouping and the initiation of monotherapy grouping. The outlier analyses were conducted using cutoffs proposed by the division. The sponsor provided additional analyses that identified subjects with outlier values at consecutive visits.

Baseline and end study ECGs were collected in many of the studies included in the primary database. The sponsor had the ECGs from 3 protocols forwarded to a central site for reading and evaluation of mean changes for intervals. In addition, the sponsor provided narratives for the patients who had normal or clinically significant baseline ECGs and developed clinically significant abnormalities during the study.

4.3 Audit Findings and Evaluation of the Specificity of the AE coding

I reviewed the investigator verbatim terms listed in the CRFs of the oxcarbazepine subjects who died and from a sample of serious AEs and AEs leading to discontinuation. The information was congruent with the data contained in the narrative summaries and the tabulations (electronic datasets).

The grouping of preferred terms into body systems for SAEs was performed differently than the grouping of AEs leading to dropout and treatment emergent AEs. SAEs were presented grouped by the Drug Safety Organ Class Classification (DSOC) while the treatment emergent AEs and AEs leading to discontinuation were grouped using COSTART body systems. Specific examples of the differences are illustrated below.

Serious Adverse Event Body Systems DSOC	Treatment Emergent Adverse Events COSTART
Cardio-vascular disorders, general	Cardiovascular disorders
Heart rate and rhythm disorders	
Myo, endo, pericardial and valve disorders	
Vascular disorders, extracardiac	
Gastrointestinal system disorders	Digestive system disorders
Liver and biliary system disorders	
Hemic, lymphatic, reticuloendothelial	Hemic and lymphatic disorders
White cell disorders	
Platelet, bleeding and clotting disorders	
Resistance Mechanism disorders	Infections and Infestations
Central and Peripheral NS disorders	Nervous System disorders
Psychiatric disorders	

During the course of the review, this lack of consistency occasionally made it difficult to locate and describe events identified from the different listings.

I reviewed the results of the coding process that the sponsor used to aggregate the investigator provided adverse event terms. In their discussion of serious adverse events, (p.76, ISS) the sponsor mentioned that investigator terms were standardized to preferred terms using the International Medical Nomenclature/International Therapy Dictionary (IMN/ITD). The IMN/ITD terms were used in the summary tables displaying the risks of adverse events and in tables listing individual subjects with SAEs or listing subjects who prematurely discontinued. The sponsor included information related to coding within appendix III of the ISS. Appendix III.2 is a list of the adverse experiences with the corresponding dictionary terms. I reviewed this listing as part of an evaluation of the coding process. In addition, I compared the coded terms of selected events (ex. rash, hepatic necrosis, etc.) to the description in the CRF and narrative summary.

I came across terms in which the coding process seemed to split potentially related events. Specifically, the terms for edema were split into several preferred terms, which seemed somewhat arbitrary. EDEMA included the investigator term trace pedal edema, EDEMA PERIPHERAL included swollen hands, ankle swelling, edema of feet, edema fingers, EDEMA DEPENDENT included ankle swelling, EDEMA GENERALIZED included fluid retention in lower and upper extremities and puffiness in hands. The sponsor also used the preferred terms EDEMA LEGS and FACE EDEMA. There appeared to be considerable overlap in the coding of these edema related terms. The sponsor also split skin rashes into several preferred terms including RASH, RASH ERYTHEMATOUS, RASH FOLLICULAR, RASH MACULOPAPULAR, RASH PURPURIC and RASH PUSTULAR.

The sponsor grouped accidental injuries into two separate preferred terms: INJURY and TRAUMA. In reviewing the investigator terms for these events it appeared that there was considerable overlap for these two categories. For example, both preferred terms included investigator terms describing animal bites, and lacerations.

In addition, the sponsor included preferred terms with little clinical value including THINKING ABNORMAL, FEELING ABNORMAL and MALAISE, which included investigator terms such as generally unwell, neurovegatative disturbance, facial color changes, and sensitivity in changes to the weather.

In general, with the exception of the events listed above and the foreign language investigators' terms, which were not translated prior to coding to a preferred term, the coding of adverse event terms appeared appropriate.

4.4 Human Pharmacokinetic Considerations

The sponsor reports that the absorption of oxcarbazepine is complete and that after oral administration the compound undergoes reduction by cytosolic enzymes to an active metabolite (MHD). Food has no effect on bioavailability. Following a single dose, the mean apparent elimination half-life is 8-9 hours. After IV administration of MHD, 80% is excreted in the urine as free MHD and glucuronides of MHD. In patients with moderate to severe renal impairment, (creatinine clearance<30mL/min) elimination of MHD is prolonged with a corresponding 2 fold increase in the AUC. Children with normal renal function exhibit higher clearance of MHD then adults, with a corresponding reduction in terminal half-life. Mild to moderate hepatic impairment had no effect on the pharmacokinetics of MHD. At steady state, MHD displays linear pharmacokinetics at doses ranging from 300mg to 2,400mg. The sponsor reports that oxcarbazepine and MHD have low protein binding. The sponsor states that oxcarbazepine/MHD

at high doses may slightly increase phenobarbital and phenytoin plasma concentrations. Carbamazepine, phenobarbital, and phenytoin have been shown to reduce MHD levels by 30-40% when co-administered with oxcarbazepine. Oxcarbazepine reduces the plasma levels of oral contraceptives and may lead to contraceptive failure.

4.5 Safety in the CP/PK studies

As stated earlier, the sponsor did not provide an overall separate presentation of safety data collected during CP/PK trials. Data for epilepsy subjects studied during CP/PK trials were pooled with the data for all oxcarbazepine exposed epilepsy subjects and presented in the all oxcarbazepine exposed analyses. Data for healthy volunteers and those with hepatic impairment exposed during CP/PK trials were presented separately. In this section I will summarize the safety data for healthy volunteers and those with hepatic impairment who were exposed to oxcarbazepine in CP/PK studies.

There were no deaths reported from the CP/PK trials. The sponsor reported that there were no SAEs for the healthy volunteers participating in the CP/PK trials. One of the 26 subjects from the hepatic impairment trial 003 developed an SAE. That event is summarized below.

USA/Zinney/102, a healthy 45 YO healthy male volunteer experienced a decrease in creatinine clearance following exposure to a single dose of oxcarbazepine, 900mg. On enrollment the subject's creatinine clearance was between 80 and 86 ml/min and serum creatinine was 1.2mg/dl. Five days after oxcarbazepine administration, the subject's creatinine clearance was 75ml/min and serum creatinine was 1.3 mg/dl. Fifteen days post dosing, the subject's creatinine clearance was 35ml/min but no serum creatinine was available at that time. At 21 and 30 days post dosing, the creatinine clearance was 70 and 95 ml/min and the serum creatinine was 1.3mg/dl.

No subjects from the hepatic impairment trial prematurely withdrew for adverse events. Four healthy volunteers withdrew from CP/PK trials for adverse events. Those events are summarized below.

OT/E27/SF/1/009 a 24YO male with no significant past medical history developed urticaria one day after initiation of oxcarbazepine that was treated with hydrocortisone and Zyrtec. The subject discontinued from the trial and the event completely resolved.

009/I/1/1006 a 28YO female developed fever, hepatomegally, vomiting, lymphadenopathy, and urticaria 12 days after initiation of oxcarbazepine. The sponsor commented that the fever, vomiting, urticaria, and lymphadenopathy but not the hepatomegally resolved following discontinuation (interval not specified).

009/I/2/1015 a 22YO female developed muscle weakness, ataxia, abnormal gait, and headache 2 days after initiation of oxcarbazepine. The AEs resolved following discontinuation.

009/I/1/1005 developed bronchitis 15 days after initiation of oxcarbazepine. When the subject discontinued from the trial, the bronchitis was completely resolved.

The most common treatment emergent AEs (>10%) in healthy volunteers were headache 41% (n=47), fatigue 34% (n=39), dizziness 27% (n=31), nausea 22% (n=25), somnolence 21% (n=24) and pharyngitis 10% (n=12) Safety Update, p.56. Events reported during the hepatic impairment trial included constipation (n=3), somnolence (n=2), headache, pruritis, dry mouth, dizziness, and decreased creatinine clearance (n=1, each) ISS p.770.

4.6 Mortality

The sponsor's cutoff date for deaths in the Safety Update was 8/31/98 (extended 5 months beyond the Safety Update cutoff date of 3/31/98). The sponsor reports knowledge of 52 deaths in individuals exposed to oxcarbazepine during development and post marketing use. For the clinical trial data included in the primary database, the sponsor provided information about 29 deaths (22 oxcarbazepine exposed within 30d of last exposure, 2 oxcarbazepine exposed >30d after last exposure, and 5 other AED or placebo). The remaining deaths are from pre-GCP trials

(n=1), the Named Patient Program (n=18) and post-marketing experience (n=9) Safety Update, p.68.

4.6.1 Deaths from the Primary Database

As stated above, there have been 29 deaths identified in the primary database through 8/31/98. Twenty-two of these deaths were oxcarbazepine exposed subjects, within 30d of their last dose. One of these deaths occurred after the cutoff for the Safety Update (3/31/98), therefore there are 21 oxcarbazepine deaths for which there is information about exposure. Two deaths (002 USA/M7415D/1(501), and OT/F10 (D)/105/56) were in patients previously treated with oxcarbazepine but the interval between death and last dose was more than 1-month (p. 142 ISS). Five deaths occurred in subjects not exposed to oxcarbazepine (randomized to other AEDs or placebo). The sponsor calculated a mortality rate for the oxcarbazepine exposed epilepsy patients in the primary database of 8/1,000PY (21/2,581PY Safety Update p.68).

4.6.1.1 Controlled Trial Mortality Primary Database

Mortality in adjunctive and monotherapy substitution trials

Since there were no additional deaths from controlled trials reported in the Safety Update, I used the sponsor's listing in the ISS (p.143) to identify those deaths from controlled trials. I then selected the deaths from the controlled trials that the sponsor grouped as adjunctive and monotherapy substitution, and listed them in the following table:

Deaths in subjects exposed to oxcarbazepine during adjunctive and monotherapy substitution controlled trials, primary database*

Study	Patient	Demographic	Daily Dose
OT/E25	F/5/286	28 F	1,200mg
OT/PE1	GB/19/933	34 M	600 mg
OT/PE1	I/4/646	60 M	2,400mg
OT/PE1	ZA/6/583	58 F	600mg
OT/PE1	14/1/4458	20 M	600mg
011	USA/M87836/733	5 M	600mg
026	USA/M8707U/522	50 M	2,400mg
OT/F10	1/302/179	34 M	450mg

*The number of deaths listed above differs from the sponsor's presentation by one because the sponsor misclassified a death (OT/F10/D/112/79) that occurred in an extension trial to the adjunctive/monotherapy substitution controlled trial category.

Deaths in "other" exposed during adjunctive and monotherapy substitution controlled trials, primary database

Study	Patient	Demographic	Exposure
OT/PE1	NZ/12/4 050	33 M	Placebo
OT/PE1	CDN/4/2 41	29 M	Placebo

For all adjunctive and monotherapy substitution trials the mortality risk for oxcarbazepine exposed subjects was 6.3/1,000 (8/1,272). In the comparator group, the mortality risk was 3.7/1,000 (2/539). The sponsor calculated mortality rates by treatment for these trials (Safety Update p. 70). The mortality rate for oxcarbazepine was 14.6/1,000PY (8/548PY)[§] for placebo was 17.2/1,000PY* (2/116PY) and for carbamazepine and phenobarbital was 0 (0/97PY and 0/54PY, respectively).

[§]The sponsor provided an oxcarbazepine mortality rate of 1.6/100PY in exhibit 6.2.2.-2 of the Safety Update that was calculated using 9 deaths in the numerator, but as explained above, one of these deaths was misclassified.

*The sponsor's calculated placebo mortality rate of 2.6/100PY in exhibit 6.2.2.-2 of the Safety Update was incorrect.

Since the above analysis resulted from pooling across several studies with different designs and treatments, I reviewed the 6 deaths from a single study, OT/PE1. In this study, the mortality risk for oxcarbazepine exposed subjects was 7.7/1,000 (4/519) and for the placebo group was 11.6/1,000 (2/173). In addition, I used exposure information from p.43 of the study report for OT/PE1 to calculate person time by treatment. I attributed the full amount of time for subjects completing an interval and half the amount of time for subjects dropping during an interval and then summed across intervals to estimate total person time exposure. Using this method I estimated 190PY exposure to oxcarbazepine and 85PY exposure to placebo. I then divided the number of deaths by the exposure to calculate mortality rates. The mortality rate for oxcarbazepine in this study was 21/1,000PY (4/190PY) and for placebo was 23.5/1,000PY (2/85PY). Three of the 4 oxcarbazepine subjects who died were taking 600mg per day, the lowest possible dose in this trial, and one was taking 2,400mg per day. The oxcarbazepine deaths were attributed to a seizure (found dead in bed), a pulmonary embolism following orthopedic surgery, an intracerebral bleed, and a motorcycle accident. The placebo deaths were attributed to seizures (both subjects found dead in bed).

I examined the mortality risk for the initiation of monotherapy trials. The following tables identify the deaths from these trials.

Deaths in subjects exposed to oxcarbazepine during initiation of monotherapy controlled trials, primary database

Study	Patient	Demographic	Dose
OT/TE1 (010)	GB/5/22	88 F	600mg
OT/F01	E5/7109	48 M	900mg

Deaths in "other" exposed during initiation of monotherapy controlled trials, primary database

Study	Patient	Demographic	Exposure
OT/F02	BR/8/19/7	26 M	Phenytoin
OT/F02	ZA/02/42	21 M	Phenytoin
OT/F01	E/03/328	54 M	Valproate

The mortality risk for the oxcarbazepine exposed subjects from initiation of monotherapy trials was 4.5/1,000 (2/440). For the "other" exposed, the mortality risk was 9.1/1,000 (3/329). The mortality rates by treatment in these trials were 5.8/1,000PY (2/343PY) for oxcarbazepine, 10/1,000PY (2/201PY) for phenytoin and 9/1,000PY (1/111PY) for valproic acid (person time was provided by the sponsor on p.82 of the Safety Update).

4.6.1.2 Extension trial deaths

Using the sponsor's table on p. 146 of the ISS, I identified 12 deaths from extension trials. Those deaths are listed in the following table.

Deaths in subjects exposed to oxcarbazepine during extension trials, primary database

Study	Patient	Age/Gender	Dose
OT/E25E	F/51/203	36/F	600mg
OT/E25E	F/50/537	60/M	900mg
OT/F02E	BR/1/110	63/M	1,500mg
OT/F02E	BR/3/189	20/M	900mg
026E	USA/M8707U/103	31/M	2,400mg
026E	USA/M0206C/109	58/F	1,800mg
OT/F10E	D/112/79	64/F	1,500mg
FTRI02E	F/09/919	12/M	600mg
OT/PE1E	GB/20/8104/952	32/F	1,800mg
OT/PE1E	I/7/689	47/M	1,800mg

004E	USA/M8456A/514	37/M	2,400mg
OT/E25E	74/301	49/M	900mg

Eleven of these deaths occurred by 3/31/98, the cutoff for which exposure data is available. Using the estimated exposure in open label trials (1,690 person years, see above) the mortality rate was 6.5/1,000 person years (11/1,690PY) in the open label and extension trials.

4.6.2 Deaths from other sources

As mentioned above, the sponsor has included information about deaths from sources that are not considered part of the primary database. These include pre-GCP trials (n=1), the Named Patient Program (n=18), and Post-marketing reports (n=9). Since there are uncertainties about these data (i.e. were all events captured, do we have accurate exposure estimates?) the deaths were not used to calculate mortality rates, but were reviewed to identify any unusual or unexpected events. The circumstances surrounding those deaths are briefly summarized below.

4.6.3 Clinical descriptions of the deaths

4.6.3.1 Clinical Trial deaths, primary database through 8/31/98

The sponsor reported that 29 subjects enrolled in oxcarbazepine trials through 8/31/98 had died. Twenty-two of these subjects were treated with oxcarbazepine and the death occurred within 30 days of last dose. I reviewed the narrative summaries and CRFs for these deaths and have summarized the events below. In general, most of the deaths were sudden and often attributed to seizures. In many cases there were insufficient details provided to support conclusions about the cause of death.

(GB)/5/22 This 88 YO female with a history of hypothyroidism, ischemic heart disease, s/p mastectomy for breast cancer, s/p femur fracture, and pernicious anemia was randomized to oxcarbazepine 600mg/day. Eighty-six days after randomization, she dropped out for feeling unwell. Liver function tests were reported as elevated at that time (ALP 563, LDH 723, and AST 39). The patient died 19 days after her last dose and her death was attributed to congestive heart failure, breast cancer, bronchopneumonia and fracture of the neck of the femur.

USA/M8783G 109(733) This 4 YO male with a history of behavioral problems and heart murmur was randomized to oxcarbazepine and was receiving 450mg/day in the titration period when he apparently experienced a seizure and fell down 25 steps. He was pronounced dead upon arrival to the emergency department. Autopsy did not reveal fractures, intracranial hemorrhage, or other signs of trauma and therefore death was attributed to seizures.

USA/M8707U 107(522) This 50 YO male with a history of hearing loss, MVA, amnesia, and emphysema had completed the open label conversion and baseline phases but died prior to starting the double blind phase. Autopsy revealed acute ischemic damage to the heart.

USA/M02306C/109 This 58 YO female with a history of smoking was in an open label extension receiving oxcarbazepine 1,800mg/day when her husband found her dead. An autopsy revealed "complete blockage of 3 coronary arteries" although the narrative did not mention if there was evidence of an acute occlusive event.

USA/M8707U/102(518) This 31 YO male with no significant medical history was in an open label extension receiving oxcarbazepine 1,300mg/day when he was found dead in bed. The sponsor commented that the patient died of cardiopulmonary arrest resulting from a seizure. An autopsy was not performed.

(F)/09/919 This 12 YO male was receiving oxcarbazepine 600mg/day and had a total treatment time of 3 years, when he presented in status epilepticus which had a fatal outcome. No autopsy information was available.

(F)/05/286 This 27 YO female with a history of ankylosing spondylitis and obesity apparently experienced repetitive seizures yet refused to go to the hospital and died later that evening. Death occurred 10 months after randomization and the dose at death was 2,400mg/day. No autopsy was performed.

(F)/50/537 This 60 YO male with a history of ventricular extrasystoles, syncope, bradycardia, and a heart murmur was receiving oxcarbazepine 900mg/day when while swimming he felt faint, got out of the water and died suddenly. There was no mention of an autopsy in the narrative summary.

(F)/51/203 This 36 YO female with a history of hyalinosis cutis while in an open label extension and after 18 months of treatment with oxcarbazepine (dose at death 600mg/day) died from acute laryngeal spasm. The sponsor suggested that the event was related to hyalinosis cutis.
(E)/5/7109 This 48 YO male with a history of lymphadenopathy and neurosarcoidosis was taking oxcarbazepine 900mg/day at the time he died in a traffic accident. The sponsor stated that they did not have any information about thee circumstances of this event.
(Br)/1/110 This 63 YO male with a history of tobacco abuse was taking oxcarbazepine 1,200mg/day. He died at work (no details) and death was attributed to possible myocardial infarction. No autopsy was performed.
(Br)/3/189 This 20 YO male with no significant medical history died from head injuries sustained during a motorcycle accident. The last prescribed dose of oxcarbazepine was 900mg/day.
(D)/112/79 This 64 YO female was taking oxcarbazepine 1,500mg/day when she fell and died. The death was described as a sudden cardiac death and no autopsy was performed.
(I)/302/179 This 34 YO male died following an accidental fall from a balcony. The dose of oxcarbazepine at the time of death was 450mg/day.
(GB)/19/933 This 34 YO male was found dead 120 days after randomization. He was taking oxcarbazepine 600mg/day at the time of death. Autopsy results indicated that death was due to seizure (no further information provided).
(H)/1/4458 This 20 YO male who was taking oxcarbazepine 600mg/day died following a motorcycle accident. Autopsy results documented extensive severe trauma.
(ZA)/6/583 This 58 YO female experienced an intracerebral hemorrhage 128 days after beginning treatment with oxcarbazepine (dose 600mg/day). The sponsor commented that the platelet count was normal and there was no evidence of bleeding tendency or hypertension.
(I)/4/646 This 60 YO male who was taking oxcarbazepine 2,400mg/day underwent surgery for fractured wrist and hip (circumstances surrounding the fractures were not provided). The CRF noted that the patient had been experiencing dizziness and somnolence prior, but it is unclear if they contributed to the event that resulted in the fractures. Following surgery, he developed nausea, sweating, and dyspnea and died from a suspected pulmonary embolism. An autopsy was not performed.
(GB)/20/952 This 32 YO female with Sturge Weber syndrome took oxcarbazepine 1,200mg/day during an open label extension. The patient was found dead in bed and apparently had experienced two seizures prior to the terminal event. An autopsy listed status epilepticus as the cause of death.
(I)/7/689 This 47 YO male was taking oxcarbazepine 1,800mg/day. Six and a half months after initiation the open extension phase, he developed a fever and respiratory difficulty that did not respond to antibiotics. He was hospitalized. He subsequently experienced cardiac arrest and was resuscitated (no further details provided). Oxcarbazepine was discontinued. He experienced a second cardiac arrest and died. The investigator felt the cardiac arrests were related to pneumonia.
USA/M8456A/514 This 37 YO male was enrolled in an open label extension receiving oxcarbazepine 2,400mg/day. He was brought to an ER following a seizure and was noted to be in fine ventricular fibrillation and then asystole. Resuscitation attempts failed. Following an autopsy, the cause of death was believed to be seizure disorder.
OT/E25E/F/74/301 This 50 YO male was enrolled in an open label extension receiving oxcarbazepine 900mg/day, for a total of 4 years. While walking he collapsed and suffered a generalized convulsive episode. He died despite resuscitative efforts. Death was attributed to cardiac arrest due to hypoxia after aspiration during a seizure.

4.6.3.2 Clinical Description of Pre-GCP Death

The sponsor provided a brief narrative for a death from the pre-GCP database.
-/38 Protocol OXDK01 This 68 YO male died of cardiopulmonary arrest (no details). The sponsor did note that during the trial, the patient was treated with antibiotics four times, once for pneumonia, which required hospitalization.

4.6.3.3 Clinical Description of Named Patient Program Deaths

The sponsor admitted to knowledge of 18 deaths in the named patient program. I reviewed the narrative summaries for these deaths to identify any unusual causes of death or patterns of deaths.

Those cases are summarized below. In general the narratives contained little information about the terminal event.

04/01 Protocol GB 9089/NP 27 YO female on 1,500mg/day at death, had been treated for 2 years. Her death was attributed to hypoxia and cardiac arrest following status epilepticus. Autopsy revealed cerebral edema. No other details were provided.
GB/9999 18YO male with a history of mitochondrial cytopathy on 900mg/day at death had been treated for 281 days. He developed status epilepticus that failed to respond to diazepam, paraldehyde and phenytoin. Chlomethiazole apparently controlled the status, but his condition worsened and he became comatose and died. Death was attributed to the underlying disease.
DK/9999 1 YO male on 120mg/day at death. He was hospitalized for generalized seizures and begun on oxcarbazepine and phenytoin and valproate was withdrawn. He died 8 days after initiation of oxcarbazepine and few details are provided. The narrative mentions possible viral encephalopathy.
DK/22 24YO male with epilepsy, encephalopathy and spasticity was on 600mg/day at the time of death. There are few details but apparently the patient developed pneumonia and died 6 days later.
DK/23 2 YO female with encephalopathy and sulfite oxidase deficiency. Eleven days after starting oxcarbazepine and one day after starting phenobarbital, she was hospitalized for pneumonia. Four days after admission, she died.
DK/24 1 year old female with a history of congenital encephalopathy, hydrocephalus, and microphthalmos, asthmatic bronchitis was on 420mg/day at death. One hundred ninety days after starting oxcarbazepine, she was hospitalized for status asthmaticus and died.
DK/73 74 YO male with a history of epilepsy, Parkinson disease, dementia, and somnolence was on 900mg/day at death. The sponsor described progressive deterioration due to underlying disease and did not provide details about the terminal event.
CH/70054 75 YO male on 1,500mg/day at death. He died of rectal carcinoma and had been treated with oxcarbazepine for 10 years prior to death.
16/01 Protocol 9089/NP This 17 YO male on 900mg/day, died of pneumonia and had been treated with oxcarbazepine for 37 months prior to death.
CDN/06 74 YO male treated with 1,500mg/day for trigeminal neuralgia. He was diagnosed with advanced stage lung cancer and died. He had been treated with OXC for 25 months.
DK/16 6 YO female with epilepsy and spasticity was on 600mg/day at death. She fractured her femur and subsequently developed pneumonia and died.
DK/98 56 YO male on 2,400mg/day at death. The narrative states that he was hospitalized for status epilepticus and developed a brain stem thrombosis. It is not clear if the patient was started on OXC prior to or after this event. The patient died 4 days after starting OXC.
DK/124 55 YO female with multiple sclerosis on 1,500mg/day at death. The sponsor states that she died of pneumonia.
CDN/04 This 84 YO male was treated with oxcarbazepine 2,400mg/day for trigeminal neuralgia. The patient developed acute pulmonary edema and died. He had received oxcarbazepine for 6 years prior to death.
07/22 Protocol 9089/NP This 42 YO male was on 1,500mg/day at death. The sponsor stated that the patient died of severe coronary artery disease 54 months after the start of therapy. Autopsy demonstrated rupture of a sclerotic plaque in the LAD coronary artery.
CDN/03 This 72 YO male with a history of occulo-pharyngeal muscular dystrophy was treated with oxcarbazepine 1,500mg/day, for trigeminal neuralgia. He died after choking on food and had been treated for almost 8 years prior to death.
CH/2501 This 68 YO female treated with oxcarbazepine 300mg/day was found dead and no details about the terminal event were provided.
GB/1 A narrative was not provided for this patient and the information comes from the listing in Appendix VI.1 of the Safety Update. This 39 YO female had been receiving 1,800mg/day of oxcarbazepine and the duration of exposure was 5 years. Death was attributed to bronchopneumonia.

4.6.3.4 Clinical Description of Post-Marketing Deaths

The sponsor identified 9 deaths from post marketing reports. I reviewed the narratives for these deaths to identify any unusual causes of death or patterns of deaths. Those cases are summarized below. In general the narratives contained little information about the terminal event.

96NL-10009 This 29 YO female had been treated with oxcarbazepine for partial epilepsy but the drug was gradually discontinued for psychosis (valproate started). Three days after her last dose of oxcarbazepine, she was found dead and death was attributed to status epilepticus.
S9010651 This male (age unknown) was treated with an unknown dose of oxcarbazepine for unknown duration. He died of non-Hodgkin's lymphoma.
S9202991 This 21 YO female described as "oligophrenic" died 2.5 months after starting oxcarbazepine (on 2,100mg/day at death) from idiopathic brain edema.
S9308951 This 63 YO female treated with oxcarbazepine 900mg/day, isosobide dinitrate, furosemide, albylenterosolubile developed hepatic dysfunction (attributed to oxcarbazepine) and died. No other details were available in the spontaneous report. A fifteen-day report provided some additional information. Two months after being switched from carbamazepine to oxcarbazepine she had the following test results: ALP 461, AST 254, LDH 903 (no units). Oxcarbazepine was stopped and 4 days later she had the following results: ALP 358, AST 2,995, and LDH 4,125. A laparotomy the next day (indication not mentioned) revealed hepatomegally and ascites. She subsequently developed wound rupture, sepsis and died.
96DK-10004 This 36 year old treated with oxcarbazepine unknown dose/duration, was diagnosed with aortic stenosis and subsequently died suddenly.
97SF-10014 This 82 YO female was on citalopram, furosemide isosorbide dinitrate, clonazepam and oxcarbazepine 600mg/day. Three months after starting oxcarbazepine she developed complete heart block with a rate of 33 beats per minute. Initially she responded to atropine but was found dead in bed later that night.
S9219511 This 34 YO female on oxcarbazepine 600mg/day and zopiclone prn died during her sleep 210 days after starting oxcarbazepine.
S95390871 This 26 YO male on oxcarbazepine 2,400mg/day, vigabatrin, and phenytoin 300mg died suddenly.
98D10272 The sponsor provided information about this death in a listing in the Safety Update. This female, age unknown, died 3 days after starting oxcarbazepine, 2,700mg/day and death was attributed to seizure.

4.7 Serious Adverse Events

The sponsor's discussion of Serious Adverse Events (SAEs) begins on p.139 of the ISS. The sponsor defined an SAE as *an untoward event that was fatal or life-threatening, required prolonged hospitalization, was significantly or permanently disabling or incapacitating, constituted a congenital anomaly or a birth defect, cancer, an event resulting from overdose with trial drug, and other significant medical events*. The sponsor did not define life threatening or disabling events in the ISS. The sponsor defined other significant medical events as *untoward events that might jeopardize the subject and might require medical intervention to prevent one of the outcomes listed previously* (ISS p. 139). The sponsor included information on SAEs from all safety data sources through 3/31/98 in the Safety Update. They used their Serious Adverse Event Reporting System (SAERS) database, rather than the clinical database to construct their listings and tables for SAEs (ISS p. 140). The sponsor reconciled differences between the two databases in the Safety Update (Safety Update p.72).

4.7.1 SAEs Primary database

The sponsor provided a table of the types of SAEs in oxcarbazepine treated subjects (Exhibit 6.3.2.-1 p.73 of the Safety Update). They report that 295 oxcarbazepine exposed individuals with epilepsy (13.3%, 295/2,224) developed SAEs. The greatest number of reports was for the Central and Peripheral Nervous System (149 reports for 129 subjects) and within this group, there were 92 subjects with 1 or more SAEs for "Convulsive disorders". No other serious event was reported by more than 20 individuals. For serious events of potential concern, there were 7 rashes, 1

dermatitis, 1 allergic skin reaction, 2 anaphylactoid reactions and 2 other allergic reactions in oxcarbazepine exposed subjects. There were 14 subjects with serious hyponatremia events. The sponsor reported that 2 subjects had serious hepatitis events and 1 subject had a serious liver function disorder (elevated LFTs). There were two patients with serious events described as White Blood Cells Decreased and 1 subject with pancytopenia. A listing of all serious adverse events occurring in oxcarbazepine exposed epilepsy subjects is included as an appendix to this review.

The sponsor's comparative analyses for serious event risks are based on grouping controlled trial data as previously described into monotherapy initiation trials and adjunctive and monotherapy substitution trials.

4.7.1.1 SAEs Controlled Trials, Primary Database

SAEs from the Adjunctive and Monotherapy Substitution Trials

One hundred eight of the 1,272 (8.5%) oxcarbazepine exposed patients had serious adverse events. The sponsor reported that 18 of the 353 (5.1%) placebo treated, 16 of the 134 (11.9%) carbamazepine treated, and 0 of the 52 phenobarbital treated subjects from these studies experienced one or more SAEs. In addition, the sponsor calculated rates of SAEs for the treatment groups. The SAE rate for the oxcarbazepine group was 19.7/100PY (108/548PY) compared to 15.6/100PY (18/116PY) for placebo, 16.5/100PY (16/99PY) for carbamazepine and 0 for phenobarbital (Safety Update p.77). The following table presents the SAE risk by dividing the number of subjects with an event by the number exposed to the treatment. I have omitted events occurring only in the comparator groups.

Serious Adverse Event Risk for the adjunctive and monotherapy substitution trials by treatment

Drug Safety Organ Class	Oxcarbazepine (n=1,272)	Placebo (n=353)	Carbamazepine (n=134)
Skin and Appendages	**0.2% (3)**	**0**	**0.7% (1)**
Rashes	0.2% (2)	0	0
Teeth/mucosal disorder	<0.1% (1)	0	0
Musculoskeletal	**0.2% (2)**	**0**	**0**
Joint Disorder	0.2% (2)	0	0
Central/Peripheral NS	**4.3% (55)**	**2.3% (8)**	**3.7% (5)**
Convulsive disorders	2.8% (36)	2.3% (8)	2.2% (3)
Balance/gait disorders	1.1% (14)	0	0.7% (1)
Consciousness/mentation	0.2% (2)	0	0
Intracranial/spinal cord	0.2% (2)	0	0
Headache	<0.1% (1)	0	0.7% (1)
Movement disorder	<0.1% (1)	0	0
Psychiatric Disorders	**0.9% (11)**	**0.6% (2)**	**0.7% (1)**
Delirium/Psychosis	0.4% (5)	0	0
Excitation	0.2% (3)	0	0
Affect disorders	<0.1% (1)	0.3% (1)	0
Personality disorder	<0.1% (1)	0.3% (1)	0.7% (1)
Sedation	<0.1% (1)	0	0
Gastrointestinal	**0.5% (6)**	**0.3% (1)**	**2.2% (3)**
Others	0.3% (4)	0.3% (1)	2.2% (3)
Gastric ulcer	<0.1% (1)	0	0
Lower intestinal tract	<0.1% (1)	0	0
Liver/Biliary	**0.2% (2)**	**0**	**0.7% (1)**
Hepatitis	<0.1% (1)	0	0
Liver function disorder	0	0	0.7% (1)
Others	<0.1% (1)	0	0
Metabolic/Nutritional	**0.6% (7)**	**0.3% (1)**	**0**
Electrolyte disturbance	0.6% (7)	0	0
Cardiovascular	**0.3% (4)**	**0**	**0.7% (1)**
Blood pressure	0.3% (4)	0	0.7% (1)
Myo,endo,pericardial	**<0.1% (1)**	**0.3% (1)**	**0**
Myocardial ischemia	<0.1% (1)	0	0
Vascular disorders	**0.2% (2)**	**0**	**0**
Peripheral vascular	0.1% (1)	0	0
Thrombosis/embolism	<0.1% (1)	0	0
White cell disorders	**<0.1% (1)**	**0.3% (1)**	**0**
Leucopenia	<0.1% (1)	0.3% (1)	0
Urinary System	**<0.1% (1)**	**0**	**0**
Female reproductive	**<0.1%(1)**	**0**	**0**
Neoplasm	**0.2% (2)**	**0**	**0**
Body as a whole	**1.0% (13)**	**1.1% (4)**	**2.2% (3)**
Non specific	0.2% (2)	0.3% (1)	0.7% (1)
Temperature	<0.1% (1)	0	0
Infection or sepsis	0.3% (4)	0.3% (1)	0.7% (1)
Sudden death	<0.1% (1)	0	0
Resistance Mechanism	**0.2% (3)**	**0**	**0.7% (1)**
Anaphylactoid	0.2% (2)	0	0
Allergic reaction unsp	0	0	0.7% (1)
Others	<0.1% (1)	0	0

SAEs from the Initiation of Monotherapy Trials

Thirty-one of the 440 (7%) oxcarbazepine exposed subjects in these trials had one or more serious adverse events. As above, the sponsor presented the risk information for each of the comparator agents used in these trials. Five of the 66 (7.6%) placebo exposed, 14 of the 240 (5.8%) phenytoin exposed, and 12 of the 121 (9.9%) valproic acid exposed subjects experienced SAEs. The rates for SAEs in these trials were 9/100PY (31/343PY) for oxcarbazepine, 29/100PY (5/17.4PY) for placebo, 6.5/100PY (13/201PY) for phenytoin and 9/100PY (10/111PY) for

valproic acid (Safety Update p.82). The following table presents the SAE risk by dividing the number of subjects with an event by the number exposed to the treatment.

Serious Adverse Event Risk for the monotherapy initiation trials by treatment

Drug Safety Organ Class	Oxcarbazepine (n=440)	Phenytoin (n=240)	Valproic acid (n=121)	Placebo (n=66)
Skin and Appendages	**0.7% (3)**	**2.1% (5)**	**0**	**0**
Rashes	0.5% (2)	0.8% (2)	0	0
Allergic skin reaction	0.2% (1)	0	0	0
Central/Peripheral NS	**2.5% (11)**	**1.3% (3)**	**2.5% (3)**	**4.5% (3)**
Convulsive disorder	1.1% (5)	0.4% (1)	2.5% (3)	4.5% (3)
Consciousness/mentation	0.7% (3)	0	0	0
Intracranial/spinal cord	0.5% (2)	0	0	0
Balance/gait disorders	0.2% (1)	0.8% (2)	0	0
Peripheral/CN disorder	0.2% (1)	0	0	0
Psychiatric Disorders	**0.9% (4)**	**0**	**0**	**0**
Personality disorder	0.5% (2)	0	0	0
Affect disorders	0.5% (2)	0	0.8% (1)	0
Gastrointestinal	**0.2% (1)**	**0.4% (1)**	**0.8% (1)**	**1.5% (1)**
Others	0.2% (1)	0.4% (1)	0.8% (1)	0
Metabolic/Nutritional	**0.5% (2)**	**0**	**0**	**0**
Electrolyte disturbance	0.5% (2)	0	0	0
Myo,endo,pericardial	**0.2% (1)**	**0**	**0**	**0**
Myocardial ischemia	0.2% (1)	0	0	0
Heart rate/rhythm	**0.2% (1)**	**0**	**0**	**0**
Respiratory disorders	**0.2% (1)**	**0**	**0.8% (1)**	**0**
Bronchi/lower airway	0.2% (1)	0	0	0
Hemic/Lymphatic/RES	**0.2% (1)**	**0**	**0**	**0**
Pancytopenia	0.2% (1)	0	0	0
Reproductive d/o, male	**0.2% (1)**	**0**	**0**	**0**
Sexual function disorder	0.2% (1)	0	0	0
Body as a whole	**1.6% (7)**	**0.4% (1)**	**0.8% (1)**	**0**
Non specific	0.2% (1)	0	0	0
Infection or sepsis	0.2% (1)	0	0	0
Lack of efficacy	0.2% (1)	0	0.8% (1)	0
Deterioration underlying illness	0.7% (3)	0	0	0
Resistance Mechanism	**0.2% (1)**	**0.4% (1)**	**0**	**0**
Others	0.2% (1)	0	0	0

Ongoing trials

In the Safety Update, the sponsor reports 22 new SAEs in 20 patients in ongoing, open label, long-term trials from the Safety Update cutoff, 3/31/98, through 8/31/98. Seven subjects had seizures that met the serious criteria. There were 2 subjects with gastritis, an event not previously appearing in the SAE listings, and 2 additional reports of hyponatremia (1 of these patients previously had an SAE report for hyponatremia).

4.7.1.2 SAEs from the Mania Trial

There were no new SAEs reported for this trial in the Safety Update (Safety Update, p.84) In the ISS, the sponsor reported that 2 of the 26 subjects enrolled in the mania trial experienced a SAE. Those cases are summarized below.

Subject USA/M7413T/11(506) a 42 YO male reported lethargy 3 days after his first dose and the dose was lowered Two days later, two hours after his last dose, while eating, he had trouble speaking and experienced weakness and tremors in his arms, along with diplopia. These symptoms resolved by the following day and the patient dropped out of the trial.

Subject **USA/M7416I/2(502)**, a 42 YO male experienced a drop in sodium from 138 mEq/L at baseline to 127 mEq/L, four days after his first dose. The next day he experienced one episode of nausea and vomiting

and two days later experienced nausea and withdrew from the study. Ten days after termination, his serum sodium was 141mEq/L.

4.7.1.3 Secondary database/Postmarketing SAEs

In the 62 pre-GCP trials the sponsor identified a total of 1 SAE (pneumonia with pancytopenia) through the Safety Update cutoff. In the Named Patient program, the sponsor identified 59 patients (2%, 59/2950) who experienced SAEs. In the post-marketing database, the sponsor identified 100 reports classified as serious.

4.7.2 Clinical descriptions of serious adverse events from the Primary Database

I reviewed narrative summaries, case report forms, and line listings to identify those patients with specific serious adverse events from the primary database.

4.7.2.1 Skin Related SAEs

From Listing 6.3.1-1: Serious or potentially serious adverse experiences by Drug Safety Organ Class for all oxcarbazepine-treated subjects with epilepsy in the Safety Update, I identified 13 subjects with serious skin reactions (7 rashes, 1 dermatitis, 1 allergic skin reaction nos, 2 anaphylactoid reactions without shock and 2 other allergic reactions). I reviewed the narrative summaries and case report forms for these patients to summarize these events. In many of these cases the sponsor did not provide extensive details of the events of interest.

Subject ***OT/FO1 GB/2 215*** was a 41 YO female who was taking oxcarbazepine 900mg/day and, developed a maculopapular rash with fever, hematuria, malaise and nausea that began on the day that treatment was initiated. Trial treatment continued for 12 days. The rash was described as involving most of her body. There was no mention of mucosal involvement. Oxcarbazepine was discontinued and the subject was treated with chlorpheniramine. The investigator reported that there was persistent disability, which was not described.

Subject ***OT/F02 MEX/1 26*** was a 27 YO female who had been exposed to oxcarbazepine 900mg/day and within days developed a maculopapular rash over arms, A&P thorax, and less intense over the abdomen and crural extremities. Exam also revealed puntiform petichial lesions on the soft palate and redness of the anterior pillars of the pharynx. Oxcarbazepine was stopped and the subject was treated with oral steroids, and antihistamines with complete resolution of the rash.

Subject ***OT/FO1D/3 31***, a 28 YO female with a history of psoriasis was taking oxcarbazepine 900mg/day and within 11 days of initiation of treatment, developed erythema and pruritis without mucosal involvement. Study drug was discontinued and she was treated with an antihistamine. The rash completely resolved within 1 week.

Subject ***26 USA/M0206C 114*** a 44YO female developed a fever and was prescribed an antibiotic (not identified) and subsequently developed a generalized body rash. The narrative did not provide the outcome for this event or mention any treatment.

Subject***OT/FO1E D/2 17*** developed a generalized rash almost 1 year into treatment that appeared to resolve with discontinuation of oxcarbazepine but later recurred on phenytoin.

Subject ***FTRI02 F/9 925*** had a worsening of underlying eczema.

Subject ***OT/PE1 RA 21 461*** had a rash that was attributed to an ant bite and was treated with dexamethasone (patient continued in the trial).

Subject ***OT/F10 I/305/162***, a 28 YO female taking oxcarbazepine 1,200mg/day developed a hypersensitivity reaction approximately 2 months after initiation of therapy. Symptoms included an extensive maculopapular rash and edema of the lips. Oxcarbazepine was discontinued and the rash resolved and there was no mention of other treatments.

Subject ***OT/E25 F/38 149***, a 59 YO male, with a 30 year history of angioedema developed angioedema within the first 2 weeks of exposure to oxcarbazepine. He was hospitalized, treated with antihistamines and continued in the study.

Subject ***OT/PE1 CDN/3 263*** was a 24 YO male with a history of rash and jaundice following exposure to carbamazepine. Four hours after the first dose of oxcarbazepine, he developed a pruritic total body erythematous rash with myalgias, arthralgias, headache and throat tightness. Oxcarbazepine was

discontinued, he was hospitalized and treated with an antihistamine and acetaminophen. The symptoms began to resolve with treatment and he was discharged the next day. The symptoms were completely resolved 4 days later.
Subject ***OT/FO1 D/3 39***, a 29 YO female developed a rash, pruritis, lymphadenopathy, and conjunctivitis approximately 10 days after randomization. She was treated in an emergency room with an antihistamine and oxcarbazepine was discontinued. Her symptoms completely resolved within a few days.
Subject ***04E/M8464U/511***, a 34 YO male who had been receiving oxcarbazepine 3,000mg/day for 2 years, developed a generalized macular rash and a dermatology consultant ruled out a drug reaction. The rash resolved within 4 days with topical triamcinolone and temporary discontinuation of drug.
Subject ***USA/M0206C/124***, a 36 YO female receiving oxcarbazepine 2,100mg/day for 6 months developed fever, diffuse rash, and dry cough. She was also noted to have leukopenia and SIADH. Her lamictal and oxcarbazepine were stopped and her condition was reported as improving.

4.7.2.2 Liver related SAEs

The sponsor listed 5 serious liver related adverse events in the epilepsy trials (2-hepatitis, 1-liver function disorder, 2-cholelithiasis). I reviewed the narrative summaries and case report forms and summarized the events other than cholelithiasis in the following paragraphs.

Subject ***FTRI02 F/13 1303*** was a 4 YO male with a history of cerebral anoxia at birth and diabetes mellitus. Approximately 545 days after starting trial medication, while taking oxcarbazepine 750mg/day, insulin, phenytoin, and baclofen, his LFTs were noted to be elevated (SGOT 67, SGPT 71, bilirubin not tested). Five months later, LFTs remained elevated (SGOT 62, SGPT 73 ALP 307, GGT 292). Two months later, LFTs continued to be abnormally high (SGOT 97, SGPT 172, GGT 281) and the investigator discontinued oxcarbazepine at that time. One month after stopping, the LFTs were still elevated (SGOT 116, SGPT 233) but the sponsor reported that they gradually returned to normal over the next 2 months.
Subject ***OT/PE1 I/6 686*** was a 49 YO male with no significant past medical history taking oxcarbazepine 2,400mg/day in addition to phenobarbital, carbamazepine and lamotrigine. Approximately 32 days after the initiation of study treatment he had a serious adverse event diagnosed as toxic hepatitis. When hospitalized for several tonic clonic seizures, blood chemistry results revealed total bilirubin of 3.3 mg/dl, SGOT of 1,186IU/L and SGPT of 1,623 IU/L. The patient had normal LFTs approximately 1 month prior to this event. The sponsor reported that tests for viral hepatitis A, B, and C were negative and that trauma, food toxicity and chemical exposure were excluded as possible causes. Oxcarbazepine was discontinued. The patient was treated with glutathione. The sponsor reported that the patient was discharged within a month with liver test result values in the normal range.
Subject ***4 USA/M8464U 508*** was a 33 YO female taking oxcarbazepine 1,200mg/day and lorazepam who apparently developed elevated liver enzymes which resolved. There were no abnormal LFTs among the patient's lab data listings and apparently the event did not lead to premature discontinuation. *Brief narrative.

4.7.2.3 Hematological SAEs

There were 2 cases of granulocytopenia (OT/PE1 CDN/1 256, 026E/USA/M8712Z 118/600) and one case of pancytopenia (OT/F01 D/3) among the serious hematological adverse events. The narrative summaries and case report forms for these patients were reviewed and the cases summarized below.

Subject ***OT/F01 D/3/98*** was a 26 YO female with a history of chronic juvenile polyarthritis, ankylosing spondylitis on sulfasalazine, voltaren and methotrexate who developed toxic megacolon and a mild anemia and leucopenia and underwent a bone marrow examination which revealed depression of hematopoesis. The investigator felt that the hematological findings were related to the patient's underlying rheumatological disease. The prescreening hemoglobin was 9.6g/dl, the lowest value recorded in the CRF (the rest were above 10 g/dl). The CRF for this subject did not include a WBC count $<7.0 \times 10^9$/L.
Subject ***026E/USA/M8712Z 118/600*** was a 49 YO male who had been receiving oxcarbazepine 3,000mg/day for 6 months and depakote for approximately 1½ months developed a sore throat and fever. His WBC count was checked and was 1,800. Depakote was discontinued and phenytoin started. The sponsor reported that the patient completely recovered and that oxcarbazepine was maintained unchanged.

Subject *OT/PE1 CDN/1 256* was a 35 YO female treated with oxcarbazepine 1,200mg/day which was added to a regimen of phenytoin and carbamazepine. Twenty days after the addition of oxcarbazepine, her WBC count was $1.4x10^9$/L (from $4.3x10^9$/L). In addition, the subject admitted to taking Keflex 250mg qid just prior to when the low WBC count was detected. She weaned herself off oxcarbazepine. Approximately one week later, her WBC was $1.7x10^9$/L. Labs from the CRF included: Baseline WBC $4.2x10^9$/L 72% neutrophils Hgb 14.4g/dl; WBC $4.3x10^9$/L 75% neutrophils Hgb 13.8g/dl; WBC $1.4x10^9$/L 41% neutrophils (ANC 574) Hgb 13.4g/dl. The sponsor reported that subsequently, off oxcarbazepine, she had a normal bone marrow biopsy and WBC counts in the 4.0-4.7 range.

4.7.2.4 Hyponatremia SAEs

I have summarized the clinical events for the 14 patients with serious hyponatremia reported by the sponsor.

Subject *04E/USA/M8454Q 505* was a 44 YO female receiving oxcarbazepine 1,800mg/day. Seventeen days after initiation of therapy her serum sodium was 126mEq/L and she was hospitalized. Hospital course was complicated by increased seizure activity (complex partial seizure every hour x 10) and she experienced lethargy and mild headache. She was discontinued from the trial and her serum sodium increased to 140mEq/L.

Subject *04E/USA/M8462K 502* was a 30 YO female receiving oxcarbazepine 2,400mg/day. Five days after entering the open label extension her serum sodium was 126mEq/L, which was not treated and apparently was not associated with symptoms. Five days later she was discontinued from the trial and serum sodium was 137mEq/L at that time.

Subject *011 RA/M0657D 1080* was a 17YO female enrolled in an oxcarbazepine trial. Seventy-two days after randomization she attempted suicide by ingesting approximately 9,300mg of oxcarbazepine and 5,400mg of carbamazepine. Signs and symptoms related to this event included lethargy, hyperkinesia, hyponatremia (not quantified). She was treated with 20% NaCl and forced diuresis and reportedly recovered.

Subject *026 USA/M8712Z 108* was a 47YO female receiving oxcarbazepine 2,100mg/day. Fifty-nine days after initiation of therapy her serum sodium was 125mEq/L and she apparently had an increase in seizure frequency. She was hospitalized, was discontinued from the trial, and reportedly recovered.

Subject *026 USA/M8707 101* was a 22YO female receiving oxcarbazepine 2,400mg/day. Seventy-one days after initiation of therapy She experienced a prolonged seizure, and then a second seizure and was hospitalized. She was noted to be lethargic and her serum sodium was 115mEq/L. Oxcarbazepine was tapered and she was treated with normal saline. She reportedly recovered.

Subject *OT/E25 F/13/1435/464* was a 52YO female. Five days after initiation of therapy (900mg/day), her serum sodium was 128 mEq/L and this was reported as an adverse event. Nine months later she experienced parasthesias of her hands, muscle cramps and her serum sodium was 126mEq/L at that time. She discontinued from the trial.

Subject *OT/E25 F/66/1334/330* was a 69YO male receiving oxcarbazepine 900mg/day. Three hundred and thirty four days after randomization he was hospitalized for malaise and his serum sodium was 130mEq/L. This finding was attributed to concomitant diuretic therapy. He continued in the trial with no additional therapy or dose alterations.

Subject *OT/FO1E D/1 Z* was a 26YO female receiving oxcarbazepine 900mg/day. Twenty-six months after randomization her serum sodium was 129mEq/L and was reportedly asymptomatic. She was treated with oral NaCl and continued to have a low serum sodium (133mEq/L).

Subject *OT/FO1E D/1 8* was a 53YO female receiving oxcarbazepine 1,800mg/day. Despite a history of hyponatremia, her baseline serum sodium was 144mEq/L. During the double blind phases, she had serum sodium levels of 132mEq/L and 129mEq/L. During the open label phase, 14 months after randomization, her serum sodium was 123mEq/L and she reported feeling depressed and having concentration problems. She was hospitalized, oxcarbazepine dose was reduced to 1,500mg/day and her serum sodium increased to 131mEq/L. She continued in the trial. *This subject was also taking HCTZ.

Subject *OT/PE1 CDN/5 247* was a 39YO female receiving oxcarbazepine 2,400mg/day. Twenty-one days after randomization, her serum sodium was 121mEq/L. This was re-checked 4 days later and was 124mEq/L. The investigator discontinued oxcarbazepine and the hyponatremia resolved.

Subject *OT/TE1 GB/14 85* was a 69YO male receiving oxcarbazepine 600mg/day. Twenty-two days after randomization and 7 days after entering the maintenance phase his serum sodium was 124mEq/L. A repeat