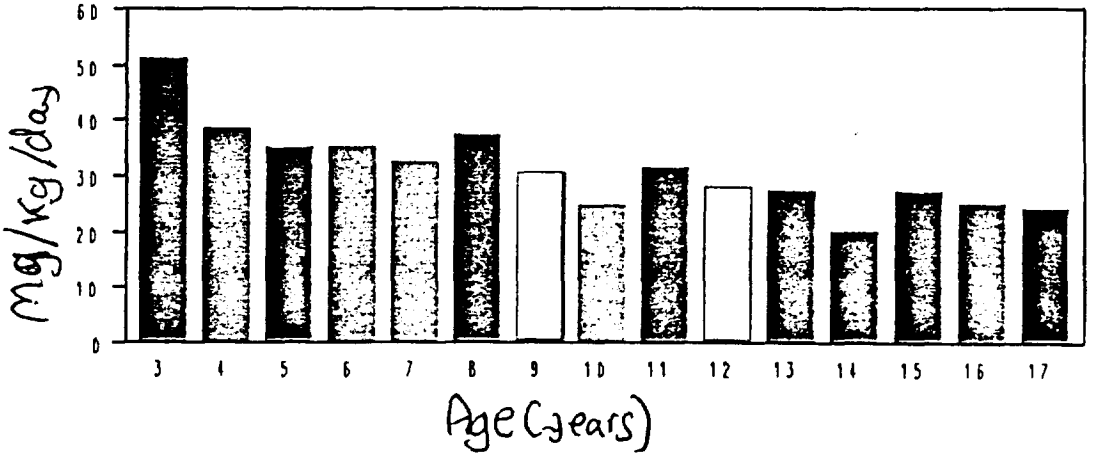
of the fact that younger children exhibit a 50% greater clearance. Nonetheless this agent was approved for use in pediatrics for the inclusive age range studied.

2.1.5 Conclusions regarding adjunctive age range

This reviewer agrees that although statistical significance can not be proven for a younger age subset there does not appear to be a trend that would indicate less efficacy. This reviewer feels that an argument can be made that justifies dosing down to age 4 (age 3 included only a single drug exposure). Nonetheless, there appear to be age dependent pharmacokinetic differences that need to be addressed in the labeling. Although protocol 011 utilized a target dose with a mg/kg range that straddled the highest adult therapeutic, actual experimental design was sufficiently flexible to allow a very wide range of dosing. The design essentially allowed the investigator to adjust dosage to that which he/she felt gave optimal therapeutic effect with minimal toxicity. This is very much like the way these drugs are used in the clinic. Thus, whereas recommended target dose was 30 to 46 mg/kg the, actual maintenance dosage ranged from 6.4 to 51.4 mg/kg. This meant that different age groups might have received very differing mg/kg dosages. I have plotted the mean mg/kg/day dose Vs age in the histogram presented below. It is apparent from this figure that mean dosage tended to increase with decreasing ages. When mean mg/kg/day dose is broken into two groups age group a statistically significant greater dose (Student's t test; p=0.0001) is noted to have been used in the younger age group (see table immediately below histogram). These data probably resulted from the aforementioned age-dependent pharmacokinetic differences. These data may be useful in dosing recommendations in the labeling.



	<12 years old	≥ 12 years old
mg/kg dose (±S.E.)	33.7 ± 12	26.7 ± 1.2
n	66	70

A principal issue that concerned this division in our initial evaluation of this problem was that while there may be no reason to theoretically believe that OXC would lack a therapeutic effect in a younger age group there was question as to what the labeled dose should be. With the demonstration of the lack of age dependent trend in therapeutic effect and the demonstration that an increased mean dose was required for this effect I feel that it is safe to recommend dosing in the lower age range. Age 3, however should be excluded, as there was only one patient of this age who received drug. I would recommend adjunctive pediatric labeling in a pediatric population of ages 4 to 17. Including these lower ages however would require an appropriate change in dosing recommendation (see next section).

2.2 Dose recommendations for OXC adjunctive therapy in children (Item b on page 6)

The Sponsor concludes that their adjunctive dosing recommendations in pediatric labeling are adequate and consistent with other labels. This labeling is based upon mg/kg dosing used in the 011 protocol and like this protocol allows for a very wide range of dosing. These recommendations, however, do not differentiate old and young pediatric groups. As we are including labeling in a younger group this reviewer would recommend a revision in the labeling.

This reviewer would argue that while the recommended starting and target doses are adequate more information regarding expected means and dosing ranges observed for different age groups in clinical trials should be added to the labeling. Dosing populations should be appropriately grouped (e.g. $\leq$ 8 and 9$\geq$). This reviewer sees two potential ways to handle this issue. The first is to simply note mean concentrations (and ranges) derived from study 011 that were thought to be efficacious[4]. The second is to recommend dosing based upon pharmacokinetic modeling[5].

2.3 Monotherapeutic Efficacy in Pediatric age groups (8-17) (item "c" page 6)

Our division noted that "while the agent is likely to be effective in pediatric patients as monotherapy" insufficient data was submitted to support a dose range that might be considered effective and safe. The following table (from my original review) summarizes numbers of pediatric patients who participated in predominately adult monotherapy clinical trials.

[4] This recommendation is base upon proof of principal; i.e. it was the dose used in the study.
[5] Dr. Tammara (Biological Pharmacology) is presently examining this issue.

Table 1 Pediatric Age Distribution in Pivitol Monotherapy Trials

		Study 04	Study 25	Study 026*	Study 028*	Total
6 -11 years	OXC	1	2	0	0	3
	Control	0	1	0	2	3
12 - 17 years	OXC	3	6	2	4	15
	Control	4	3	0	3	10

* Control in these cases constitutes of low dose (300 mg/day) monotherapy treatment. All other cases patients in control group receives placebo.

The Sponsor notes that under the final rule that the FDA provides for extrapolation from adequate studies. Usually this extrapolation requires some certainty that the disease process is similar in children and adults and that the beneficial and adverse effects also are similar in both populations. The sponsor supports this contention by noting that the ILAE has acknowledged the similarity between adult and childhood epilepsy. This reviewer feels that this is not an unreasonable assumption. To support this extrapolation the Sponsor provides the following information:

1. The meta-analysis of the 29 pediatric patients (ages 8-17) that were included in pivotal monotherapy trials.
2. Pharmacokinetic data on the equivalence clearance between pediatric and adult populations in a monotherapy setting.
3. Safety data supplied on 1070 children including 185 patients on monotherapy.
4. ILAE statement.

They also argue that acceptance of these data as sufficient are consistent with the guidelines the FDA has used for the approval of other anticonvulsant agents.

All these issues will be discussed in more depth in the following sections:

2.3.1 Meta-analysis

The Sponsor has submitted a meta-analysis of the primary endpoint (time to exit) for all pediatric patients included in the pivotal monotherapy trials. These data are presented in the table below and demonstrate rather dramatic differences between control and experimental groups and were found to be statistically significant.

Exhibit L1-3. Meta-analysis of time to meeting the efficacy endpoint for children (8-17 years of age) in monotherapy trials 004, 025, 026, and 028 (intent-to-treat patients)

Treatment Group	N	Median (days)	IQ Range[3]	P-value
OXC (2400, 1200 mg/day)[1]	17	60.0	(32.0, NA)	0.0172*
Placebo/low-dose control[2]	12	12.0	(1.0, 43.0)	

[1] This treatment group includes 9 children who received 2400 mg/day and 8 children who received 1200 mg/day.
[2] This control group includes 5 children who received 300 mg/day and 7 children who received placebo.
[3] *The interquartile (IQ) range denotes the interval between the time where 25% of the patients and 75% of the patients have met the protocol-specific efficacy endpoint. Note that NA denotes that these statistics could not be computed because fewer than the 75% of the patients met the efficacy endpoint*
*Denotes significance at 0.05 level based on log-rank test.

While meta-analysis is fraught with pitfalls this particular case of meta-analysis suffers from a specific identifiable problem. It compares patients from very different population with disparate baseline seizure frequencies. This resulted from the different inclusion/exclusion criteria used in each study. This can be appreciated in the figure below that presents the median time to meeting exit criteria of the placebo/low dose control groups during the experimental phase in each pivotal monotherapy protocol. This becomes even more of a problem when it is realized that patients receiving placebo (or low dose) and drug (or high dose) are not evenly distributed across studies (see table).

Protocol Number	Median Exit Time for Placebo Controls (days)	Number of Patients Used for Meta-analysis from Protocol	
		Placebo/low dose Control	Drug
004	1.25	3	4
025	3.2	8	3
026	28	2	0
028	18	4	5

2.3.2 Equivalence of clearance between pediatric and adult populations in a monotherapy setting

The sponsors state that "overall it can be concluded that pharmacokinetics of MHD is similar in *older* children and adults, and the higher apparent clearance in younger children may not require any adjustment in dose." To support this claim the Sponsor presents a table (Exhibit L1-4, see table below) entitled "Comparison of pediatric and adult pharmacokinetics of MHD for monotherapy." The data is not sufficiently broken down by appropriate age groups (see the column under ages). In some cases clearance is included as a range. The meaning of these ranges is rather unclear. Certainly no statistical conclusion can be drawn from this data. If anything, examination of the table

gives the impression that greater clearance is observed in pediatric patients even at ages as old as 15 years. It is noteworthy that the table included data from the large pediatric adjunctive trial (011). While not explained, the Sponsor presumably removed patients whom were receiving drugs known to pharmacokinetically interact with OXC such as Phenobarbital and Carbamazepine. It should be noted that there are some anticonvulsants (i.e. the benzodiazepines) for, which patients were on in study 011, whose PK interaction is unknown. Nonetheless, this table does not substitute for careful pharmacokinetic analysis.

Exhibit L1-4. Comparison of pediatric and adult pharmacokinetics of MHD for monotherapy

Age (yrs)	Weight (kg)	Significant Concomitant AEDs	Average Clearance [Cl/F] (L/hr/kg)	Analysis Method	Reference
3-5 (N=11)	16-26	None	0.068-0.083	Population PK model	Study 011
4-5 (N=4)	15-22	None	0.073	Non-compartmental	Study OT/F11
6-17 (N=96)	26 to 85	None	0.046-0.068	Population PK model	Study 011
9-15 (N=8)	26-74	None	0.061	Non-compartmental	Study OT/F11
8-63 (N=24) Children and Adults	26-103	None	0.043*	Population PK model	Study 025**
12-65 (N=104) Children and Adults	41-152	None	0.041*	Population PK model	Study 026***
Adult		None	0.046*	Population PK model	Study 011
Adults (N=20)		None	0.042*	Non-compartmental	Study 029

*Based on a typical adult weight of 70 kg.
**N=6 for age 8-16 yrs.
***N=7 for age 12-20 yrs.

It should additionally be noted that dosing differences might not only depend upon pharmacokinetic differences in an adjunctive and monotherpeutic setting but pharmacodynamic interactions between different anticonvulsants. Although not carefully studied, many epileptologists[6] feel that there may exist a greater then additive effect between certain anticonvulsants with regard to therapeutic and perhaps toxic effects. This synergistic effect could complicate attempts to generalize optimal dosing in monotherapy when only adjunctive information is available.

[6] SeeLeech JP. CNS Drugs 8: 366-375, 1995, Piasani et. al. Epilpesia 40:1141-1146, 1999.

2.3.3 Safety data supplied on 1070 children including 185 patients on monotherapy

The Sponsor has provided this division with an age/dose breakdown of 185 pediatric patients with monotherapeutic exposures to the drug. Included are those noted in the meta-analysis as well as those who were evaluated in other non-pivotal monotherapy studies (e.g. active control). The following table presents an age and dose breakdown of this safety data.

Exhibit L1-8. Frequency distribution of the maximum dosage per body weight (mg/kg/day) for children in monotherapy trials[1] by age group

OXC	Total (≤17 yrs)		<6 yrs	6-11 yrs	12-17 yrs
mg/kg/day	N	%	N	N	N
≤ 20	90	48.7	3	28	59
> 20 – 30	70	37.8	6	33	31
> 30 – 40	14	7.6	1	11	2
> 40 – 50	4	2.2	0	2	2
> 50	7	3.8	1	3	3
Total	185	100.0	11	77	97
Median	20.5				
Range	4.4 – 68.6				

[1]Protocols 004+E, OT/F04+E, 006, OT/F11, OT/F01, OT/F02, OT/F10, 025+E, 026, 028

While this information is important it alone does not address the complete problem. The issue is not of drug toxicity alone but of therapeutic index; i.e. what dose can be recommended in the labeling that will provide a therapeutic effect without significant toxicity.

2.3.4 ILAE statement

As noted above, while this reviewer theoretically agrees with the ILAE statement that "the efficacy of AEDs seems to be the same in childhood," I disagree that clinical trials are unnecessary. Such trials are required because of the existence of pharmacokinetic and pharmacodynamic differences between adults and children. These studies are necessary to identify an optimal dosing window so as to allow labeling recommendations. While such studies were performed for adjunctive therapy none are presented for monotherapy.

2.3.5 Consistency with the Guidelines the FDA has used for approval of other anticonvulsant agents

The Sponsor "requests" adjunctive and monotherapy labeling based in part on consistency with "...recent FDA approval of other antiepileptic drugs...." This division has not recently approved any anticonvulsant drugs with

monotherapy pediatric labeling based upon pediatric adjunctive and adult monotherapeutic/adjunctive controlled clinical trials. Our recommendation to not allow monotherapeutic labeling in the absence of monotherapy placebo or low dose controls is consistent with decisions made in the labeling of recently approved anticonvulsants.

Perhaps the closest analogy to the present situation is that of lamictal. Like Trileptal, Lamictal had positive adequate pediatric and adult adjunctive studies as well as monotherapeutic adult studies. In this case the division permitted adjunctive but not monotherapeutic pediatric labeling. It is noteworthy, that in this case the Sponsor requested only an indication for pediatric adjunctive and not monotherapeutic treatment.

2.3.6 Conclusions regarding monotherapy in the pediatric patient population

This reviewer concludes that the Sponsors do not present sufficient additional information to allow pediatric labeling in a monotherapy setting. The two principal arguments against the Sponsor's justification are the inadequacy of meta-analysis and the lack of sufficient studies that outline probable significant PK differences between age groups in a monotherapeutic setting. This decision is not inconsistent with others made by this division. Indeed this issue has no recent precedent.

Because there is a lack of clearly identified principals of pharmacokinetic and pharmacodynamic anticonvulsant differences in the adult Vs pediatric populations and in adjunctive Vs monotherapeutic settings this reviewer would prefer the performance of an adequately (placebo or low dose) controlled monotherapeutic trial to write labeling. This reviewer is aware that there are ethical reasons that make the performance of such studies difficult. However, this division must be careful not to allow the promulgation of dosing information based upon faulty data that have the potential to harm the public health.

Because of the ethical difficulties in performing adequately controlled pediatric monotherapy studies an argument might be made that extrapolation should be permitted with sufficient supportive data in the absence of adequately controlled trials. In such a case the minimal data that should be required would derived from pharmacokinetic studies that adequately group pediatric populations within well defined age ranges and is that is sufficiently large. The final targeted dose would be one that achieves serum concentrations that have been demonstrated to be efficacious in adult monotherapy trials. Perhaps a further restriction might be placed to confirm the pharmacodynamic equivalency between pediatric and adult populations. In this case the Sponsor might be asked to demonstrate that sufficient therapeutic serum concentration range overlap could be demonstrated between adult and pediatric patients from the adjunctive studies.

This issue is not an easy one to resolve and will likely be raised in the future. Perhaps, at some time, this issue should be presented to the advisory committee.

2.4 Dose recommendations for OXC monotherapy in children (item d)

The sponsors proceed to make recommendations that are based on the limited number of pediatric patients included in the pivotal monotherapy trials and data from a phenytoin active control trial. These data may be considered moot in view of this reviewer's decision to not allow monotherapeutic labeling in this population. Nonetheless it should be noted that the dosing is similar with that recommended in adjunctive labeling.

3. Other Labeling Issues

The reviewer agrees that the starting dose in the FDA revised FDA labeling sections "Conversion to monotherapy" and "Adjunctive Therapy" is incorrect. This was an apparent typographical error. This should read 600 mg/day (given in a BID regimen). Moreover this reviewer agrees with the fact that Trileptal titration ought not to be forced and the word "should" was inappropriate. The Sponsors substation of the word "may" is appropriate.

/S/

N. Hershkowitz MD,PhD
Medical Reviewer
R. Katz, M.D. _____

APPEARS THIS WAY
ON ORIGINAL

Review of Clinical Data

Safety Team Leader Review of NDA

NDA:	**21-014**
Sponsor:	**Novartis**
Drug:	**Oxcarbazepine**
Route of Administration:	**PO**
Reviewer:	**Greg Burkhart, M.D., M.S.**
Review Completion Date:	**August 25, 1999**

/S/ 8-25-99

Development of oxcarbazepine as a treatment for partial epilepsy began in the 1970's. It was first marketed in Denmark in 1990 and is now marketed in about 50 countries. Several countries including Australia and Sweden did not approve the initial application purportedly because of the small size of the safety database and an uncertain clinical significance of hyponatremia. Hyponatremia was recognized early in oxcarbazepine's development as a risk associated with its use.

Novartis began a new development program in 1991 designed to expand the size of the database as well as study the occurrence of hyponatremia. The NDA was submitted to the FDA on September 25, 1998. Dr. Boehm completed the primary safety review on July 23, 1999 finding the safety experience described in the NDA to be valid and sufficient in scope to support approval.

Extent of Exposure

The NDA contains experience from 2390 patients who had about 2581 person-years of exposure to oxcarbazepine. This experience includes that from 2224 epilepsy patients enrolled in trials for adjunctive therapy, monotherapy substitution, and monotherapy initiation. Of these 2224 patients, more than 1000 were exposed for longer than 1 year. There also appears to be significant experience at doses up to 1800 mg per day but it is unclear how much experience exists at 2400 mg per day, the maximum dose proposed by the sponsor.

The NDA also includes the experience from a secondary database consisting of older clinical trials that enrolled about 1500 epilepsy patients and that from compassionate-use programs that enrolled about 3000 patients. Both of these sources of data had low standards for data collection precluding their use as valid denominator-based experience. The collective experience from the secondary database is analogous in value to that from

the estimated 150,000 person-years of post-marketing use, which was also summarized in the NDA.

Significant Safety Findings

Hyponatremia

In the RCTs, about 3% of patients assigned oxcarbazepine had sodium levels less than 125 compared to none with placebo or active comparators which included carbamazepine.[1] The rates of discontinuation and serious event occurrence each attributable to hyponatremia were also greater on oxcarbazepine. In the NDA database, 3 patients had sodium less than 115 with 1 reportedly asymptomatic. The other two patients were hospitalized at the time the hyponatremia was detected and it is unclear whether they were symptomatic from the hyponatremia.[2] In the post-marketing experience, there were reports of patients having clinically significant hyponatremia and two deaths where cerebral edema was identified at autopsy.

There are several points of disagreement between Novartis and the safety team (Dr.Boehm and myself) regarding several aspects of the risk for hyponatremia. There is no disagreement, however, that oxcarbazepine causes hyponatremia.

First, Novartis believes that the risk is only present shortly after initiation of drug, an important issue since a risk that was only present early after initiation of the drug would likely mean that any serum monitoring should only be performed early. I have attached the KM curves showing the risk for hyponatremia over time, first for sodium less than 135 and then for sodium less 125. On page 3 of Novartis's 7/19/99 submission this statement gives the sponsor's interpretation of these curves - "hyponatremia occurs early (within 1 month) during oxcarbazepine therapy and thereafter poses no risk". I see no basis for such a conclusion. In fact, there is not even a suggestion of an early hazard when focusing on sodium less than 125 and while the risk is somewhat greater in the first month for having a sodium less than 135, the risk clearly persists in time. We also determined that a significant number of discontinuations and serious hyponatremia events also occurred after 2 months of use.

Perhaps Novartis' interpretation is influenced by the findings from Dr. Wasserstein's study. Dr. Wasserstein is the sponsor's expert renal consultant who's study showed that the physiologic effect (the initiation of the decline in sodium) begins early – within the first couple weeks of starting the drug. In my view, while an interesting observation, it

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[1] Current carbamazepine labeling mentions clinically significant hyponatremia under the *Adverse Reactions* section.

[2] There are several problems in determining whether hyponatremia is "symptomatic" in this patient population. First, epilepsy patients experience fluctuations in seizure frequency. An increase in seizure frequency could be a symptom of hyponatremia. Likewise, oxcarbazepine and other AEDs are associated with CNS toxicity, the symptoms of which are similar to those from hyponatremia.

should not be confused with the clinical event of interest – clinically significant hyponatremia that can be first detected after long term use.

There is also some disagreement about whether any of the hyponatremia events in the NDA were clinically symptomatic. The sponsor examined this question by comparing the risk for selected AEs by sodium level. Dr. Boehm shows some of these findings on page 54 of his review. Unfortunately, this analysis is flawed. Since patients have been classified by their lowest sodium level (not as time-dependent as it clearly is since sodium changes in time and is not a fixed value) they have confounded the onset of the AE of interest and the time that a patient reached the specified sodium level. AEs that began before reaching a selected sodium level are incorrectly classified as occurring after that sodium level. Even give this problem, the increase in events identified as "convulsion" in patients with sodium < 125 suggests that patients may have been symptomatic. This analysis needs to be repeated since the consultant partially based his opinion about the relevance of hyponatremia on these data

There is disagreement about how to describe the effect in labeling. Novartis mentions hyponatremia only in the laboratory and in the post-marketing sections. Dr. Boehm and I both recommend that the risk be described as a warning since it can be a life-threatening event. A strong argument can be made for making it a boxed warning given the clinical consequences of hyponatremia and the fact that it is preventable by early detection.

I think the warning should specifically recommend that patients undergo periodic monitoring of serum sodium. However, I am uncertain about whether the warning should be explicit about a frequency of monitoring. The controversy that currently surrounds monitoring of liver enzymes seems driven by the rarity of the event of interest (clinically significant hepatic injury including liver failure) and in the lack of evidence that early detection of elevated LFTs prevents clinically significant injury. In this case, the situation is different since we have a relatively common but clinically serious event that seems attributable to a pharmacological action of the drug. Early detection and discontinuation of drug would be expected to prevent more serious consequences and this has generally been the experience in the NDA.

An additional argument for recommending periodic monitoring can be made based upon the fact that the development program effectively monitored all patients for hyponatremia throughout treatment. In effect, oxcarbazepine's use in a setting of no monitoring has not been studied. Even given the monitoring used in the NDA, at least 2 patients had detection of severe hyponatremia at the time of a hospitalization, implying that the monitoring utilized in these patients failed (I don't think we yet know how frequently these patients had been monitored). Although the frequency varied somewhat from trial to trial, patients were monitored about every two weeks in the controlled trials and never more than monthly in open extensions.

Suggested wording for a warning statement:

Hyponatremia: Clinically significant hyponatremia (sodium < 125 mmol/L) can develop during oxcarbazepine use. During the 14 controlled epilepsy studies in the development program, X.X% of patients assigned oxcarbazepine had a sodium less than 125 mmol/L compared to no patients assigned placebo or active control (carbazepine and phenobarbital for adjunctive and monotherapy substitution studies, and phenytoin and valproate for the monotherapy initiation studies). While not all these patients were clinically symptomatic during the episode of hyponatremia, patients with serum sodium less than 125 were more likely to have seizures than patients with normal sodium levels. Cases of symptomatic hyponatremia have also been reported during post-marketing use.

The risk of developing clinically significant hyponatremia (Na less than 125 mmol/L) is present both during early and long-term use. Increasing dose is associated with a greater risk for hyponatremia (This sentence may need to be modified depending on the findings from additional analyzes by the sponsor). Concurrent use of some medications known to be associated with hyponatremia may increase the risk with oxcarbazepine use. These include (provide list).

Monitoring of serum sodium levels is recommended at baseline and periodically thereafter. While it generally true that more frequent monitoring increases the chance of detecting hyponatremia soon after it develops, the precise schedule for monitoring is a matter of clinical judgment. In the clinical trails, patients were monitored as frequently as every 2 weeks. Of the 2224 patients in the development program, 3 developed a serum sodium less than 115 even under monitoring (list the frequency of monitoring in these patients).

Patients who develop signs and symptoms of hyponatremia (eg. List) or have an increase in seizure frequency should have determination of the serum sodium. Patients should ordinarily be discontinued from oxcarbazepine if their serum sodium falls below 125 mmol/L. Patients who have hyponatremia but where the sodium is greater than 125 mmol/L may be at greater risk for subsequent decreases in some situations (provide list). Increasing the monitoring frequency may be prudent in such patients.

CNS Toxicity

As in the NDAs for other recently approved AEDs, there is some suggestion that CNS events were more frequent on oxcarbazepine than placebo. As described by Dr. Boehm, there was a clear excess in ataxia and gait abnormalities, some of which were serious in nature and associated with confusion and nystagmus. There were also increases in confusion without ataxia, events coded as "thinking abnormal", depression and psychosis.

As in the action letters for topiramate and tiagabine, the sponsor needs to examine these events in more detail. A warning may be necessary in labeling. We also need to check the sodium levels in these patients at the time of the event.

Status

The sponsor did not examine the rate of status on drug in the NDA.

Hematological Events

There was 1 case of aplastic anemia in the primary database. In the compassionate use and secondary clinical trial databases there was 1 case each of agranulocytosis and pancytopenia (no bone marrow reported). There were 4 poorly described cases that could have been aplastic anemia reported in the post-marketing experience. While, we need additional information on these cases and a formal risk assessment by the sponsor, there may be a signal for aplastic anemia.

Hepatic Events

In the adjunctive/monotherapy substitution trials, there was an excess of patients having AST > 100 on drug compared to placebo but not for ALT. None of these patients had concurrent elevations in bilirubin.

In the monotherapy initiation trials, there were increased risks of elevated AST and ALT when oxcarbazepine was compare to placebo, but the placebo group was small. None of these patients had concurrent elevations in bilirubin. There were 2 patients who had an elevated bilirubin but did not have concurrent increases in LFTs.

In the NDA, there were no cases of liver failure resulting in death or transplant. There was 1 case in post-marketing but that patient was also taking VPA. There was one patient on oxcarbazepine in the NDA who developed markedly elevated LFTs and a concurrent increase in bilirubin to 3.3 and was diagnosed as having hepatic necrosis. The details reported on the case was limited, but no cause could be found for the event and the abnormalities resolved after discontinuation of oxcarbazepine.

In my view, there is some concern that oxcarbazepine may cause an elevation in liver enzymes at least when initiated as monotherapy presumably in patients who have not had preceding AED exposure.

QT interval

The sponsor provided findings from analyzes of the effects of oxcarbazepine on the QT interval in the 3 studies that used a central laboratory for reading the ECGs. There were 10 additional studies that also collected ECG data, but no analyses were presented for these studies. No explanation was give for why these 3 studies were selected for central reading or whether the other 10 studies were also analyzed for ECG effects.

As shown in the following table, there was no evidence that QT increased in the 3 studies.

Mean QT by study and assigned group				
Study Number	**Drug**		**Placebo***	
	Baseline	**Last Visit**	**Baseline**	**Last Visit**

Study 11	**383.9**	**383.0**	**383.7**	**383.4**
Study 25	**406.2**	**380.6**	**383.3**	**360.4**
Study 26	**418.0**	**419.3**	**414.3**	**416.4**

*For study 26, the placebo column represents group assigned to 300 mg per day while the drug group was dosed at 2400 mg per day.

Other Events

Oxcarbazepine use appears to cause a decrease in T4 without any effect on TSH. Similar effects have also been observed with carbamazepine. There was also a clear decrease in uric acid. Both of these events should be mentioned in labeling under the laboratory section. There also appeared to be 4 patients on oxcarbazepine who had an increase in creatinine compared to none on placebo. The sponsor has not scrutinized this finding.

In the controlled studies there was a significant excess of events coded as hypertension on oxcarbazepine compared to placebo, but there was no evidence of an increase in BP in the vital sign database. We do not know what these events represent or whether there was an increased frequency of new onset hypertension during study.

There was also a clear increase in weight gain and edema reported with oxcarbazepine. It use also seems to be associated with skin rash and there may have been cases of SJS and 1 case of TEN reported in the post-marketing experience. Weight gain, edema and serious skin rash may require some description in labeling depending on the findings from additional analyzes to be conducted by the sponsor.

Several patients who developed hypersensitivity reactions may have had similar reactions to carbamazepine. We should consider recommending against the use of oxcarbazepine in patients who had significant events with carbamazepine. This may need a warning.

Conclusion

While there are clear risks associated with use of oxcarbazepine, none of these alone or in the aggregate would preclude approval assuming the drug is effective in epilepsy.

Questions for the Action Letter

Extent of use

You have proposed an upper dose limit of 2,400mg per day in labeling. However, the extent of experience at doses greater than 1,800mg/day is not well defined. Provide a duration by dose table (using the same format as exhibits 4.2.2.-1 and 4.2.3.-1 in the ISS) that stratifies the experience by: >1,800mg/day to <2,400mg/day, and at 2,400mg/day. In one study, the protocol was amended to a maximum dose of 1800 mg/day because of AEs. Please separately examine the safety experience in patients reaching doses greater than 1800 mg and justify recommending a maximum dose of 2400 mg/day.

Risk of Hyponatremia

Conducting a more formal analysis of hyponatremia in the NDA would allow for better description of its risk in labeling. Since sodium changes in time, determining whether oxcarbazepine dose, the frequency of prior monitoring and the preceding sodium level affect the risk for sodium less than 125 is not straight forward. We would suggest that you conduct a Cox style analysis using sodium less than 125 as the event of interest. In addition to examining the factors already mentioned, also consider patient attributes such as age and gender, and concurrent medications.

Your analysis of whether any AEs are associated with hyponatremia is flawed. You have confounded the time of the AE event with the timing of hyponatremia. Please reconsider this question by looking at selected AE risk after patients reach selected sodium levels. You could, for example, look at AE risk within 1 month of reaching such levels.

Please provide time plots for sodium in all patients dropping below 125. Include a summary for each patient that notes all AEs, concurrent medications and when the drug was stopped.

Did the protocols employ a discontinuation rule for patients reaching a specified sodium level?

CNS Toxicity

From review of treatment emergent events from controlled trials, there is an increased risk among oxcarbazepine exposed subjects of CNS events including ataxia, gait abnormalities, concentration impaired, thinking abnormal, psychosis and other events. (Insert language from our recent AED action letter on this topic.)

Hematological Risk

There seems to be a pretty good signal of concern for aplastic anemia – 1 case in the primary database, 1 case of pancytopenia (no bone marrow) in the compassionate use program and 4 potential cases from post-marketing surveillance. Please conduct a risk assessment of this issue and propose appropriate labeling to describe the event, if appropriate.

Hepatic Risk

There is some concern that oxcarbazepine may have increased risk for hepatic injury. The evidence mostly comes from the monotherapy initiation trials where there was an increase in the percentage of patients whom had ALT/AST compared to placebo, but the placebo group was small. There was also 1 patient who had hepatic necrosis. Please conduct a risk assessment of this issue. Did any patients other than the one with hepatic necrosis have concurrent increases in LFTs and bilirubin? Are there more details about the patient with hepatic necrosis regarding the course in the hospital? Was a liver biopsy performed? Do you have any proposal for studying the question further? Perhaps a large surveillance study focused on serious medical events could be helpful following approval.

Other Issues

1) Patient 011EUSAM0230N107 had an AE listed as uremia but did not appear to have abnormal BUN or Creatinine results in the CRT dataset. Please explain what occurred with this event, including pertinent lab results, workup, and outcome.

2) Patients 004EUSAM8459P101 and 026EUSAM8706P111 both had jaundice listed as AEs but did not appear to have elevated bilirubin results in the CRT dataset. Please explain what occurred with these events including pertinent lab results, workup, and outcome.

3) There was a large percentage of patients lost to follow-up in some trials. Please explain this finding.

4 Evaluate the lupus-like reactions that have been observed with oxcarbazepine use. Propose appropriate labeling.

5) There is a clear increase in edema and weight gain on oxcarbazepine. Please evaluate this issue. Are these events related to hyponatremia or the hypertensive AEs?

6) There seemed to be an increase in the number of patients with creatinine increases compared to placebo? Please summarize these patients and evaluate this issue.

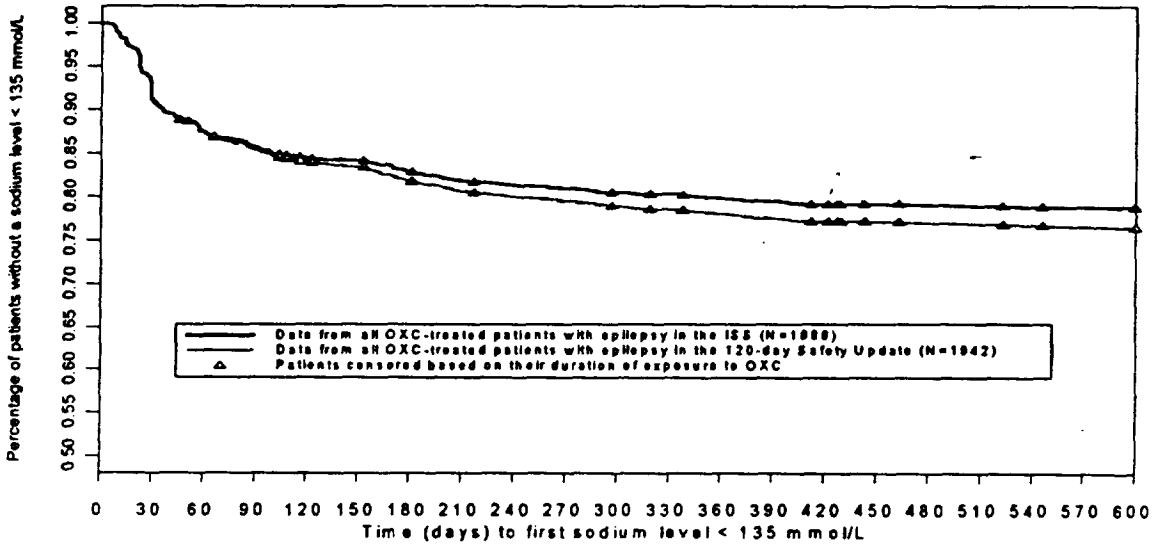
7) In the primary database, there was a clear excess in AEs coded as hypertension. Please summarize patients having these events specifically noting which were started on antihypertensive medications while they were oxcarbazepine use.

8) Please evaluate all patients in the NDA with skin reactions or sensitivity reactions for preceding carbamazepine use. Propose a warning statement describing the risk.

9) Also conduct a risk assessment for serious rash including the cases of SJS and TEN reported in the post-marketing experience.

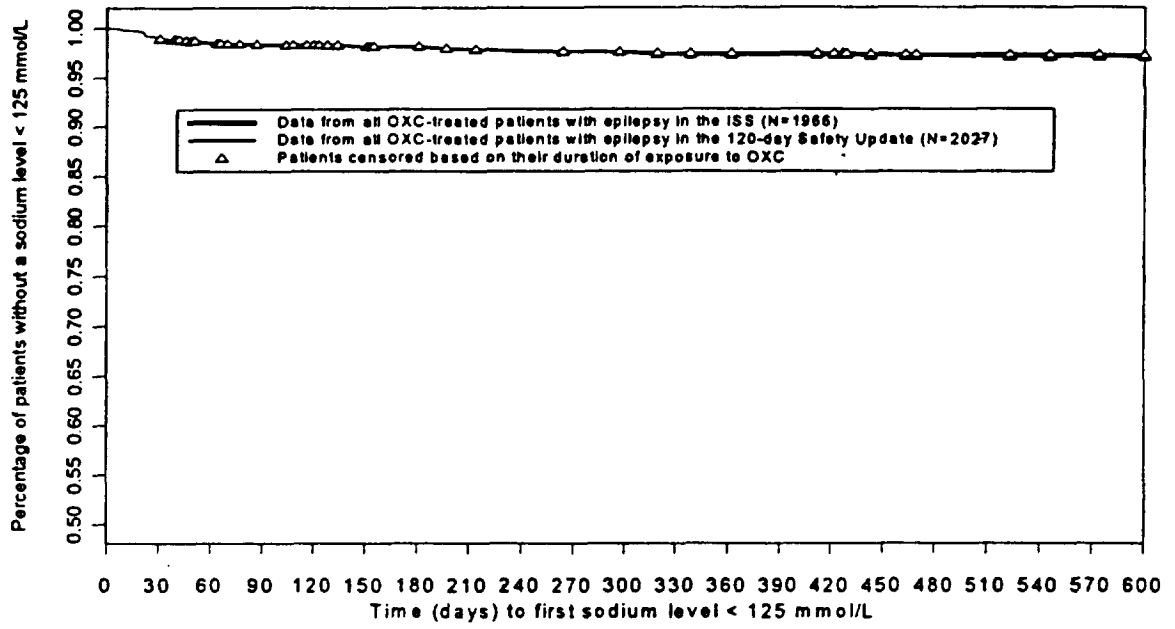
10) Provide the rate of status for all treatment groups in the NDA.

Figure 1. **Time to first occurrence of sodium level < 135 mmol/L in the Integrated Summary of Safety and the 120-day safety update (all OXC-treated patients with epilepsy)**



APPEARS THIS WAY
ON ORIGINAL

Figure 2. Time to first occurrence of sodium level < 125 mmol/L in the Integrated Summary of Safety and the 120-day safety update (all OXC-treated patients with epilepsy)



The plot of first serum sodium <125 mmol/L shows that the incidence of serum sodium <125 mmol/L was low and occurred early (within 1 month) during therapy, and thereafter the rate decreased as indicated by the flat curve throughout the treatment period.

Of the 2027 oxcarbazepine-treated patients evaluated from the 120-day Safety Update with baseline serum sodium levels, 60 (2.96%) patients had a serum sodium value <125 mmol/L and in 22 patients (1.1%) this occurred within 1 months of therapy.

In conclusion, the overall incidence of serum sodium levels <135 mmol/L over the first 20 months of therapy was 24.5% (476/1942). The incidence rate (9.0 %) was highest during the first month of therapy. The overall incidence of serum sodium levels <125 mmol/L (clinically relevant) was low (2.96 %, 60/2027) and occurred early during therapy, within 1 month, and thereafter the rate decreased indicating that there is no increased risk over time.

Review of Clinical Data

NDA:	21-014
Drug Name:	Generic: Oxcarbazepine Proposed trade name: Trileptal™
Sponsor:	Novartis
Materials Reviewed	Response to Approveable letter (11/15/99), Pre-Approval Safety Update (11/15/99) Response to Request for additional information (12/15/99), Response to Request for additional information (12/23/99)
Reviewer:	Gerard Boehm, MD, MPH
Completed:	1/3/2000

The following is a review of the oxcarbazepine safety issues addressed in the sponsor's 11/16/99 submission. The submission included responses to questions asked of the sponsor by the division in the Approveable letter for oxcarbazepine. The sponsor also provided a pre-approval safety update. Additional tables were requested from the sponsor during the review and were provided in submissions dated 12/15/99 and 12/23/99. Since these submissions addressed a variety of safety topics, rather than providing an overall discussion at the end, I have provided separate discussions for specific topics through the review.

1.0 Hyponatremia

1.1 Sodium Monitoring in NDA Trials

The agency asked the sponsor to summarize the lab collection schedules for the NDA trials. In response, the sponsor explained that monitoring was generally done twice during the first month of treatment, then monthly until the third month, and then every 3 months until 2 years. There were no strict rules about discontinuing subjects for low sodium in the clinical trials, but the sponsor discussed decisions about continued participation for these patients with investigators on a case by case basis.

1.2 Cox analysis of time to hyponatremia

The sponsor was asked to further clarify hyponatremia risk associated with oxcarbazepine by conducting a proportional hazards analysis, focusing on sodium <125mmol/L as the event of interest and examining, in addition to previously considered factors, the effect of age, gender, and concurrent medication. In their Cox proportional hazards analysis, the sponsor examined the effect of oxcarbazepine dose, age, gender, baseline sodium, and selected concomitant medications associated with hyponatremia (specifically antidepressants, cathartics, carbamazepine, diuretics, female hormones, vasodilators, and steroids). The following table provides the risk ratios and p-values for the covariates.

Proportional hazards hyponatremia analysis results

Variable	Risk Ratio	P-value
Oxcarbazepine dose	2.084	0.020
Age	1.037	<0.001
Sex	1.474	0.145
Baseline Sodium	0.819	<0.001
Received concomitant medications	2.488	0.005

The sponsor noted that there were 2 children identified with hyponatremia, and that children infrequently use the identified concomitant medications, and the population size for the elderly was small (n=41) and they frequently used the identified concomitant medications. Therefore, the sponsor excluded both the children and the elderly from the remaining analyses in order to avoid confounding with other factors in the model.

After removing the elderly, and children, the sponsor noted the following results.

Proportional hazards hyponatremia analysis results for selected subgroups

	All adults		Adults without Cmeds		Adults with Cmeds	
Variable	Risk Ratio	P-value	Risk Ratio	P-value	Risk Ratio	P-value
Oxcarbazepine dose	1.858	0.060	5.142	0.064	1.659	0.155
Age	1.026	0.034	1.037	0.151	1.021	0.151
Sex	1.455	0.184	0.640	0.521	1.772	0.079
Baseline Sodium	0.808	<0.001	1.0	0.993	0.786	<0.001
Received Cmeds	2.629	0.007	NA	NA	NA	NA

The sponsor commented that when the analysis was conducted for patients without exposure to the identified concomitant medications, 10/632 (1.6%) developed hyponatremia and they state that none of the factors from the original model were significant risk factors for hyponatremia. An interesting finding that was not mentioned by the sponsor was that the point estimate for the dose variable increases by more than 2 fold when adults without concomitant use of medications that can lead to sodium reduction are viewed as a group. In addition, baseline sodium did not appear to be a risk factor in this group. Even though the p-value increased to >.05, the point estimate for age changed very little following the removal of the youngest and oldest subjects or stratification by concomitant medication use.

The sponsor reviewed the 10 hyponatremia events that occurred in subjects not taking one of the identified concomitant medications and found that for 5 subjects, the abnormally low sodium occurred once, was transient and not associated with symptoms and sodium increased on oxcarbazepine. For the 5 remaining patients, 2 had low baseline sodium results, and 3 had persistent low sodium-1 was also receiving valproic acid and oxcarbazepine was stopped, 1 was receiving oxcarbazepine 3,600mg/day and continued treatment, and 1 discontinued for unrelated vasospasm.

For oxcarbazepine subjects taking one of the identified concomitant medications associated with hyponatremia, the risk for hyponatremia was 45/810 (5.6%). When the Cox analysis was performed on this subset of patients, the sponsor commented that only baseline sodium was a significant risk factor for hyponatremia. Based on this analysis, the sponsor concludes that baseline laboratory measurements are only indicated in those patients who are currently receiving comedications known to decrease sodium levels.

Discussion

There appeared to be a subset of subjects at increased risk for reaching a sodium <125mmol/L, specifically, those concomitantly receiving a medication with an increased risk of hyponatremia. Those not also receiving a medication with an increased risk of hyponatremia were not free of risk, and in fact 1.6% of these patients developed a serum sodium <125mmol/L. From the sponsor's analyses, it appears that among subjects not concomitantly receiving these medications, higher doses of oxcarbazepine were associated with increased risk of hyponatremia, as evidenced by the substantial increase in the point estimate for dose in this subset. In the subjects concomitantly receiving these medications, the point estimate for dose was notably less than that in the complementary group. The sponsor does not specifically address this finding. I would interpret it to mean that those not also taking one of the medications associated with hyponatremia and taking a low dose of oxcarbazepine were at low risk for having a sodium <125mmol/L. In those taking medications with an increased risk of hyponatremia, oxcarbazepine dose was less associated with risk, presumably because even those at low dose had were at increased risk for developing a serum sodium <125mmol/L.

1.3 Assessment of Associated AEs

Referencing their previously submitted Kaplan-Meier curve, the sponsor maintains that hyponatremia generally occurred in the first 3 months and decreased over time. They examined their clinical trials database to identify subjects on fixed maintenance doses of oxcarbazepine for at least 3 months in order to determine the frequency of sodium measurements required during this period. They found that 19/730 (2.6%) of adult patients on fixed doses for up to 3 months experienced hyponatremia. They note that all cases occurred in adjunctive therapy trials (706 exposed to a fixed dose for 3 months) and none in monotherapy initiation trials (24 exposed to a fixed dose for 3 months). They then calculated the cumulative incidence rate of hyponatremia in these patients on fixed doses of oxcarbazepine at 1 month and three months. Those results are displayed in the following table.

Cumulative incidence of hyponatremia at 1 month and 3 months in subjects receiving fixed doses of oxcarbazepine

Oxcarbazepine dose (mg/day)	Cumulative incidence			
	1 month		3 months	
	N	%	n	%
300 (n=40)	0	0.0	0	0.0
600 (n=153)	2	1.3	2	1.3
1,200 (n=182)	5	2.7	7	3.8
1,800 (n=37)	1	2.7	1	2.7
2,400 (n=318)	5	1.6	9	2.8
Total (n=730)	13	1.8	19	2.6

The sponsor interprets the above results as showing no clear dose related increase in the incidence of treatment emergent hyponatremia at 1 and 3 months (supported by a Cox analysis, which showed no dose response at 1 month- RR 0.9 and 3 months- RR 1.2). They also note that 18 of 19 patients in this analysis who developed a sodium <125mmol/L received concomitant medications known to be associated with an increased risk of hyponatremia. They conclude there is no need to measure sodium levels in patients on fixed doses of oxcarbazepine unless medications known to decrease sodium levels are added or symptoms of hyponatremia develop.

Discussion

The sponsor has maintained that sodium <125mmol/L occurs during the first 3 months of therapy and decreases with time. We have examined their Kaplan Meier curve and have concluded that

the most important finding is that cases continue to occur over time. This perhaps is best demonstrated by the information included in the sponsor's exhibit W1-2 in the response to the approveable letter.

Time to sodium <125mmol/L from oxcarbazepine clinical trials

Time interval (months)	# with sodium <125mmol/L
≤1	22
>1-3	11
>3-6	5
>6-9	11
>9-12	7
>12-24	4

This table clearly demonstrates that cases continue to occur after 3 months, with 4 events occurring at least 1 year after starting treatment.

1.4 Hyponatremia Cases in Young and Elderly

The sponsor provided a review of the cases of hyponatremia in the young and in those >65 years of age. In one of the 2 cases of hyponatremia occurring in children, the subject had excessive vomiting that may have contributed to the occurrence of the event. In the three cases of hyponatremia in the elderly, the sponsor noted that 2 patients were taking diuretics and 1 was taking captopril.

1.5 Hyponatremia associated Adverse Events

In the NDA, the sponsor provided an analysis of the relationship between hyponatremia and selected AEs. In that analysis, a subject was classified according to their lowest recorded sodium and then adverse events risks were calculated for selected strata of sodium levels. Dr. Burkhart recognized the potential for confounding of the relationship between dose and hyponatremia symptoms by time (Team Leader Memo dated 8/15/99). It was possible that the occurrence of the event was not temporally related to the finding of hyponatremia. The sponsor agreed that a better approach would be to examine risk for adverse events occurring ± 7 days of reaching selected serum sodium levels (<125mmol/L, <125-129mmol/L and ≥ 130mmol/L). They examined the risks for various symptoms including abnormal vision, headache, dizziness, nausea, vomiting, diplopia, convulsions, a collection of psychiatric symptoms, cognitive symptoms, and somnolence. In their analysis the sponsor looked for events that occurred more commonly in oxcarbazepine exposed than placebo and that increased in frequency with decreasing sodium. Depression, abnormal thinking, convulsions, and aggravated convulsions occurred at the highest frequency in patients with the lowest sodium but the sponsor points out that the number of events was small and these events also occurred in placebo patients. It is important to note that for thinking abnormal, convulsions and convulsions aggravated the relationship between risk and sodium is based on a single event in the lowest sodium group. Only vision abnormal had a large relative risk compared to placebo and demonstrated an increased frequency with declining sodium. The table of these adverse event risks is provided as an appendix to this review.

Discussion

It is interesting to note that there were relatively few patients reporting adverse events within 14 days of recorded low sodium values (particularly for those with sodium<125mmol/L). The risk for Vision abnormal (generally blurred vision) appeared to be related to hyponatremia in this analysis. There were additional events for which the risk appeared to be related to low sodium but in general there were too few events to be able to exclude chance associations as an explanation for the apparent relationship.

1.6 Plots of sodium values for patients with hyponatremia
The sponsor provided plots of sodium values versus time for the 60 patients who developed a serum sodium <125mmol/L on oxcarbazepine. They noted that 37/60 patients had a single measurement <125mmol/L and 11 stopped treatment within 14 days of reaching a sodium <125mmol/L. The plots provided by the sponsor were not uniform in appearance. Most patients experienced a decline in sodium following initiation of treatment that subsequently reached <125mmol/L. There were patients with little change in sodium following initiation of treatment that later developed a low outlier <125mmol/L.

Overall Discussion of Trileptal related hyponatremia
In a water load study, the sponsor demonstrated that oxcarbazepine, in the proposed recommended dose range, alters an individual's ability to excrete free water. In the primary database, 3% of oxcarbazepine patients had a serum sodium of <125mmol/L at some point during a clinical trial. No comparator patients developed a serum sodium <125mmol/L. Concomitant use of medications associated with hyponatremia were associated with an increased risk of developing a sodium <125mmol/L but there were patients who developed serum sodium <125mmol/L who did not also take these medications. Although the event of sodium <125mmol/L was generally identified early (during the first months of treatment), there were patients who first developed a sodium <125mmol/L more than 1 year after initiation of therapy. Most patients with hyponatremia were asymptomatic although patients in the clinical trials were monitored and some were discontinued which may have prevented the occurrence of events of greater severity. There were cases of symptomatic hyponatremia identified from post marketing reports.

2.0 Evaluation of Cognitive Neuropsychiatric events
During the NDA review, we noted that CNS adverse events risks (events/number exposed) were greater for the oxcarbazepine than placebo (specifically ataxia, gait abnormalities, diplopia, nystagmus, confusion, thinking abnormal, concentration impaired, depression, and psychosis). The sponsor was instructed to identify the subjects with mental status change, and then classify these patients into one of the three following categories: psychiatric symptoms, psychomotor symptoms, and somnolence. The sponsor examined adverse events terms, identified those suggestive of suggestive of mental status change and re-grouped them. The listing of these event terms and groupings is provided as an appendix to this review.

For these analyses, the sponsor calculated and then compared risks (#events/subjects) and incidence rates (#events/person-time exposure) for each treatment group. Incidence rates were calculated because the sponsor demonstrated differences in mean exposure time between the placebo group and oxcarbazepine group. The mean duration of exposure for oxcarbazepine was longer than the mean duration for placebo, particularly in the initiation of monotherapy trials. In the initiation of monotherapy trials, the mean duration of exposure to placebo was 3.1 months compared to 9.4 months for oxcarbazepine. This difference occurred because of pooling of different length studies rather than differences in observation time within studies. There were 6 initiation of monotherapy trials, 3 comparing fixed dose oxcarbazepine to placebo and 3 comparing oxcarbazepine titrated to tolerance and effect with active comparator. The three trials using placebo lasted 12 weeks (006), 51 weeks (010) and 18 (025) weeks and 2 of these trials were terminated early due to poor enrollment (010, 006). The lengths of the trials using active comparators (OT/F01, OT/F02, OT/F04) were 56 weeks each. For the initiation of monotherapy trials the sponsor pooled the entire experience for oxcarbazepine from 6 trials of different length and design and compared risk to a pool of placebo experience from 3 trials. When this was done, the pooled mean exposure to oxcarbazepine was greater than the mean exposure to placebo.

Psychiatric Events

The following table provides the sponsor's analyses of incidences for psychiatric adverse events occurring in the overall database, monotherapy initiation controlled trials, and the adjunctive/monotherapy substitution controlled trials. The sponsor intended to present incidences as events/100PY, but their tables provided events/1PY. I have presented the results as events/100PY in the tables below.

Incidence rates for Psychiatric adverse events by treatment group

	OXC	CBZ	PHT	PB	VPA	PLB
All epilepsy Patients	n=2,224 2,581 PY	n=134 97 PY	N=252 210 PY	N=52 54 PY	N=121 111 PY	n=464 133 PY
# of events	485	19	60	5	26	54
Incidence	19/100PY	20/100PY	30/100PY	9/100PY	23/100PY	41/100PY
Monotx initiation	N=440 344 PY		N=240 201 PY		N=121 111 PY	n=66 17 PY
# of events	83		59		20	7
Incidence	24/100PY		29/100PY		18/100PY	40/100PY
Adjunct tx Monotx sub	n=1,272 548 PY	n=134 97 PY		n=52 54 PY		n=353 116 PY
# of events	185	18		5		45
Incidence	34/100PY	19/100PY		9/100PY		39/100PY

From this table, there did not appear to be an increased risk of psychiatric events in the oxcarbazepine treated subjects when compared to placebo for any of the pooled groupings. The incidence of psychiatric events was higher for oxcarbazepine than carbamazepine in the adjunctive/monotherapy substitution trials.

Because of the issues related to pooling raised above, I examined psychiatric adverse event risks from trial 025, a placebo controlled initiation of monotherapy trial. There did not appear to be evidence of a difference in risk for psychiatric events within this trial, based on limited exposure (32 subjects exposed to oxcarbazepine, 35 subjects exposed to placebo).

Because of uncertainties about the effects of pooling data from adjunctive and monotherapy substitution trials, I looked at adverse event risks within a single, large add-on trial (OT/PE1). Using the adverse event tables in the study report submitted with the NDA, and the same grouping of events used by the sponsor in their analysis, I calculated the incidence of psychiatric events in the adjunctive trial OT/PE1. Those risks are provided in the following table.

Risk of Psychiatric adverse events from adjunctive trial OT/PE1

	Oxcarbazepine psychiatric events	Placebo psychiatric events
#events/subjects	15% (78/519)	12% (20/173)
#events/person time	41/100PY (78/190PY)	23.5/100PY (20/85PY)

Description of calculation of person time for study OT/PE1 is on p. 15 of the NDA safety review

Within this trial there was an increased risk of psychiatric events in oxcarbazepine exposed subjects. None of these psychiatric events met the regulatory definition of a serious adverse event but some of these events led to discontinuation. Using the adverse events leading to discontinuation table from the study report of OT/PE1, I calculated the incidences for these events leading to discontinuation by treatment. The incidence of discontinuation for an event

included in the psychiatric group was 7.9/100PY (15/190PY) in those exposed to oxcarbazepine compared to 1.2/100PY (1/85PY) in the placebo group.

Cognitive Adverse Events
The following table provides the sponsor's comparisons of incidence rates for cognitive adverse events.

Incidence rates for Cognitive adverse events by treatment group

	OXC	CBZ	PHT	PB	VPA	PLB
All epilepsy Patients	n=2,224 2,581 PY	n=134 97 PY	N=252 210 PY	n=52 54 PY	N=121 111 PY	n=464 133 PY
# events	261	15	28	6	15	18
Incidence	10.1/100PY	15.5/100PY	13.3/100PY	11.1/100PY	13.5/100PY	13.5/100PY
Monotx initiation	n=440 344 PY		N=240 201 PY		N=121 111 PY	n=66 17 PY
# events	37		25		13	4
Incidence	10.8/100PY		12.4/100PY		11.7/100PY	23.5/100PY
Adjunct tx Monotx sub	n=1,272 548 PY	n=134 97 PY		n=52 54 PY		n=353 116 PY
# events	106	14		6		14
Incidence	18.2/100PY	14.4/100PY		11.1/100PY		12.1/100PY

The sponsor noted that the incidence of cognitive adverse events for oxcarbazepine was lower than placebo in the overall and initiation of monotherapy groupings. They also identified a slightly increased incidence of cognitive adverse events in the adjunctive therapy/monotherapy substitution trials. They concluded that there was no strong association of cognitive symptoms with oxcarbazepine and that no warning should be required in the labeling.

Because of the pooling issues raised above for the initiation of monotherapy trials, I looked at cognitive adverse events from trial 025 and there did not appear to be evidence of a difference in risk for cognitive events by treatment within this trial.

Using the adverse event tables from the study report submitted with the NDA, and the grouping of events used by the sponsor, I calculated the incidence of cognitive events in trial OT/PE1, a large add-on trial. The results are presented in the following table.

Risk of Cognitive adverse events from adjunctive trial OT/PE1

	Oxcarbazepine cognitive events	Placebo cognitive events
#events/subjects	7% (36/519)	2% (20/173)
#events/person time	19/100PY (36/190PY)	4/100PY (20/85PY)

Within this adjunctive trial, oxcarbazepine exposed subjects were at increased risk for cognitive adverse events. None of these cognitive events met the regulatory definition for a serious adverse event. Using the adverse events leading to discontinuation table from the study report for trial OT/PE1, I calculated the incidences of cognitive AEs leading to discontinuation by treatment. The incidence of discontinuation for an event included in the cognitive group was 11.6/100PY (22/190PY) in those exposed to oxcarbazepine compared to 1.2/100PY (1/85PY) in the placebo group.

The following table provides the sponsor's incidence rates for somnolence adverse events.

Incidence rates for Somnolence adverse events by treatment group

	OXC	CBZ	PHT	PB	VPA	PLB
All epilepsy Patients	n=2,224 2,581 PY	n=134 97 PY	N=252 210 PY	n=52 54 PY	N=121 111 PY	N=464 133 PY
# of events	793	54	82	21	44	73
Incidence	30.7/100PY	55.7/100PY	39.0/100PY	38.9/100PY	39.6/100PY	54.9/100PY
Monotx initiation	n=440 344 PY		N=240 201 PY		N=121 111 PY	N=66 17 PY
# of events	123		80		42	10
Incidence	35.8/100PY		39.8/100PY		37.8/100PY	58.8/100PY
Adjunct tx Monotx sub	n=1,272 548 PY	n=134 97 PY		n=52 54 PY		N=353 116 PY
# of events	432	49		21		59
Incidence	78.8/100PY	50.5/100PY		38.9/100PY		50.9/100PY

The sponsor noted that the incidence rate for somnolence adverse events in the oxcarbazepine group was lower than the incidence rate in the placebo group in the overall and monotherapy initiation trials analyses. They admit that in the adjunctive/monotherapy substitution trials, the risk of somnolence was higher for oxcarbazepine compared to placebo.

Because of the pooling issues raised above for the initiation of monotherapy trials, I looked at somnolence adverse events from trial 025 and there did not appear to be evidence of a difference in risk for somnolence events by treatment within this trial.

I also calculated the incidence of adverse events coded as somnolence in the adjunctive trial OT/PE1.

Risk of Somnolence adverse events from adjunctive trial OT/PE1

	Oxcarbazepine somnolence events	Placebo somnolence events
#events/subjects	26.3% (137/519)	11.5% (20/173)
#events/person time	72/100PY (137/190PY)	23.5/100PY (20/85PY)

Within this trial, oxcarbazepine exposed subjects were at increased risk for somnolence adverse events. None of these events met the regulatory definition of a serious adverse event. Using the discontinuation due to AE table from the study report for OT/PE1, I determined that the incidence of somnolence leading to discontinuation for oxcarbazepine subjects was 24/100PY (45/190PY) compared to 2.4/100PY (2/85PY) for placebo subjects.

In the response to the approveable letter, the sponsor included a table with data from 2 add-on studies (OT/PE1, 011), which provided the number of somnolence adverse events and the % of patients with adverse events stratified by time in the study. They noted that the absolute risk for somnolence adverse events declined in the oxcarbazepine group over time.

Cumulative incidence of somnolence at 1 and 3 months in patients on fixed doses of oxcarbazepine compared to placebo (studies OT/PE1 and 011)

Time interval (months)	% OXC patients with somnolence	% PLB patients with somnolence	Relative Risk
≤0.5	24.8%	10.6%	2.3
>0.5-1	21.4%	8.8%	2.4
>1-2	16.5%	8.3%	2.0
>2-3	10.6%	4.7%	2.3
>3-6	8%	3.8%	2.1
>6	5%	2.6%	1.9

The sponsor concluded that these data support that somnolence tends to occur when initiating treatment and then abates with continued usage.

2.1 Discussion

Using pooled data, the sponsor found little difference in risk for psychiatric adverse events, a slightly increased risk for cognitive adverse events and a larger increased risk for somnolence adverse events in oxcarbazepine subjects. Differences in study design and length may effect the validity of comparisons based on pooled data and therefore, I compared risks within single studies. I found no difference in risks for psychiatric, cognitive of somnolence events within the initiation of monotherapy study 025, although this was a small trial. Within add-on study OT/PE1 there were increased risks for psychiatric, cognitive, and somnolence AEs in oxcarbazepine subjects. Although they did not meet the regulatory definition for serious AEs, they were associated with an increased risk of discontinuation from this trial.

The sponsor intended to state in labeling that the risk for somnolence events is increased with oxcarbazepine but that somnolence decreases with time. The analysis provided by the sponsor does not support the statement that somnolence abates with continued use. To conclude that somnolence abates, one would have to identify patients who develop somnolence and determine if the event resolved with continued treatment. Their analysis suggests that the relative risk for this event remains fairly constant through time.

3.0 Extent of Use

In the NDA and safety update, the sponsor described use by dose with >1,800mg/day as the highest dose grouping. Since the sponsor proposes to have a recommended upper dose limit of 2,400mg/day, we requested information about the extent of exposure to this dose. In addition, we requested an analysis of safety for the higher dose groups since these were not examined separately in the NDA. The sponsor provided a table demonstrating that 234 subjects were exposed to a mean dose >1,800 to 2,399mg/day, and that 277 subjects were exposed to a mean dose ≥2,400mg/day. In addition, 129 subjects were exposed to a mean dose of 1,800 to 2,399mg/day for more than 1 year, and 120 subjects were exposed to a mean dose ≥2,400mg/day for more than 1 year.

The sponsor provided a table illustrating exposure by mean daily dose for pediatric patients (≤17 years old). The sponsor reported that 536 pediatric patients were exposed to a mean daily dose of <1,800mg/day, 53 to a mean daily dose of >1,800-<2,400mg/day, 27 to a mean daily dose of 2,400-3,000mg/day and 6 to a mean daily dose of 3,000 to 3,600mg/day. The sponsor reported that 1 pediatric patient was exposed to a mean daily dose >3,600mg/day, for 12-24 months. Exposure by dose and duration are summarized in the following table.

Exposure, mean daily dose in pediatric patients (≤17 years old) in the Trileptal database

Number exposed	<1,800mg	>1,800-<2,400mg	2,400-3,000mg	3,000-3,600mg
Exposed <6 mos	179	3	12	1
Exposed 6-12 mos	51	8	3	2
Exposed>12mos	306	42	12	3
Total	536	53	27	6

Safety experience by dose

Serious Adverse Events by Dose

To explore the dose relationship for SAEs in the higher dose groups the sponsor focused on the experience in the adjunctive/monotherapy substitution controlled trials (there was very little exposure to higher doses in the monotherapy initiation trials). The sponsor included tables of the occurrence of serious adverse events by mean daily dose that separated out higher dose groups. There was an increased risk for all serious adverse events when comparing the 2,400mg/day group (12.3%, 22/179) to the >1,800-<2,400mg/day (5.6%, 10/177) <1,800mg/day (8.9%, 80/896) and placebo (5.4%, 19/353). In the following table I identified selected serious AEs occurring in at least 1% of the 2,400mg/day group and that appeared to demonstrate a dose response.

Selected serious adverse events from adjunctive/monotherapy substitution trials by mean daily dose

Event	<1,800mg/day	>1,800-<2,400mg/day	2,400mg/day	>2,400mg/day	Placebo
Total n	896	177	179	20	353
Nausea	0.9% (n=8)	0	1.7% (n=3)	0	0
Ataxia	0.6% (n=5)	0.6% (n=1)	2.8% (n=5)	0	0
Somnolence	0.6% (n=5)	0.6% (n=1)	1.7% (n=3)	0	0
Dizziness	0.6% (n=5)	0.6% (n=1)	1.1% (n=2)	0	0
Gait abnormal	0.3% (n=3)	0	1.7% (n=3)	0	0
Tremor	0.3% (n=3)	0	1.1% (n=2)	0	0
Vertigo	0.2% (n=2)	0	2.2% (n=4)	0	0
Diplopia	0.1% (n=1)	0.6% (n=1)	1.7% (n=3)	0	0

* Source- Sponsor's table S3C-3, 12/15/99 submission

Discontinuations by dose

The sponsor provided a table listing the risk for discontinuation due to specific adverse events by mean daily dose for the adjunctive/monotherapy substitution trials using the same groups as above. The risk of discontinuation for an adverse event was 51% (92/179) in the 2,400mg/day group compared to 5.1% (9/177) in the >1,800mg-<2,400mg/day group, 21% (188/896) in the <1,800mg/day group and 5.7% (20/353) in the placebo group. AEs leading to discontinuation in at least 1% of the 2,400mg/day group and with evidence of dose response are listed in the following table.

Selected adverse events leading to discontinuation from adjunctive/monotherapy substitution trials by mean daily dose

Event	<1,800mg/day	>1,800-<2,400mg/day	2,400mg/day	>2,400mg/day	Placebo
Total n	896	177	179	20	353
Fatigue	1.8% (n=16)	0.6% (n=1)	10.1% (n=18)	0	0.3% (n=1)
Vomiting	4.9% (n=44)	0.6% (n=1)	18.4% (n=33)	0	0.3% (n=1)
Nausea	4.7% (n=42)	0.6% (n=1)	14.5% (n=26)	0	0.8% (n=3)
Pain abdominal	0.7% (n=6)	0	2.2% (n=4)	0	0.3% (n=1)

Anorexia	0.1% (n=1)	0	1.1% (n=2)	0	0.3% (n=1)
Hyponatremia	0.4% (n=4)	0.6% (n=1)	1.1% (n=2)	0	0.3% (n=1)
Dizziness	5.6% (n=50)	0	20.7% (n=37)	0	1.4% (n=5)
Ataxia	5.0% (n=45)	1.1% (n=2)	18.4% (n=33)	0	1.1% (n=4)
Somnolence	3.1% (n=28)	1.1% (n=2)	13.4% (n=24)	5.0% (n=1)	0.8% (n=3)
Nystagmus	3.1% (n=28)	0	8.4% (n=15)	0	0.8% (n=3)
Headache	2.7% (n=24)	0	7.3% (n=13)	0	0.3% (n=1)
Gait abnormal	1.7% (n=15)	0	6.7% (n=12)	0	0.3% (n=1)
Tremor	1.2% (n=11)	0	7.3% (n=13)	0	0.6% (n=2)
Confusion	0.3% (n=3)	0.6% (n=1)	1.1% (n=2)	0	0
Speech disordr	0.4% (n=4)	0	1.1% (n=2)	0	0
Think abnrml	0	0.6% (n=1)	2.8% (n=5)	0	0
Diplopia	5.2% (n=47)	0	17.9% (n=32)	0	0.6% (n=2)
Vertigo	2.1% (n=19)	0	8.9% (n=16)	0	0
Vision abnrml	2.2% (n=20)	0.6% (n=1)	5.0% (n=9)	0	0.3% (n=1)

* Source- Sponsor's table S3C-4, 12/15/99 submission

This table suggests that the mean daily dose of 2,400mg was associated with increased risk of discontinuation for several adverse events.

Adverse events by dose

The sponsor noted that the adverse event risk in the <1,800mg/day group was 77.8% and that in the higher dose groups, the risk ranged from 91.2% to 95%. The sponsor also noted that vomiting, viral infection, and abnormal vision were the three common adverse events that occurred at least twice as frequently in the >1,800-2,400mg/day group compared to the ≤1,800mg/day group. The risk for dizziness, diplopia, fatigue, ataxia, and abnormal vision in the 2,400-3,000mg/day, 3,000-3,600mg/day, and >3,600mg/day dose groups was at least twice the risk in the ≤ 1,800mg/day group. The sponsor commented that dizziness was the only adverse event that appeared to have a dose relationship across the dose groups. To identify common events with potential dose response relationships, I looked for adverse events where the risk in any of the higher dose groups was at least double the lowest dose group and the overall risk (all dose groups) was at least 5%. The following table summarizes those events.

Selected adverse event risks stratified by mean daily dose

Adverse Event	≤1,800mg n=1693	>1,800-<2,400mg n=90	2,400-3,000mg n=593	>3,000-3,600mg n=80	>3,600mg n=30
Dizziness	19.3%	26.7%	47.9%	46.3%	56.7%
Nausea	13.9%	26.7%	30.7%	31.3%	26.7%
Vomiting	13.4%	27.8%	26.5%	21.2%	20%
Diplopia	9.3%	13.3%	31%	28.7%	43.3%
Infection viral	13.3%	26.7%	15.5%	23.7%	20%
Fatigue	9.6%	18.9%	26%	27.5%	26.7%
Ataxia	7.4%	14.4%	17.9%	21.2%	33.3%
Vision abnormal	6.1%	12.2%	18.4%	20%	16.7%
Diarrhea	5.8%	13.3%	12.1%	13.8%	16.7%
Upper Resp Inf	5.1%	14.4%	9.6%	16.2%	30%
Tremor	4.6%	11.1%	11.8%	17.5%	13.3%
Rash	5.7%	8.9%	8.3%	11.3%	20%
Insomnia	2.9%	4.4%	13.2%	12.5%	16.7%
Dyspepsia	3.5%	4.4%	9.9%	15%	30%
Gait abnormal	3.8%	4.4%	8.9%	12.5%	10%

Depression	3.9%	7.8%	6.2%	15%	23.3%
Injury	2.4%	10%	8.6%	22.5%	30%
Pharyngitis	4.1%	10%	6.1%	8.8%	6.7%

Placebo controlled trials

The sponsor provided a table with adverse events by dose for the Placebo controlled adjunctive therapy and monotherapy substitution trials. This table included risks for the 2,400mg/day dose group and a >2,400mg/day dose group (mean daily dose). To look for evidence of dose response, I identified those common events occurring twice as frequently among the oxcarbazepine exposed subjects compared to placebo exposed subjects. I then selected the events where the risk was higher dose in at least one of the higher dose groups compared to the ≤1,800mg/day group. Those events are summarized in the following table.

Adverse Events by mean daily dose for adjunctive/monotherapy substitution controlled trials

Adverse Event	≤1,800 n=740	>1,800-<2,400 n=170	2,400 n=170	>2,400 n=20	Placebo n=214
Dizziness	20.3%	28.8%	45.9%	5.0%	12.6%
Somnolence	24.1%	18.2%	33.5%	20%	9.3%
Nausea	14.9%	22.4%	30.0%	5.0%	8.9%
Diplopia	14.3%	12.9%	32.4%	0	3.7%
Vomiting	11.8%	9.4%	21.4%	0	4.7%
Fatigue	10.5%	21.2%	18.8%	10.0%	5.6%
Ataxia	9.1%	7.6%	24.7%	0	4.2%
Vision abnormal	7.3%	11.2%	14.7%	5.0%	3.3%
Nystagmus	7.3%	1.8%	20.0%	0	3.7%
Vertigo	6.8%	2.9%	13.5%	10.0%	2.3%
Gait abnormal	4.9%	1.2%	12.9%	0	1.4%
Insomnia	3.2%	8.8%	5.3%	5.0%	0.9%
Nervousness	2.6%	5.3%	4.1%	0	0.9%
Upper Resp Inf	2.3%	6.5%	3.5%	0	1.4%
Weight Inc	2.8%	2.9%	1.8%	15.0%	0.9%

*Number of patients differs slightly from previous tables because this table includes only subjects >17 years old

Discussion

From the tables provided by the sponsor, there appeared to be adequate exposure to the 2,400mg/day dose, which the sponsor intends to recommend as the upper dose limit in their labeling. They have also demonstrated that the 2,400mg/day dose was associated with increased risk for several adverse events and was associated with increased risk of discontinuation. The sponsor proposes to include the following statement in labeling for adjunctive therapy "Daily doses from 600-2,400mg/day have been shown to be effective in controlled trials, although most patients were not able to tolerate the 2,400mg/day dose, primarily because of CNS effects." They also claim in labeling that 2,400mg/day was well tolerated in monotherapy substitution trials, although they have not provided the monotherapy substitution data separately to support such a statement. These comparisons were based on pooled data and the effects of pooling on the dose relationships has not been explored.

4.0 Hepatic Risk

In the NDA lab data, there appeared to be an increased risk for AST but not ALT outliers in the oxcarbazepine-exposed group in controlled trials. The sponsor was asked to assess this apparent discrepancy between the AST and ALT outlier risks and to address hepatic failure risk.

In response, the sponsor noted that there were a total of 14 patients with increases in AST (>2xULN) in the controlled trials and that 10 of these did have some increase in ALT as well. They provided a listing for the patients with increases in AST and a brief narrative about their clinical course. One of the outliers was due to incorrect conversion of lab units and did not represent an abnormality. One of the patients had an elevation at baseline that continued through the study. For 9 of the 14 subjects with abnormalities, the elevations were described as transient, occurring at one visit and then resolving on oxcarbazepine. The remaining 3 patients discontinued treatment (1 for the lab abnormality, the others for seizure, drowsiness/depression). None of the 3 had an associated increase in bilirubin.

The sponsor provided incidence rates for AST increases >3xULN for the controlled trials by treatment. Those rates are provided in the table below.

Incidence rates for AST>3xULN by treatment group, controlled trials

	OXC	CBZ	PHT	PB	VPA	PLB
Monotx initiation	n=440 344 PY		n=240 201 PY		n=121 111 PY	n=66 17 PY
# of events	2		1		1	0
Incidence	0.6/100PY		0.5/100PY		0.9/100PY	0
Adjunct tx Monotx sub	n=1272 548 PY	n=134 97 PY		n=52 54 PY		n=353 116 PY
# of events	7	1		1		0
Incidence	1.3/100PY	1.0/100PY		1.9/100PY		0

* P=.27 (binomial probability) for difference between Oxc and PLB in the adjunctive/monotx substitution trials

The sponsor noted that the incidence of AST outliers among oxcarbazepine exposed subjects was comparable to the incidence for other anticonvulsants and higher than the incidence for placebo.

The sponsor provided additional details for a liver injury case that was described in the NDA review. This 49-year-old male treated with phenobarbital, lamotrigine, and carbamazepine was randomized to receive oxcarbazepine and had normal baseline transaminases and bilirubin. Thirty-one days after beginning oxcarbazepine, he was hospitalized for increased seizure activity and confusion (attributed to seizures) and on the day of admission he had the following lab test results: total bilirubin 3.3mg/dL, SGOT 1,186U/L, SGPT 1,623 U/L, CPK 1,000U/L, and LDH 2,157 U/L. Oxcarbazepine was discontinued and the carbamazepine dose was increased.The following day, this subject had his highest recorded transaminases (AST 4,128U/L, ALT 8,691U/L). An ultrasound examination was notable for liver enlargement with "steatotic hepatopathy signs", some small simple cysts 1cm in diameter and no ascites. A second ultrasound reportedly demonstrated slight increases in liver volume, simple cysts (the largest 1.5cm in diameter), no bile duct dilatation, and an enlarged spleen. Tests for viral hepatitis (A, B, C) were negative and other causes of liver dysfunction (trauma, food toxicity, chemical toxicity) were ruled out. The subject did not have a liver biopsy. The patient was discharged 24 days after admission with liver test result values in the normal range. The sponsor obtained additional recent information from the patient's sister that the patient has not had additional episodes of hepatic dysfunction since the event described above.

The sponsor considered the rate of AST >3x ULN low and reported that the elevations were not associated with increases in bilirubin. The sponsor commented that there does not appear to be a strong clinical signal of significant risk for hepatic injury. In their assessment of the liver injury case, they state that the patient's rapid recovery raises doubts about a diagnosis of hepatic

necrosis, suggest that the case may represent cholestasis, and state that no definitive causality is apparent.

4.1 Discussion
The sponsor demonstrated that for oxcarbazepine subjects there was a higher incidence of AST >3x ULN compared to placebo (no cases) and there appeared to be similar incidence for oxcarbazepine and the active comparators. The evidence for a difference in risk between oxcarbazepine and placebo based on incidence of outliers >3xULN is not robust and the observed outcome could be explained either by chance or a small increased risk with insufficient experience in the database to accurately describe the finding. For the hepatic injury case, the sponsor suggests that that this may represent a cholestatic picture, but the finding of alkaline phosphatase <1.5xULN at the time of the recorded elevated bilirubin does not seem consistent with a cholestatic event. I am unsure how to interpret the elevated CPK results in this patient. In my opinion, on the basis of the elevation in transaminases and bilirubin, the data are consistent with hepatocellular injury. Even though, as the sponsor correctly states no definite causality is apparent, they did not identify a non-drug related etiology for this event.

With inconclusive evidence of an ability to cause LFT elevations and a case of hepatic injury somewhat suspicious for a drug related event, at this time there does not appear to be sufficient evidence to conclude that oxcarbazepine is associated with of increased risk of hepatic injury.

5.0 Hypertension
In the NDA, there was an excess of adverse event terms coded as hypertension among the oxcarbazepine exposed subjects compared to placebo subjects in the controlled trials. We asked the sponsor to summarize pertinent information for the patients with these events and to note if any required antihypertensive treatment. The sponsor identified 16 oxcarbazepine patients from the controlled trials with hypertension listed as an adverse event. Five had histories of hypertension prior to enrollment in the study. Eleven had either a baseline SBP≥140 or a baseline DBP≥90 or both. The sponsor included a column that provided the date an antihypertensive medication was started. Seven patients were started on an antihypertensive medication after initiation of oxcarbazepine.

The sponsor calculated incidence rates for hypertension for the controlled trials. In the Monotherapy Initiation trials, the incidence of hypertension in oxcarbazepine subjects was 1.2/100PY compared to 1.5/100PY, 0.9/100PY and 0 in the phenytoin, valproic acid, and placebo subjects respectively. In the Adjunctive/Monotherapy substitution trials, the incidence of hypertension in oxcarbazepine subjects was 1.3/100PY compared to 4.1/100PY, 0, and 0 in carbamazepine, phenobarbital, and placebo subjects respectively. The sponsor concluded that the incidence of hypertension was similar to the incidence for the active comparators and lower than carbamazepine in the controlled trials.

Discussion
There was an excess of hypertension AEs among oxcarbazepine subjects compared to placebo subjects enrolled in controlled trials but some of these subjects had a history of hypertension or had baseline blood pressures that were above normal. Seven oxcarbazepine subjects were started on antihypertensive medications following initiation of oxcarbazepine. Hypertension was a serious adverse event for 2 oxcarbazepine subjects from the clinical trials and led to the discontinuation of one subject (one of the SAEs). A previous analysis of BP outliers (NDA review p.50) did not suggest an increased risk of elevated blood pressure associated with oxcarbazepine. Considering the conflicting evidence of increased AE risk with no increase in

outlier risk, and the small number of events that were serious or led to discontinuation, I do not believe that hypertension requires a warning or precaution statement in labeling.

6.0 Edema and Weight Gain

The sponsor was informed that there appeared to be evidence of an increased risk of edema and weight gain in subjects exposed to oxcarbazepine. They were asked to evaluate this finding and to assess if these events were related to hypertension or hyponatremia.

The sponsor calculated incidence rates for weight increase for the controlled trials. In the monotherapy initiation trials, the incidence of weight increase was 5.53/100PY in oxcarbazepine exposed subjects compared to 5.75/100PY in placebo exposed subjects. In the adjunctive/monotherapy substitution trials, the incidence of weight increase in the oxcarbazepine-exposed subjects was 6.02/100PY compared to 4.32/100PY in the placebo-exposed subjects. The sponsor concluded that the incidence rates did not support a difference in risk for weight increase. Because of the data pooling issues raised above (see Cognitive Neuropsychiatric section) I looked at the risk for weight increase in single studies. In study OT/PE1 (large add-on trial) the incidence of weight increase was 3.7/100PY (7/190PY) compared to 3.5/100PY (3/85PY). Weight increase was reported for 1 oxcarbazepine subject and 1 placebo subject in study 025 (initiation of monotherapy trial).

The sponsor noted that edema was coded to several different preferred terms (ex. edema, generalized edema, peripheral edema, dependent edema, leg edema, etc.). In their evaluation of edema adverse events, the sponsor combined the various edema-related terms and then calculated incidence rates for "edema events" by treatment for the controlled trials. In the monotherapy initiation trials, the incidence of edema related events was 1.75/100PY in oxcarbazepine exposed subjects compared to 5.75/100PY in placebo exposed subjects. In adjunctive/monotherapy substitution trials, the incidence of edema related events in oxcarbazepine exposed subjects was 6.57/100PY in oxcarbazepine subjects compared to 3.46/100PY in placebo treated subjects. The sponsor concluded that the incidence rates did not support an increased risk of edema related events among oxcarbazepine subjects. As was done for weight increase, I looked at the risk for edema adverse events within single studies. In study OT/PE1 (large add-on trial) the incidence of edema related adverse events was 9.5/100PY (18/190PY) compared to 3.5/100PY (3/85PY). An edema related event was reported for 1 oxcarbazepine subject and 1 placebo subject in study 025 (initiation of monotherapy trial).

To assess if edema related events or weight increase were related to hyponatremia or hypertension, the sponsor first identified subjects with edema related adverse events or weight increase adverse events. For these subjects, they determined if any also had a serum sodium <125mmol/L or hypertension related adverse events. In the monotherapy initiation trials, 0/6 with edema related AEs had a sodium <125mmol/L or a hypertension related AE. In addition, 0/19 with weight increase had a serum sodium <125mmol/L or a hypertension related AE. In the adjunctive therapy trials, 3/36 subjects with edema related AEs had a serum sodium <125mmol/L and 1/36 had a hypertension related AE. Also, 1/33 subjects with a weight increase AE had a serum sodium <125mmol/L and 1/33 had a hypertension related AE. The sponsor concluded that there did not appear to be clear evidence of an increased incidence of hyponatremia and/or hypertensive related events in patients with edema or weight gain in oxcarbazepine treated patients.

Discussion

Looking at both pooled and single study analyses, there did not appear to be an increased incidence of weight increase for oxcarbazepine. From the sponsor's pooled analyses there did not

appear to be an increased incidence of edema in initiation of monotherapy trials nor was there evidence of increased risk within study 025. Oxcarbazepine appeared to be associated with an increased risk of edema events for the pooled adjunctive/monotherapy substitution analysis and within study OT/PE1. Neither hypertension nor hyponatremia appeared to be strongly associated with edema or weight gain adverse events.

7.0 Lupus-like reaction

The NDA contained reports of lupus-like reaction in oxcarbazepine exposed patients and the sponsor was asked to further evaluate these events. They reviewed their databases and identified 1 lupus like reaction in 3,053PY in the primary database, no such reactions in the Pre-GCP database or Named Patient program, and 2 reports in 200,000PY of post-marketing use. The sponsor provided an estimate of the background prevalence of SLE in the general population of 10-59/100,000 and stated that drug-induced lupus represents less than 5% of all cases. They used this information to estimate a prevalence of drug induced lupus of 0.5 to 2.5 per 100,000. They calculated an incidence rate for the primary database of 33/100,000 PY (95% CI 0.8-182). Their reporting rate estimate for the spontaneous report database was 1/100,000PY (95% CI 0.1-1). They concluded that these rates were not higher than the overall estimate for the general population.

The sponsor provided additional details for the cases they identified as lupus. For the case from the primary database, the subject was taking oxcarbazepine and carbamazepine at the time of the event (carbamazepine has been suspected as a cause of drug induced lupus). Both drugs were discontinued and the patient's condition improved. The spontaneous reports were less detailed. One of the cases did not resolve after withdrawal of oxcarbazepine and therefore the drug was re-started. The other case was anti-histone + and resolved with discontinuation of oxcarbazepine. Three additional cases with mention of lupus (discoid lupus, LE rash, lupus like eruption) but little supporting information were also present in the post marketing database (see NDA review) but the sponsor did not included these cases in the rate calculation.

Discussion

In their analysis, the sponsor compares the incidence of drug induced lupus to an estimated background prevalence. The accuracy of their background estimate is questionable since it is derived by multiplying the estimated percentage of SLE cases due to drug by the prevalence of SLE, but I could find no other estimates of risk for drug induced lupus. In any case, the incidence of SLE in the primary database (based on 1 case) exceeds the sponsor's estimated prevalence and the spontaneous reporting rate (based on 2 cases) is near the prevalence. The use of concomitant suspect medications in the primary database case complicates our interpretation of the relationship between oxcarbazepine and this event. The lack of improvement following discontinuation of oxcarbazepine in one of the spontaneous reports is not consistent with drug induced SLE. The remaining case from the spontaneous report database is consistent with drug induced SLE. There is insufficient evidence to conclude that oxcarbazepine causes drug induced lupus. The sponsor's inclusion of this event in the labeling as an event observed during therapy appears appropriate.

8.0 Serious Skin Reaction

The sponsor was asked to provide a risk assessment for serious skin rashes including SJS and TEN. They noted that in their primary database with approximately 3,000 person years of exposure to oxcarbazepine there were no cases of Stevens-Johnson Syndrome or Toxic Epidermal Necrolysis. They provided a comparison by treatment of the incidences of skin rashes that were SAEs in their primary database. The following table summarizes the information provided by the sponsor.

Incidence rates of SAE Skin Reactions by Treatment in the Oxcarbazepine database

Treatment	N	Patient Years exposure	# with serious rash	Incidence per 100PY
Oxcarbazepine	2,486	3,053	14	0.46*
Phenytoin	240	201	5	2.49
Pheobarbital	52	54	1	1.84
Carbamazepine	134	97	1	1.03
Valproic Acid	121	111	0	0
Placebo	419	133	0	0

*Sponsor had calculated incidence as 0.29/100PY

The sponsor felt that the rate of serious skin rashes with oxcarbazepine compared favorably with the rates for the other anti-epileptic medications studied in the primary database.

The sponsor provided estimates for the background incidence of Toxic Epidermal Necrolysis (0.4-1.2 per 1,000,000PY) and Stevens-Johnson syndrome (1.2-6/1,000,000PY). They identified one case of Stevens-Johnson syndrome in an oxcarbazepine treated subject from the Named patient Program and calculated an incidence of 200/1,000,000 person years based on this one case.

Named Patient program case
The following is a time-line presentation of events occurring in the case of SJS from the Named Patient Program database.

2/91 started treatment with diphantoine (narrative mentions he had previously been treated with carbamazepine and noted a rash severity not described.
12/5/91- Subject developed bronchitis
12/7/91- treatment begun with intravenous Augmentin through 12/9/91
12/7/91 Status epilepticus treated with clonazepan .5mg i.v. and diphantoine 500mg i.v., 250mg i.v.
12/8/91 Started on oxcarbazepine
12/9/91-12/23/91 treatment with p.o. Augmentin
12/12/91 developed edema, facial rash, bullous eruptions, desquamation, oral mucosal involvement. Oxcarbazepine discontinued and the subject recovered.

The description is consistent with Stevens-Johnson syndrome although the report did not mention the extent of skin involvement. Oxcarbazepine and Augmentin were initiated just prior to the event. According to the information provided by the sponsor, oxcarbazepine was discontinued while Augmentin was continued and the patient recovered.

Post-marketing Spontaneous reports
In an estimated 200,000 person years exposure the sponsor identified 1 spontaneously reported case of TEN and 2 cases of Stevens-Johnson syndrome. Those cases are summarized below.

An 8-year-old female patient on Trileptal 300mg/day for 16 days and co-medication with Orfiril (valproate) and Duphalac (lactulose) was reported with a Stevens-Johnson syndrome. The description specified erythema and bullae on neck and trunk, lips, and oral cavity had lesions. Trileptal was discontinued; intravenous nutrition was administered, in addition steroids and Zinacef for local treatment of the lesions. The outcome was reported as "recovery".

A 26-year-old female patient on Trileptal 900mg/day for 10 days was reported with Stevens-Johnson syndrome. The patient presented with a generalized bullous erythema, edema of the lip, erosions of the