CLINICAL REVIEW

Application Type	NDA
Submission Number	21-014 (S-013) & 21-285 (S-008)
Submission Code	SE5
Letter Date	12/13/04
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Reviewer Name	Norman Hershkowitz, MD, PhD
Review Completion Date	6/14/05
Established Name	Oxcarbazepine
(Proposed) Trade Name	Trileptal
Therapeutic Class	Anticonvulsant
Applicant	Novartis
Priority Designation	Priority
Formulation	Tablets and Oral Suspension
Dosing Regimen	BID
Indication	Partial Seizures
Intended Population	Pediatric: 1 month to 17 years

1 EXECUTIVE SUMMARY

Recommendation on Regulatory Action

Approvable. See below:

- Trileptal is presently approved for the monotherapeutic treatment of partial seizures in the pediatric population down to the age of 4 years old. Because of the absence of monotherapy trials in the pediatric population for this indication, its labeling has been based upon Pharmacokinetic/Pharmacodynamic (PK/PD) analysis of data from adjunctive therapy and monotherapy adult studies as well as an adjunctive pediatric study. The present monotherapy trial (protocol 2339), which examined patients 1 month to <17 years of age, however, failed to demonstrate a therapeutic effect. This failure is likely a result of design flaws, some of which resulted from limitations in design because of ethical restrictions. There is no scientific reason to believe that if this drug is effective as adjunctive treatment in a pediatric population and as monotherapy and adjunctive therapy in an adult population that it should not also be effective as monotherapy in children. Because of this the drug should maintain its labeling for monotherapy in children. The dosage and indication labeling should be restricted to previous PK/PD analysis.
- Trileptal is presently labeled for adjunctive treatment of partial seizures in the pediatric population down to the age of 4 years old. These data were based upon a prior pediatric study reviewed by the FDA as part of this agent's original approval. The present submission has provided substantial evidence to extend Trileptal labeling for adjunctive therapy for partial seizures down to the age of 2 years old. Although the study providing this evidence (protocol 2340) included patients as young as 1 month, a subgroup analysis failed to find a consistent therapeutic effect below the age 2 years. Dosing information for patients 2 to 4 years old should be based upon the regimen used in the new adjunctive trial.
- There was no evidence that Trileptal possesses any additional safety concerns other than those already described in the labeling for the pediatric population.

Recommendation on Postmarketing Actions

1.1.1 Risk Management Activity

No risk management actions are taken as a result of this submission.

1.1.2 Required Phase 4 Commitments

There are no required phase 4 commitments.

1.1.3 Other Phase 4 Requests

This reviewer would recommend a PK/PD analysis to determine pediatric monotherapy dosing in children 2 to 4 years old

Summary of Clinical Findings

1.1.4 Brief Overview of Clinical Program

Trileptal (oxcarbazepine) is presently indicated as monotherapy or adjunctive therapy in adults and children 4 to 16 years old with partial seizures. Prior adjunctive therapy approval is based upon a placebo control trial in pediatric patients who were predominately ages 4 to <17 years old. Prior monotherapy approval was based upon a previous PK/PD analysis of available information (see above). The present submission includes two pivotal efficacy/short term safety trials: a monotherapy study that examines patients 1 month to <17 years and an adjunctive therapy study that examines patients 1 month to <4 years. Ninety two patients were examined in the former study and 128 patients were studied in the latter study. Additional safety information was derived from 7 more open label studies, some of which were long term, accounting for 234 patients exposed to Trileptal. Also included in this submission was a brief review of pertinent literature and pediatric postmarketing reports.

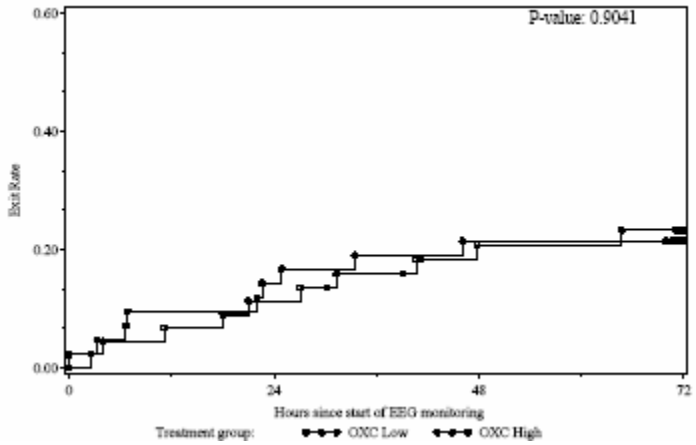
1.1.5 Efficacy

As described above, two efficacy trials were performed. Both were rater-blinded, multi-center, parallel-group, randomized low/high dose comparison studies for pediatric patients with seizures of partial origin.

- **Trial 2339 (monotherapy)**
    - **Design:** Trial 2339 examined Trileptal monotherapy in patients from 1 month to <17 years old. Patients were either with newly diagnosed or were presently on monotherapy. Patients were required to have 2-30 partial seizures during a 7-day pre-randomization period. The primary endpoint was the time to meeting specified exit criteria based upon a central rater blinded (investigational staff was not blinded) reading of a 72-hour video-EEG. To be identified as a partial seizure, the seizure was required to have an EEG (for at least 20 seconds) and behavioral manifestation. These seizures are referred to as Study Seizure Type 1

(SST1). Exit criteria included one of the following: 1) three "Study Seizure Type 1" (SST1) seizures with or without secondarily generalized seizures or 2) a prolonged SST1 seizure with an electrographic duration of at least 5 minutes. Secondary endpoints included percent of patients meeting exit criteria and the number of any partial seizure as determined by electrographic manifestations alone. The study compared patients receiving a low dose of Trileptal (10 mg/kg/day) with those receiving a high dose. High dose patients were to be titrated over a 4 to 5 day period up to 60 mg/kg/day (no greater then 2400 mg/day in any one patient). Dosage adjustments were permitted depending upon the discretion of the investigator. Patients included both those with newly diagnosed epilepsy and those with a history of epilepsy who were presently treated for seizures. Patients were admitted to an investigational unit on day 1 at which time low dose control was started or high dose titration was initiated. Concomitant anticonvulsants were withdrawn on day 1 and day 2 and high dose titration was completed on day 4. Video-EEG was begun on day 3 and continued to day 5 at which time the study was completed.

- **Results:** Survival curves for patients in the two treatments meeting exit criteria based upon the primary endpoint is presented in the figure below. There was no difference between the two groups (p=0.90; Cox regression model). Secondary endpoints were not found to be statistically different. It is noteworthy that over half of patients experienced no seizures during the observation period. No therapeutic trend or significant differences were observed in the other secondary endpoints.



- **Discussion:** This study failed to demonstrate a difference between high and low dose groups. This failure is likely a result of design flaws, some of which result from ethical limitations in design. Efficacy cannot be concluded from this study. There are, however, no scientific reason to believe that if this drug is effective as adjunctive treatment in a pediatric population and as monotherapy and adjunctive treatment in an adult population that it should be effective as monotherapy children. Design flaws included: 1) possible unanticipated high efficacy of the Trileptal low dose, 2) anticipated exit rates were overestimated because of differences in

patient populations and methods of measuring seizures, 3) because of the latter, observation time should have been longer, 4) the time permitted for the titration off prior anticonvulsant therapy was insufficient to allow adequate washout in some patients.

- Trial 2340 (adjunctive therapy)
  - **Design:** Trial 2340 examined Trileptal adjunctive therapy in patients from 1 month to <4 years old. Patients were required to be on 1 or 2 anticonvulsants and have 2 SST1 type seizures (see above) during a 24-72 hour baseline video-EEG monitoring period. The primary endpoint was the absolute change in frequency per 24 hours from baseline in SST1 seizures during 72 hour experimental video-EEG monitoring. The secondary endpoints included:1) percentage change in SST1 frequency per 24 hours from baseline, 2) absolute change from baseline in the frequency of all electrographic seizure 3) Response to treatment (e.g. patients with a 50 % response reduction in seizures). Patients in the low dose group received 10 mg/kg/day for 6 days as an outpatient and was subsequently evaluated as an inpatient by a 72 video-EEG. Patients in the high dose group were treated as an outpatient for 32 days with a flexible dosing schedule. The dose started at 10 mg/kg/day and was followed by a slow upward titration to 60 mg/kg/day as tolerated. Down titration was permitted for reasons of tolerability. Patients were subsequently admitted for a 72 video-EEG monitoring. Concomitant anticonvulsants were maintained throughout the study.
  - **Results:** Examination of the primary endpoint revealed a statistically significant (p=0.043; Rank Analysis of Covariance) greater absolute reduction in the numbers of seizures from baseline in the high dose as compared to the low dose group. Thus, the mean $\pm$ S.D. changes in absolute seizure number for low and high dose groups were -2.8$\pm$ 16.0 and -7.6$\pm$ 17.4, respectively. There was also a statistically significant greater reduction in the high dose as compared to the low dose treatment group in the secondary endpoints of the percentage change in the SST1 frequency from baseline and absolute change from baseline in all electrographic seizure. A therapeutic trend was observed in the 50% response rate, but this was not found to be statistically significant. A statistical examination of the data by this division revealed that the baseline seizure frequency was a factor in seizure reduction (the higher baseline seizure frequency the greater absolute reduction in seizure frequency following treatment). As a result, this division performed a statistical analysis of residuals using a regression analysis. Changes in absolute seizure frequency and residuals are presented in the table below. The p-value is based upon analysis of the residuals. As apparent from the p-value and magnitude of difference between the high and low dose residuals, when baseline frequency was factored in little, little or no difference can be appreciated between low and high dose groups for patients under 24 months. An obvious therapeutic effect is seen for older children.

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Age Group	Low Dose		High Dose		Nominal p-value
	Mean (SD)	Median	Mean (SD)	Median	
< 6 months					
n	7		10		
Change	-11.75(20.18)	-3.50	-8.62 (8.61)	-6.78	
Residual	0.02 (3.64)	-1.37	-0.02 (2.32)	-0.60	.9762
6 months to < 12 months					
n	12		12		
Change	-5.84 (13.01)	-3.65	-4.69 (10.06)	-0.98	
Residual	0.26 (6.49)	-2.16	-0.26 (5.15)	-2.93	.8218
12 months to < 24 months					
n	16		18		
Change	0.08 (24.16)	-0.92	-9.93 (22.92)	-2.28	
Residual	0.17 (8.23)	-2.78	-0.15 (6.65)	-2.98	.8962
24 months to < 48 months					
n	22		19		
Change	-0.37 (4.22)	-0.57	-6.68 (19.13)	-1.97	
Residual	3.88 (11.83)	1.39	-4.49 (9.59)	-4.43	.0204

- **Discussion:** A previous study, reviewed by this division as part of initial NDA application, led to Trileptal labeling for adjunctive treatment of partial seizures in children 4 years and older. The present study demonstrated an effect in a group of patients from 1 month to < 4 years. However, when patients were sub-grouped by age and corrected for a baseline effect little or no effect was appreciated for children <2 years old. This reviewer recommends the extension of labeling for adjunctive treatments down to 2 years old.

1.1.6 Safety

- **Database:** Safety database consisted of 337 patients exposed to Trileptal. Greater then 60% of these patients were exposed to a period equal to or exceeding 3 months and greater then 40% of patients had exposures equal to or greater then 6 months. Seventy two percent of patients in the safety database were < 4 years of age and 47 % were <2 years of age. It is noteworthy that the database for the

initial submission of this NDA, which led to approval, contained a total of 581 patients between the ages of 6 and 17 and 21 patients younger than 6 years old.[1]

- **Deaths:** Five deaths were noted in the database. There was a predominance of deaths (n=3) that were related to respiratory pathology: e.g. "pneumonia," "bronchoaspiration," and "pneumopathy secondary to an increase in seizures." These were not thought to be drug related as studies have demonstrated that pneumonia is a common cause of mortality the pediatric population with epilepsy. Moreover, underlying neurological pathology in these patients (e.g. encephalopathy) likely contributed to a respiratory risk. The remaining two cases appear to be also related to the seizure disorder (sudden death 2 ½ weeks following seizure surgery and death due to progression of seizure disorder, 8 months after drug was discontinued).
- **Serous Adverse Events:** The most common serious adverse events included convulsions and status epilepticus. Both of these would be expected for the present population. Pneumonia was an also common serious adverse event. As noted this is not uncommon in the present population and likely was not a result of drug treatment. Comparison of dose relation in controlled studies suggested a slightly higher rate in for these common serious adverse events in patients receiving high doses. This, however, was likely the result of an unbalanced database. Thus, high dose patients in protocol 2340 were exposed for a longer time period then those in the lower dose group (compare 35 days Vs. 9 days or high and low dose groups, respectively). It is noteworthy that patients with pneumonia had other risk factors for pneumonia and, with one exception, was not associated with a reduction in white cells. Even in the latter case white cell reduction was borderline.
- **Discontinuations:** Nervous system causes appeared to be the most common reasons for discontinuation from the trial. Seizures were a common cause under this rubric and not unanticipated. Also commonly observed was discontinuation from tremor, somnolence and ataxia. The rates of withdrawal from these events were actually less then the prior NDA database. Withdrawals from skin reactions were also commonly observed, but again the rates observed in the present study are no greater then that observed in the prior NDA database. Moreover, no serious skin reactions were observed: i.e., there were no cases of Stevens-Johnson syndrome, toxic epidermal necrolysis or erythema multiforme. One case of dropped out because of transaminase elevation (GOT and GPT approximately 4 X upper normal limit) was noted. Bilirubin was not noted to be elevated in this case. Transaminase returned to normal following drug discontinuation. Similar cases were reported in the original NDA.
- **Special Adverse event analysis:**
    - **Hyponatremia:** Hyponatremia is a commonly observed adverse event associated with Trileptal. The incidence of hyponatremia in the present pediatric population (0.6% based upon Na<125mM) on the whole was somewhat less then prior adult populations (2.5 %). Hyponatremia,

1 See the original safety review by Dr. Gerard Boehm 7/23/99.

however, appeared more common in children < 2 years of age then those > 2 years of age.

- **Cognitive Effects:** The Sponsor performed a study to compare cognitive affects of Trileptal with other anticonvulsants in patients with partial epilepsy. The primary endpoint was "Computerized Visual Searching Task (CVST)." Other cognitive secondary endpoints were also examined. There was no significant difference in the change in primary endpoint and most secondary endpoint when Trileptal was compared to other anticonvulsants. These results can only be considered tentative as it is beyond the scope of the present review to examine the clinical value of such endpoints and the power of the analysis.
- **Cardiac Intervals:** Because of the absence of cardiac interval information the Sponsor was requested to incorporate an analysis of routine EKGs obtained in the present studies. The Sponsor performed such an analysis in children < 4 years. No significant prolongation was noted for mean QTcB or QTcF intervals. No patient experienced a QTcB or QTcF greater then 500 msec. As these studies were not designed to examine EKG intervals, the absence of effect is helpful but not definitive.

- **Common Adverse Events:** Common adverse events in the complete submission database included those related to infections (e.g. upper respiratory tract infection, nasopharyngitis, otitis media, cough, pneumonia etc.), central nervous system symptoms (somnolence, ataxia, irritability, dizziness, fatigue and headache), GI disturbance (vomiting, constipation and diarrhea), rash and convulsions. Because of the unbalanced nature of the study (described above) and the use of a low dose control it was difficult to attribute drug causality to these adverse events. In general one should defer to previous long term pediatric placebo controlled studies for a definitive attribution of causality. However, convulsions are probably related to the underlying disorder and infections likely represents background infection rate for this population. Of interest, the incidence of common adverse events described in the present study was generally lower then the rates for the same adverse described in the present label for pediatric patients that were based upon previous reviewed controlled studies.
- **Clinical Laboratories**
  - **Hematology:** In minor outlier analysis increases in total WBCs were observed in some patients and appeared transient in nature. These were considered to have resulted from the occurrence of infections. Consistent with this, transient increases in lymphocyte count was also noted patients. Small reductions in neutrophils count were also noted in minor outlier analysis. These did not appear to be clinically significant. Thus, only one was reported as part of a serious adverse event (pneumonia) with absolute neutrophils being only borderline low. Drug was continued following resolution of the pneumonia. Neutrophile outlier analysis failed to indicate a signal for significant blood toxicity.
  - **Clinical Chemistry:** Issues relative to serum sodium are discussed above. In minor outlier analysis 3 patients exhibited elevation in bilirubin. These were minor in magnitude and transient and/or either not associated with

transaminase elevation or small transaminase with alkaline phosphatase elevations. Small elevations were observed in transaminase in a small number of patients. Only two were reported as part of a serious adverse event. One case involved a very minor increase in transaminase without bilirubin elevation associated with an increase in seizures. The elevation in transaminase resolved with drug continuation. Another case involved elevation of transaminase by 4 fold but bilirubin was normal Trileptal was discontinued and transaminase returned to normal. These data do not suggest a strong signal for hepatotoxicity and such reports do not differ greatly from those reports previously described in the prior NDA.

1.1.7 Dosing Regimen and Administration

- **Monotherapy:** Because of the failure to identify an adequate monotherapy dose in patients in present study, this reviewer recommends that the present labeled dose, based upon a PK/PD analysis, should remain unchanged.
- **Adjunctive:** Adjunctive treatment should be limited to patients 2 and above. Recommendations for ages 4 and above can remain as presently labeled. Patients 2 to 4 labeling should be based upon the present positive trial. That is, dosing should be initiated at a 10 mg/kg/day (divided BID). This may be titrated over a period of approximately 4 weeks to a desired tolerated therapeutic dose with an approximately 10 mg increment every 5 days. The maximal dose should not exceed 60 mg/kg/day.

1.1.8 Drug-Drug Interactions

There was no additional data on drug-drug interaction in the present submission.

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John Feeney
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