June 29, 2005

This review contains track change notations of information that the reviewer received late from the Sponsor. The added information is underlined. There is no significance to the underlining other than the fact that the information was added to the original version of the review.

CLINICAL REVIEW

Application Type	NDA
Submission Number	21-014 (S-013) & 21-285 (S-008)
Submission Code	SE5
Letter Date	12/13/04
Stamp Date	12/13/04
PDUFA Goal Date	6/14/05
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 (b) (4)

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1 EXECUTIVE SUMMARY

Recommendation on Regulatory Action

- 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 pertinent literature and pediatric postmarketing reports.

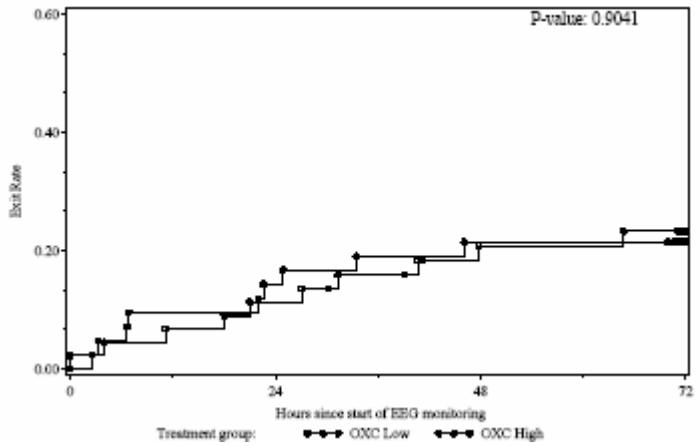
1.1.5 Efficacy

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 ± 16.0 and -7.6 ± 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.

Age Group	Low Dose Mean (SD)	Low Dose Median	High Dose Mean (SD)	High Dose Median	Nominal p-value
< 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, lead to Trileptal labeling for adjective 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

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

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, 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. (b) (4) 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.

2 INTRODUCTION AND BACKGROUND

Product Information

Oxcarbazepine (Trileptal: OXC) is an anticonvulsant, chemically related to carbamazepine, and presently manufactured under the brand name of Trileptal. It is available as tablets and oral suspension. The studies were submitted as part of a pediatric written request to support pediatric adjunctive treatment 1 month to <4 years and monotherapy treatment 1 month to < 17 years old.

Currently Available Treatment for Indications

Trileptal is presently labeled for monotherapy and adjunctive therapy in the treatment of partial epilepsy in adults and children (ages 4 to <17 years old).

Availability of Proposed Active Ingredient in the United States

This product was previously approved on 5/25/01 for the treatment of partial seizures in adults for adjunctive and monotherapy treatment and in children 4 years and older for adjunctive treatment. The product was later approved on 8/07/03 for monotherapy treatment of partial seizures in children 4 years and older. The latter approval was based upon PK/PD analysis of already existing data.

Important Issues with Pharmacologically Related Products

The Sponsor has submitted juvenile animal studies. Dr. Fisher, the pharmacology reviewer, notes that no new issues were raised by these studies.

Presubmission Regulatory Activity

The present submission is a response to a pediatric written request. This division met with the Pediatric Exclusivity Board on 3/2/05. It was felt, by this division, that the Sponsor adequately fulfilled the pediatric written request. Appendix G contains the pediatric exclusivity template prepared by this division, and distributed to the Board, that describes, in a point by point fashion, how the Sponsor fulfilled each aspect of the written request.

Other Relevant Background Information

Trileptal is approved in a number of other countries. Its approval in the European Union includes adjunctive and monotherapeutic use in adults and children down to 6 years old. Trileptal is also approved in some countries for generalized Tonic-Clonic Seizures.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

CMC (and Product Microbiology, if Applicable)

Not applicable.

Animal Pharmacology/Toxicology

As per Dr, Fisher, pharmacology toxicology reviewer, juvenile animal studies were submitted and reviewed. There were no safety issues raised by these studies.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

Sources of Clinical Data

Two pediatric studies (23239 and 2340) that utilized a randomized, multi-center, double-blind, age-stratified, parallel high/low dose comparison study was used to examine efficacy and short term safety for monotherapy and adjunctive therapy use. These are summarized in the first table in the section below. An additional 7 open label studies examined short and long term safety. These are described in the second table in the next section. Also included in the safety review was a brief examination of postmarketing as well as a literature review.

Tables of Clinical Studies

The following table describes the two controlled efficacy short term safety studies:

Study no.	Study design	Number of OXC-treated patients / ages	Treatment duration (days)	Oxcarbazepine (mg/kg/day)
[2339]	Randomized, multicenter, rater-blind, age-stratified, parallel-group, two doses of OXC monotherapy	92 1 month to <17 years	5	Low-dose OXC = 10 High-dose OXC = 40 to 60
[2340]	Randomized, multicenter, rater- blind, age-stratified, parallel-group, two doses of OXC adjunctive therapy	128 1 month to <4 years	Low-dose OXC = 9 High-dose OXC = 35	Low-dose OXC = 10 High-dose OXC = 60

The following table describes the open labeled safety studies:

Study no.	Study design	Number of OXC-treated patients / age range	Treatment duration	Oxcarbazepine (mg/kg/day)
[2337]	Open-label, randomized, active-control, multicenter, flexible dose, monotherapy	55 OXC patients / 6 to <17 yrs	6 months	Median: 19.25 Range: 2.3 to 32.2
[2338]	Open-label, age-stratified, tolerability and pharmacokinetics of ascending dose of OXC adjunctive and monotherapy	24 patients / 1 month to <4 yrs	≤30 days	10 to 60
[2338E1]	6-month open-label extension to [2338]	20 patients / 1 month to <4 yrs	6 months	Median: 44.68 Range: 8.2 to 56.6
[2339E1]	6-month open-label extension to [2339]	82 patients / 1 month to <17 yrs	6 months	Median: 37.5 Range: 1.7 to 90.8
[2340E1 [a]]	6-month open-label extension to [2340]	145 patients / 1 month to <4 yrs	6 months	Median: 37.1 Range: 7.9 to 67.9
[2341]	Open-label, age-stratified tolerability study, ascending dose of OXC monotherapy	4 patients / 1 month to <4 yrs	4 to 5 days	10 to 40
[2341E1]	6-month open-label extension to [2341]	4 patients / 1 month to <4 yrs	6 months	Median: 45.7 Range: 28.8 to 59.6

Review Strategy

All trials described above were used for this review. Information from previous studies reviewed by this division in the process of approving this drugs use for adjunctive treatment of seizures in children over 4 years of age were also relied upon for comparison. A brief postmarketing review was also relied upon. Literature was reviewed.

Data Quality and Integrity

The Division of Scientific integrity concluded:

> "Both studies appear to have been well-conducted; there is no indication of any deviation from FDA regulations at either site. All primary efficacy endpoint measurements for all subjects at both sites were verified. There was no evidence of under-reporting of adverse events at either site. Due to the difficulty in accessing the e-CRFs at the Pina-Garza site, study data for 9 subjects (other than primary efficacy and safety data) reported in e-CRFs was not verified against source documents. Overall, however, the data appear acceptable to support an approval decision for the NDA."

Compliance with Good Clinical Practices

No problematic ethical issues were identified.

Financial Disclosures

Adequate financial disclosure was made. Financial disclosure requests were sent out by the Sponsor and all were signed and returned by the investigators. Such forms requested information from investigators and sub-investigators. Based upon information provided by investigators there was no disclosable information by any investigator.

5 CLINICAL PHARMACOLOGY

Dr. John Duan reviewed the present submission.

Pharmacokinetics and Pharmacodynamics.

Oxcarbazepine is rapidly metabolized into its active metabolite, MHD, that accounts for most of its anticonvulsant action. In the following discussion serum concentration refers to this active metabolite.

The clinical pharmacology reviewer noted that based upon population pharmacokinetic modeling, and a comparison between the adjunctive study in present submission and previous studies, that the proposed dosing regimens for adjunctive therapy, which are similar to those in the clinical trials, are considered adequate. Thus, the dosing in the present adjunctive study produced similar concentrations as did previous adjunctive studies that demonstrated a therapeutic effect in both adults and older pediatric population. The weight based dosing in younger pediatric patients tended to be higher because the weight based dosing tends to underestimate clearance in the younger pediatric group: i.e. younger pediatric patients require a greater weight based dose to produce the same concentration.

An evaluation of how well the present monotherapy trial fits into a prior PK/PD analysis for monotherapy was planned. This analysis, however, was not possible because of a number of reasons. Thus, study design did not include a video-EEG seizure frequency. This makes it impossible to perform a percent change in frequency analysis for PD comparison with prior modeling[2]. Moreover the monotherapy study was a failed study.

The clinical pharmacologist performed a quantitative analysis of reasons for the monotherapy failure. That reviwer concluded that the study failed because of design flaws including the overestimation of the background seizure frequency and insufficient time allowed for washout

2 Although not included in the initial study report upon request (see below) the Sponsor provided a median baseline seizure frequency during the baseline 7 day observation period (see below).

from previous anticonvulsants. Some of these design flaws resulted from ethical restrictions. These are described, albeit in a less quantitative fashion, by this reviwer in the integrated efficacy summary.

Because the clinical pharmacologist demonstrated a relationship between the active metabolite (MHD) serum concentration and response (% change in seizure frequency) in an analysis of the adjunctive study, the possibility for a PK/PD bridging approach for children < 4years old monotherapy was suggested.
.

6 INTEGRATED REVIEW OF EFFICACY

Indication

Trileptal is presently indicted for pediatric patients age 4 to 16 as adjunctive and monotherapeutic treatment for epilepsy of partial origin. The adjunctive indication is based upon a prior adequately controlled clinical trial (011). The monotherapeutic claim, however, was based upon a prior pharmacokinetic/pharmacodynamic analysis of prior pivotal adult mono and adjunctive therapeutic trials and the pediatric adjunctive therapeutic trials. The present application, that includes two principal pivotal efficacy trials, is a response to a pediatric written request to examine Trileptal's use, as both mono and adjunctive therapy, for seizures of partial origin in pediatric patients between ages 1 month to 16 years.

6.1.1 Methods

Included in this new efficacy review are the results from two multi-center, parallel-group, randomized low/high dose comparison studies for pediatric patients with inadequately controlled seizures of partial origin for : 1) monotherapy use in patients between ages 1 month to 16 years (study 2339) and 2) adjunctive therapy use in patients between ages 1 month to 4 year (study 2340).

6.1.2 General Discussion of Endpoints

6.1.2.1 Study 2339 (Monotherapy)

The primary endpoint was the time to meeting exit criteria based upon video-EEG confirmed seizures as determined by a central blinded Reader. The central reader identified the occurrence of "Study Seizure Type 1" (SST1) that was defined by all of the following features: 1) a recognizable focal ictal pattern on EEG involving at least two contiguous electrodes which must demonstrate a spatial and temporal evolution consistent with an ictal discharge and be distinct

from the patient's background cerebral electrical activity, 2) an electrographic duration of at least 20 seconds, and 3) a behavioral correlate as observed on video or by a parent/trained site personnel. The exit criteria were defined as: 1) three SST1 seizures with or without secondarily generalized seizures or 2) a prolonged SST1 seizure with an electrographic duration of at least 5 minutes in duration with a behavioral correlate.[3] Because the identification of the occurrence of seizures were necessary in deciding whether the patient would exit the study, the EEGs would be read on a daily bases. Seizures read on days 1 and 2 were not counted in the exit criteria as this period might be considered a loading period (see schedule below). Any patient who needed to discontinue on Days 1 or 2 due to a deterioration of their seizure condition and requiring intervention or who needed to be discontinued on any other day due to other types of seizures intervention, was considered prematurely discontinued and was not considered an evaluable patient. Once the patient meet exit criteria, dropped out or completed the 5 day experimental phase the EEG was sent to a central blinded reader to determine if exit criteria were actually meet and a seizure count would be made.

A second type of seizure was defined for secondary endpoints that were referred to as Study Seizure Type 2 (SST2). This consisted of the first two above noted criteria for SST1 seizures; i.e. same as the SST1 but without the behavioral correlate.

Secondary endpoints included: 1) percent of patients meeting exit criteria based upon SST1 criteria and 2) Any electrographic seizure (SST1 and SST2) per 24 hours during the complete video-EEG monitoring period.

6.1.2.2 2340 (Adjunctive Therapy)

For the purpose of endpoint evaluation seizures were identified and classified (SST1 and SST2) by the blinded reader during the baseline and experimental period in a manner identical to that noted for study 2339. The SST1 and SST2 were defined in the same manner as that used for study 2339. A separate examiantion of seizures, however, was performed by the on-site neurologist for the purpose of the evaluation of eligibility.

The primary endpoint was the absolute change from baseline in SST1 frequency per 24 hours during 72 hour experimental video-EEG monitoring. This was defined as the seizure frequency per 24 hours observed in the video-EEG during the 72 hour maintenance minus that observed during the baseline period.

3 This was changed in an amendment (7/08/03) from partial-onset status epilepticus in an amendment to provide a standard definition to the site personnel and central reader.

The secondary endpoints included:1) percentage SST1 frequency change per 24 hours[4], 2) absolute change from baseline in SST1 + SST2 seizure frequency per 24 hours, 3) Response to treatment characterized by 50, 75 and 100 percent reduction in seizure frequency per 24 hours.

6.1.3 Study Design

6.1.3.1 Study 2339 (Monotherapy)

6.1.3.1.1 Major inclusion criteria included patients:

- 1 month to <17 years of age.
- If female of childbearing age they must be practicing adequate contraception (abstinence was considered acceptable on a case by case evaluations).
- With a diagnosis of partial seizures which can include simple, complex or partial with secondarily generalized seizures (according to the ILAE).
- Who have experienced 2-30 partial seizures during the 7-day Pre-randomization Phase, with no more than six seizures on any one day.
- On a single anticonvulsant 7 days prior to randomization or be newly diagnosed with epilepsy and on no medication.
- With a previous EEG indicting a seizure disorder and brain imaging demonstrating the lack of a space occupying lesion.
- With normal routine clinical lab results that are relatively normal.

6.1.3.1.2 Major Exclusion criteria excluded patients:

- With treatable causes of seizures (e.g. metabolic).
- With a diagnosis of generalized seizure not caused secondarily by generalized focal seizures.
- With a history of status epilepticus within 30 days.
- With a history of functional seizures.
- Who used benzodiazepines within 1 week prior to randomization, zonisamide within 1 month prior to randomization, barbiturates within 1 month (children <3 months of age) or

4 This is equal to $\frac{MFreq - BFreq}{BFreq}$ X 100, where MFreq= 24 hour maintenance frequency and BFreq= 24 hour baseline frequency.

2 weeks (children >3 months of age) prior to randomization, or felbamate within 6 months prior to randomization.

- With serum sodium levels <135 mEq/L.
- With a history of significant medical disease.
- Initially in patients with any history of OXC use. This restriction was later lessened in an amendment for the exclusion of patients who fulfills any of the following profiles: OXC treatment of >4weeks, OXC treatment with doses >20 mg/kg/day, treatment was discontinued because of adverse events, or treatment within 4 weeks of entering the pre-randomization phase.

6.1.3.1.3 Drug Dose

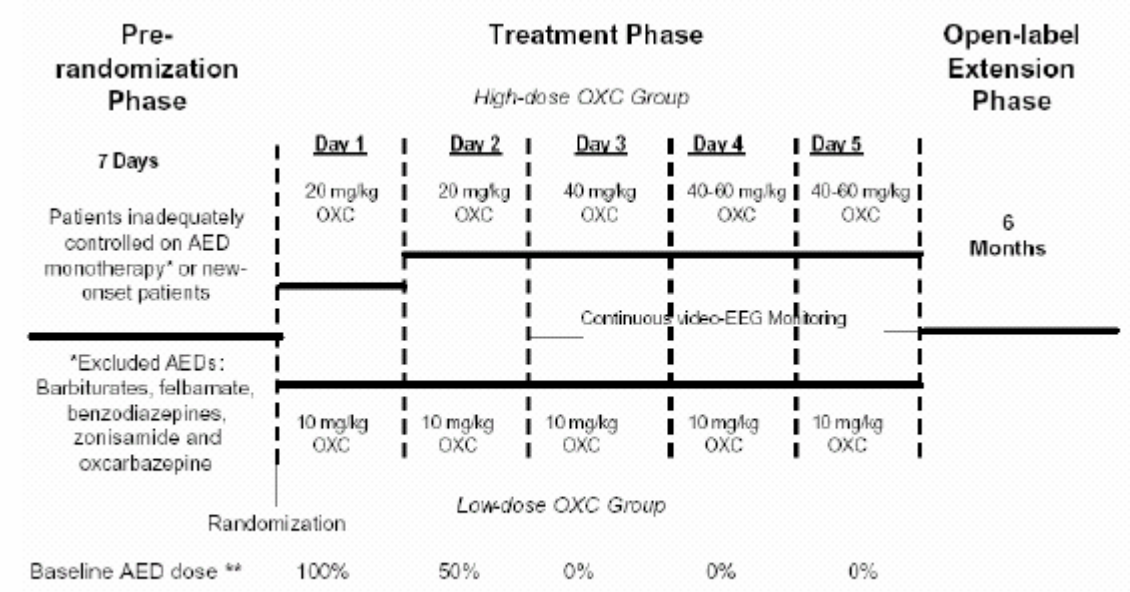
Patients were treated as an inpatient in an investigational unit for a total of 5 days. All doses were administered in a q 12 hour regimen. Patients randomized to the low dose was started on 10 mg/kg/day on day 1 and continued on this dose throughout the study. Patients randomized to the high dose were started on 20 mg/kg day on day 1 and increased to 40 mg/kg/day on day 3 and 40 to 60 mg/kg on day 4 to 5 depending upon the investigators discretion. Dosage reductions of 5 mg/kg/day down to a dose of no less then 40 mg/kg/day were permitted. Patients were to receive no greater then 2400 mg/day. For patients already on an AED, the first day AED was at full dose and subsequently decreased to 50% on day 2 and 0 on days 3 and 5.

6.1.3.1.4 Concomitant Medications

No concomitant AED use was permitted except, as noted above, for patients entering the study with prior treatment. These patients underwent withdrawal from the medication on the first two days: i.e. concomitant anticonvulsant was continued on day 1, the dose was halved on day 2 and then completely discontinued on day 3. This reviewer believes that this is not an ideal design in that some anticonvulsant may still be present but considering ethical limitations in monotherapy studies this can be considered a reasonable option. This is discussed further below.

6.1.3.1.5 Schedule and Study Design

The figure below presents the general treatment design used in this study.



** Not applicable to new-onset seizure patients

The schedule of clinical evaluations is presented in the table below.

Phase	Pre-randomization	Treatment						Post-Taper
Visit	1	2						2.01
Day	-7 days to randomization	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6 or Term	
Written Informed Consent	X							
Inclusion/Exclusion Checklist	X							
IVRS call	X	X					X	
Medical/Neuro/Seizure History/Seizure classification	X							
Complete Physical Exam/ vital signs/Neurological Exam	X						X	
Interim Physical Exam/vital signs/Neurological Exam		X	X	X	X	X		X
ECG	X						X	
Seizure Frequency/Record	X			X	X	X		
Continuous video-EEG Monitoring				X	X	X		
Concomitant Meds/Therapy	X	X	X	X	X	X	X	X
AEDs	X	X	X					X
Adverse Events		X	X	X	X	X	X	X
Routine Laboratory Analyses (Central Laboratory)	X						X	
Urinalysis (Central Laboratory)	X						X	
Serum *B*-HCG Pregnancy Test (females of child-bearing potential)	X							
Urine Pregnancy Test (females of child-bearing potential)	X							
Study Drug Levels of MHD						X	X	
Dispense Study Drug		X	X	X	X	X	X	
Termination Sheet							X	

The pre-randomization phase occurred over 7 days as an outpatient and involved the determination of seizure frequency during this period of time as well as a single visit to obtain history, physical and laboratories needed to determine eligibility criteria (see the above table). If the patient is already on monotherapy during this period the patients continued to receive a stable dose of their anticonvulsant treatment.

Patients were admitted just prior to day 1 and dosing began on day 1. As noted above, this study compared a low and high dose of OXC for the determination of efficacy. While not an ideal design, this required because of ethical considerations. Parents and central reader (an independent pediatric neurologist) was, however, blinded to treatment. Drug was started at admission on day 1 as described above. Video EEG monitoring was started on day 3 of admission into the research unit. Exit criteria also started on day 3. Termination procedures (see the above table, day 6 or term) were performed when the patient completed 5 days of treatment, met exit criteria or were prematurely discontinued.

Patients were discharged after day 5 at which time they could enter the open-label extension phase. In this study, dosage was adjusted to that perceived to be optimal and could be adjusted up to 60 mg/kg/day. Patients prematurely withdrawing or those who did not participate in the open label study were titrated down by a total daily dose reduction of 25% every 3-4 days. Patients were simultaneously started on an alternative anticonvulsant treatment. The post-tapering visit occurred at least 7 days but no more then 3 weeks after the last dose of OXC.

The Sponsor notes that:

> It was not possible to securely blind the administration of study drug in this protocol because oxcarbazepine is only available as a 6% oral suspension with no placebo or lower strength formulations. Therefore this study used a "rater-blind" design. Seizures that were to be counted toward the primary efficacy variable were assessed and recorded by a Central Reader. The Central Reader, an independent pediatric neurologist not involved with the conduct of the study, was blinded to study treatment in order to prevent potential bias during data collection and evaluation of clinical efficacy endpoints. The parents were not to be provided the treatment assignment. The investigator was unblinded to the study treatment in order to monitor patient progress.

This reviewer is not complete agreement that this was the best design of the protocol but it should suffice as the final evaluation is performed in a blinded fashion by the central reader.

6.1.3.1.6 Amendments

Principal clinical issues pertinent to amendments are described below.

Protocol Amendment 1 (28-Jun-2002): The purpose of this amendment was to increase the pediatric age range being studied to include children less than 17 years of age (originally the upper range was to <4 years). This allowed evaluation of monotherapy efficacy in all age groups in which Trileptal was not labeled at that point in time (USA). This amendment also increased the sample size to 100 (originally 88).

Protocol Amendment 2 (08-Jul-2002): The purpose of this amendment was to provide a definition of exit criterion #2, "partial-onset status epilepticus," so both the site personnel and Central Reader would have a standard definition by which to confirm exit of the protocol by this allowed exit criterion. See above discussion in endpoints.

Protocol Amendment 3 (05-May-03): The purpose of this amendment was to increase recruitment because of recruitment problems. It permitted: 1) the inclusion of new-onset seizure patients (i.e., patients recently diagnosed with partial seizures for which they were not currently receiving drug treatment) and 2) the inclusion of patients who had previously been exposed to low-dose, short-term treatment with oxcarbazepine. This amendment also added an exploratory analysis to examine the effect of including new-onset seizure patients in the primary analysis.

Protocol Amendment 4 (9-Feb-2004): The purpose of this amendment was to: 1) change the sample size from 100 patients to 80 patients based upon a statistical power reduction from 90% to 80%, because of recruitment problems (this was accepted by the FDA), 2) Remove wording from the original protocol which referenced the use of baseline seizure counts to be used as an explanatory variable in the primary and secondary efficacy analyses, as these seizure counts were not collected for the study database[5].

6.1.3.1.7 Analysis

The efficacy analysis used the intent to treat population (ITT) that was defined as all randomized patients. Baseline information on age, gender, race, previous monotherapy and ILAE classification were collected but were not analyzed unless there was an indication that they were unbalanced across treatment groups. Gender and whether the patient was previously on monotherapy were investigated (see efficacy findings below).

The primary variable was the time to meeting exit criteria based upon video-EEG confirmed seizures as determined by the Central Reader (see above) starting form day 3. If a patient did not meet the exit criteria (i.e. the blinded investigator disagreed with the termination of the study by the local investigator) the censoring time was the end of EEG. Uninterpretable EEG segments were ignored for this endpoint. An additional analysis was performed on the primary variable using Cox's proportional hazard regression model with treatment and age group (<4 years Vs $\geq$4 years) as explanatory variables.

The secondary endpoint, percentage of patients meeting exit criteria, was compared using Cochran-Mantel-Haenszel (CMH) test blocking on age groups. The percentage of patients meeting exit criteria was also analyzed using a logistic regression model with treatment and age group as explanatory variables. Again, age was divided into <4 years and 4 years or older.

5 Such data, based upon parent/caregiver identification of seizures, was not thought to be comparable to the seizure data collected during the treatment period that used video-EEG identification of seizures.

SST1+SST2 seizure frequencies per 24-hours were compared between treatment groups using the Rank Analysis of Covariance with age as the covariate.

There was no interim analysis.

The final sample size was calculated based on the time to meeting exit criteria using SST1 seizure data. The sample size was chosen to detect a 35% difference between the two treatment groups assuming that 35% of the high-dose-treated patients and 70% of the low-dose-treated patients will meet exit criteria. Given a log-rank test with a significance level of 0.05 and a statistical power of 80%, it was determined that approximately 40 patients per treatment group would be necessary. The assumptions used in the sample size calculation were based on data collected from a study of similar design performed in adults in the oxcarbazepine clinical development program. The population in this study, however, was not completely analogous to that studied in the present study. This issue will be discussed below.

6.1.3.2 2340 (Adjunctive Therapy)

6.1.3.2.1 Major inclusion criteria included patients[6]*:*

- Between 1 month and <4 years.
- With a minimum weight of 3 Kg.
- With a diagnosis of partial seizures which can include simple, complex or partial with secondarily generalized seizures (according to the ILAE).
- With a previous EEG indicting a seizure disorder and brain imaging demonstrating the lack of a space occupying lesion.
- Who have been maintained on a stable dose of one or two anticonvulsant for 7 days prior to baseline and continue to remain on a stable dose throughout the study.
- Who have at least 2 SST1 during the baseline video-EEG monitoring period. The baseline monitoring was discontinued after 24 hours if the patient had 2 or more seizures. If not they were followed for up to a maximum of a total of 72 hours and enrolled if they meet criteria of two seizures.
- With normal routine clinical laboratories.

6.1.3.2.2 Major Exclusion criteria:

These were similar to that of study 2339 except this studies criteria included patients with seizures only occurring in cluster patterns, defined as multiple seizures occurring in less than a 30-minute period.

6 Although similar to study 2339, inclusion criteria are sufficiently different and will therefore be presented.

6.1.3.2.3 Drug Dose

All dosing was divided into two equally divided doses administered approximately every 12 hours. Ten mg/kg/day was considered the lowest minimally effective dose based upon adult adjunctive studies; i.e. it was equivalent to the minimally effective dose of 600 mg/day used in adult study OT/PE1 that compared multiple doses to placebo. For this reason 10 mg/kg/day was used as the starting dose. This dose was maintained throughout the study for the low dose group. Patients in the low dose group were maintained on this dose for 6 days and for an additional 3 days during the video-EEG monitoring period. Ten mg/kg/day was used to initiate therapy in the high dose group and was subsequently titrated to 60 mg/kg/day as tolerated over a period of 26 days in increments of 10 mg/kg/day every 5 days. In case of problems with tolerability, dosage reductions of 5 mg/kg/day were permitted down to a dose if 40 mg/kg/day. Patients were required to be maintained on a stable dose of OXC for a period of 9 days that included 6 days immediately preceding video EEG monitoring and for the full three day period of this monitoring. The high dose was based upon prior pediatric adjunctive study, which was used for the present labeling, that demonstrated that the median effective dose in a, placebo-controlled, flexible dosing pediatric study (age 3-17: study 011) was 31 mg/kg/day, which correlated to the dosing range of 6 to 51 mg/kg/day.

Patients prematurely withdrawing from the study and/or patients who did not participate in the open-label extension phase had their total daily dose of oxcarbazepine reduced by approximately 25% every 3-4 days. Patients were treated with other AEDs during this time. The Post-tapering Visit occurred at least 7 days, but no more than 3 weeks, after the final administration of oxcarbazepine.

6.1.3.2.4 Concomitant Medication

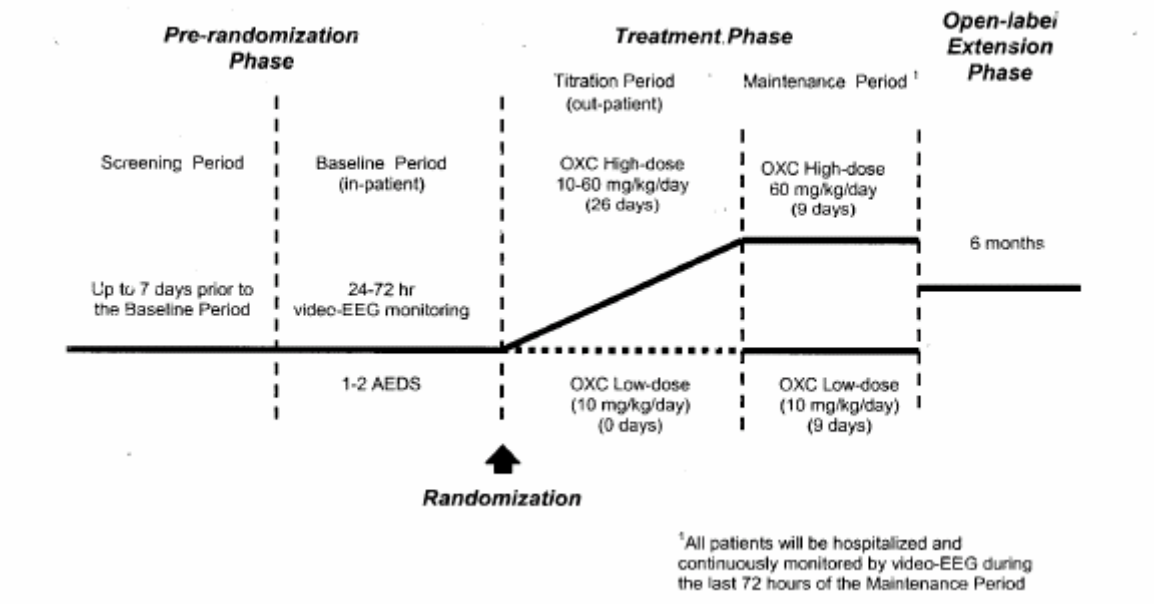
Concomitant anticonvulsants were to be maintained at a stable dose throughout the study. Use of additional medications were “to be avoided wherever possible.” Parents and guardian were to contact the investigators prior to the use of prescription and non prescription medications.

6.1.3.2.5 Study Design and Schedule

This was a multicenter, rater-blinded, randomized, age-stratified, parallel-group adjunctive therapy study comparing a high 60 mg/kg/day) and low (10 mg/kg/day) dose of OXC in pediatric patients, ages 1 month to <4 years old. A total of 128 patients were studied with a 1:1 ratio between experimental groups. Age stratification was as follows: 1 <6 months, 6<12 months, 12 to <24 months and 24 to <48 months. This was rater, but not investigator blinded, as according to the Sponsor “it was not possible to securely blind the administration of study drug in this protocol because oxcarbazepine is only available as a 6% oral suspension with no placebo or

lower strength formulations." Moreover, a low dose, rather then placebo, comparison was made according to the Sponsor because "aside from the technical aspect of the lack of matching placebo, ethical considerations surrounding the use of a placebo or pseudo-placebo treatment in this population are of concern." As a result of this, and noted above, this was a central rater blinded study. The rater was an independent pediatric neurologist not involved in the conduct of the study. Parents were also blinded as to treatment groups.

The study design and schedule of evaluations are presented in the figure and table below, respectively.



Phase	Pre-randomization				Treatment						Post-taper
Period	Screening	Baseline									
Visit	1				2	3	4/Term				4.01
		-3 days to randomization			High-dose group only		Final 72 hours of continuous video-EEG				
Day		-3	-2	-1	10	20	7 or 33	8 or 34	9 or 35	10 or 36 or Term	
Written Informed Consent	X										
Inclusion/Exclusion Checklist	X										
IVRS Call	X			X						X	
Medical/Neuro/Vital/Seizure History/Seizure classification	X										
Complete Physical with vital signs /Neurological Examination	X									X	
Interim Physical with vital signs /Neuro Exam		X	X	X	X	X	X	X	X		X
ECG	X									X	
Continuous video-EEG/hospital stay		X	X	X			X	X	X		
Seizure frequency record		X	X	X			X	X	X		
Concomitant Meds/Therapy	X	X	X	X	X	X	X	X	X	X	X
AEDs	X	X	X	X	X	X	X	X	X	X	X
Adverse Events					X	X	X	X	X	X	X
Routine Laboratory Analysis (Central Laboratory)	X				X	X				X	
Urinalysis (Central Laboratory)	X				X	X				X	
Study Drug Levels of MHD					X	X	X			X	
Concomitant AED Levels	X				X	X				X	
Dispense Study Drug				X			X	X	X	X	
Termination Sheet										X	

The pre-randomization phase consisted of two periods, the Screening Period and the Baseline Period. Screening evaluations (other then EEG) were performed during the Screening Period up to 7 days[7] prior to the Baseline Period. Patients were admitted to the study center during the Baseline Period for a continuous 24 to 72 hour video-EEG. If a patient experienced 2 seizures within the first 24 hours the video-EEG was discontinued and the patient were randomized into the study. Patients not experiencing two seizures were monitored for up a total monitoring period of 72 hours, until they experienced 2 seizures at which time they were randomized. Patients who did not experience 2 seizures were not eligible for this trial.

The treatment phase consisted of an out-patient Titration Period followed by an in-patient Maintenance Period. Patients in the high dose group were titrated as an outpatient for 26 days during the titration Period, prior to admission for the Maintenance period. Patients in the low dose group skipped the titration period and immediately entered the Maintenance Period. Seventy-two hour video-EEG was generally performed the day of admission to the study unit following 6 days of treatment as an outpatient. The starting date was allowed to be extended in case of scheduling issues for an additional 5 days. Patients who required acute seizure management (e.g. rectal diazepam) were permitted to continue in the study. If this was

7 Amendment 1, specific to France, allowed procedures to be performed up to 30 days prior to baseline evaluation. This was added because of great distances and problems with transportation which some patients had who lived great distance from the site of research.

administered within 7 days of the final 72-hour video-EEG the study would be delayed until at least 7 days elapsed between this acute drug treatment and the study. If an additional treatment was required the patients was dropped from the study. Termination evaluations followed the 72 hour video-EEG study r upon early withdrawal.

6.1.3.2.6 Amendments

Protocol Amendment 1 (14-April-2003): This amendment allowed the inclusion of patients who had previously been exposed to low-dose short-term treatment with oxcarbazepine.

Protocol Amendment 2 (10-June-2003): This amendment allowed patients to enter the Open-label Extension Phase of the Study who failed screening because they did not meet the seizure entry criteria (two SST1 seizures) following completion of the Baseline Period (72 hours of video-EEG monitoring).

Protocol Amendment 3 (17-May-2004): This amendment changed the primary efficacy variable from "percent change in SST1 seizure frequency" to "absolute change in SST1 seizure frequency" based on an agreement reached with the FDA during the pre-sNDA meeting on March 24, 2004. The absolute change was chosen as the primary variable in order to avoid the need for the imputation for randomized patients with zero seizures at Baseline. The percent change, which uses the imputation for patients with zero seizures at baseline, was now considered a secondary efficacy variable. The amendment also included clarification of the per-protocol analysis population used in the sensitivity analyses and the response-to-treatment variable for patients with zero seizures at baseline. Note, while there were very definite criteria for finite seizures during the baseline study for entry into the study, this was based upon video-EEG analysis at the site. When the final analysis was performed by the blinded centralized reader there was not complete concurrence and some patients were not found to have adequate seizures for entry based upon inclusion criteria for baseline seizures.

One minor nation specific (France) amendment was made. This is noted above.

6.1.3.2.7 Analysis

The ITT population included patients with both a baseline and treatment video-EEG study. The per-protocol analysis set included ITT patients with the exclusion of patient who had 0 seizures during baseline (this population was used to calculate power). If age, gender, race or ILAE were noted to be unbalanced between treatments groups a Cox regression analysis model, which included the variable, were to be performed.

A sample size of 128 was chosen based upon the ability to discern a 40% difference in mean percentage reduction in SST1 seizure frequency at a power of 85%. Variability determinations

for this calculation were based upon a previous adjunctive study in children (011). This number was based upon the preliminary primary endpoint; the FDA agreed that a recalculation would not be necessary when the endpoint was changed in an amendment (see above).

The primary endpoint (absolute change in frequency from baseline to treatment) was compared between ITT treatment groups using Rank Analysis of Covariance that was stratified by age groups. Analysis was two sided with a p-value of 0.05. A secondary analysis was performed on the per-protocol group.

The following secondary endpoints were analyzed in the following manner:

- Percent change in SST1 frequency per 24 hours was analyzed Rank Analysis of Covariance stratified by age groups with SST1 seizure frequency as a covariate was used. Patients with 0 seizures at baseline was imputed : 1) as 0 percent for those with 0 seizures at maintenance, 2) as the highest observed percent increase change for those with seizures during maintenance. Both an ITT and per-protocol analysis was performed. The analyses was 2 sided with a p-value of 0.05.
- The absolute change in SST1 + SST2 was calculated in the same fashion as the primary endpoint.
- The proportion of patients with different percent responses (see above) were analyzed using Cochran-Mantel-Haenszel (CMH) test blocking on age groups and secondarily with a logistic regression model with treatment, age group, and SST1 frequency as explanatory variables. Patients with 0 seizures during baseline where classified as non-responders.

6.1.4 Efficacy Findings

6.1.4.1 Study 2339 (Monotherapy)

6.1.4.1.1 Patient disposition

Patient's disposition is presented in the table below. As apparent, 92 patients were randomized with 86 completing the study. A but small percent of patients met exit criteria. A slightly larger percent of patients prematurely discontinued in the low dose group, the majority for "administrative problems."

Patient disposition	OXC Low n (%)	OXC High n (%)	Total n (%)
Screened			110
Randomized	46 (100)	46 (100)	92 (100)
Completed	42 (91.3)	44 (95.7)	86 (93.5)
Met exit criteria	10 (21.7)	9 (19.6)	19 (20.7)
Completed 5 days without meeting exit criteria	32 (69.6)	35 (76.1)	67 (72.8)
Prematurely discontinued	4 (8.7)	2 (4.3)	6 (6.5)
Administrative problems	3 (6.5)	0 (0.0)	3 (3.3)
Adverse event(s)	1 (2.2)	2 (4.3)	3 (3.3)

Two patients in each group had protocol violations: one for a history of prior OXC use (prior to amendment 3, one for participation in an investigational study within the past 30 days and two for not being on a stable anticonvulsant dose during the pre-randomization phase. All these patients were included in the analysis. The inclusion of this relatively small number of patients with relatively minor violations would likely not affect the results of the study.

Inclusion in the study was based upon the central reader. Because of unreadable or "corrupt" EEGs, 3 patients (2 in the high-dose and 1 in low dose group), who completed the study, were excluded from analysis. Two (both high dose) of the 6 patients who discontinued did so on or before day 3: these patients are not included in analysis as there is no video-EEG data. Other discontinuations are included in the analysis. This leaves an ITT population consisting of 45 low-dose and 42 high-dose patients.

6.1.4.1.2 Patient Demographics

As noted above there were allowances for dose adjustments for reasons of tolerability. Notwithstanding, there was a rather substantial difference in the dose use between the high and low dose groups. The table below summarizes the dosage used on the last day of study between both experimental groups. This table describes for the safety analysis and not the ITT group.

	OXC Low N=46 N (%)	OXC High N=46 N (%)
<=12 mg/kg	44 (95.7)	2 (4.3)
>12 - 20 mg/kg	2 (4.3)	1 (2.2)
>20 - 37 mg/kg	0 (0.0)	4 (8.7)
>37 - 60 mg/kg	0 (0.0)	33 (71.7)
>60 mg/kg	0 (0.0)	6 (13.0)

MHD (the active metabolite of OXC) were measured on the morning of day 5 before the morning dose and 0.5, 2 or 5 hours post dose, for patients meeting the exit criteria, at the time at which such criteria was meet. Trough serum concentration ranged from 4.64 – 40.2 uM/L and 44.7 to 160 uM/L for the low and high dose groups, respectively. The median values for trough MHD concentrations are presented in the table below. The Sponsor points out that the concentrations achieved in the present low dose study are comparable to the low dose concentrations in adult adjunctive studies that proved to be effective. The median low dose concentration in these adult studies were 17 uM/L. There were no monotherapy dose comparisons to placebo at the dose of 600 mg in adults.

	Low dose (uM/L)	High dose (uM/L)
<4 years	15.4	72.4
≥4 years	22.2	97.8

A total of 49 (53%) patients took concomitant medications. Overall use of concomitant medication was comparable across treatment groups (56% and 50% in the Low-dose OXC and High-dose OXC groups, respectively). There were no substantial differences in use of any such medication between both experimental groups. The most common concomitant medications (> 5% of all patients) used were the anilides (11%, mainly paracetamol) and the antihistamines (8%, mainly dyphenhydramine hydrochloride). No patients received concomitant AEDs except for concomitant benzodiazepine administered to one patient in the high-dose OXC group, who received lorazepam for sedation prior to EEG electrode placement.

A listing of prior anticonvulsant medications are presented below. As apparent most studied patients were on prior medications with carbamazepine being the most common. Use was relatively similar between groups except for slightly greater use of carbamazepine in the high dose group and greater use of levetiracetam and lamotrigine in the low dose group.

Preferred term	OXC Low N=46 n (%)	OXC High N=46 n (%)	Total N=92 n (%)
CARBAMAZEPINE	14(30.4)	18(39.1)	32(34.8)
VALPROATE SEMISODIUM	5(10.9)	5(10.9)	10(10.9)
PHENYTOIN	3(6.5)	4(8.7)	7(7.6)
CLONAZEPAM	1(2.2)	2(4.3)	3(3.3)
PHENOBARBITAL	0(0.0)	2(4.3)	2(2.2)
PHENYTOIN SODIUM	2(4.3)	2(4.3)	4(4.3)
VALPROATE SODIUM	2(4.3)	2(4.3)	4(4.3)
VALPROIC ACID	3(6.5)	2(4.3)	5(5.4)
CEREBREX	1(2.2)	1(2.2)	2(2.2)
LEVETIRACETAM	5(10.9)	1(2.2)	6(6.5)
TOPIRAMATE	2(4.3)	1(2.2)	3(3.3)
ZONISAMIDE	0(0.0)	1(2.2)	1(1.1)
FOSPHENYTOIN	1(2.2)	0(0.0)	1(1.1)
LAMOTRIGINE	5(10.9)	0(0.0)	5(5.4)
LORAZEPAM	1(2.2)	0(0.0)	1(1.1)
SULTIAME	1(2.2)	0(0.0)	1(1.1)

No information is provided by the Sponsor for baseline seizure activity. The inclusion criteria required patients who have experienced 2-30 partial seizures during the 7-day Pre-randomization Phase, with no more than six seizures on any one day. Upon an inquiry from the PK reviewerdr. Duan) the Sponsor notes: “Study 2339 did not have baseline seizures assessed and documented in the CRF. There is no dataset available” (see 21-014 submission 3/29/05). Had the study been a positive study, this information would be important to determine whether groups were well matched. The significance in the case of the failed study is only important in that it may have helped to determine the causes of the failure.

This reviewer pursued this issue further . Thus while a baseline seizure count using a video--EEG monitor was not performed, a baseline count during the pre-randomization period would have been helpful to determine the equivalency of both experimental groups. This information was requested on 6/6/05. The Sponsor responded in an e-mail by stating:

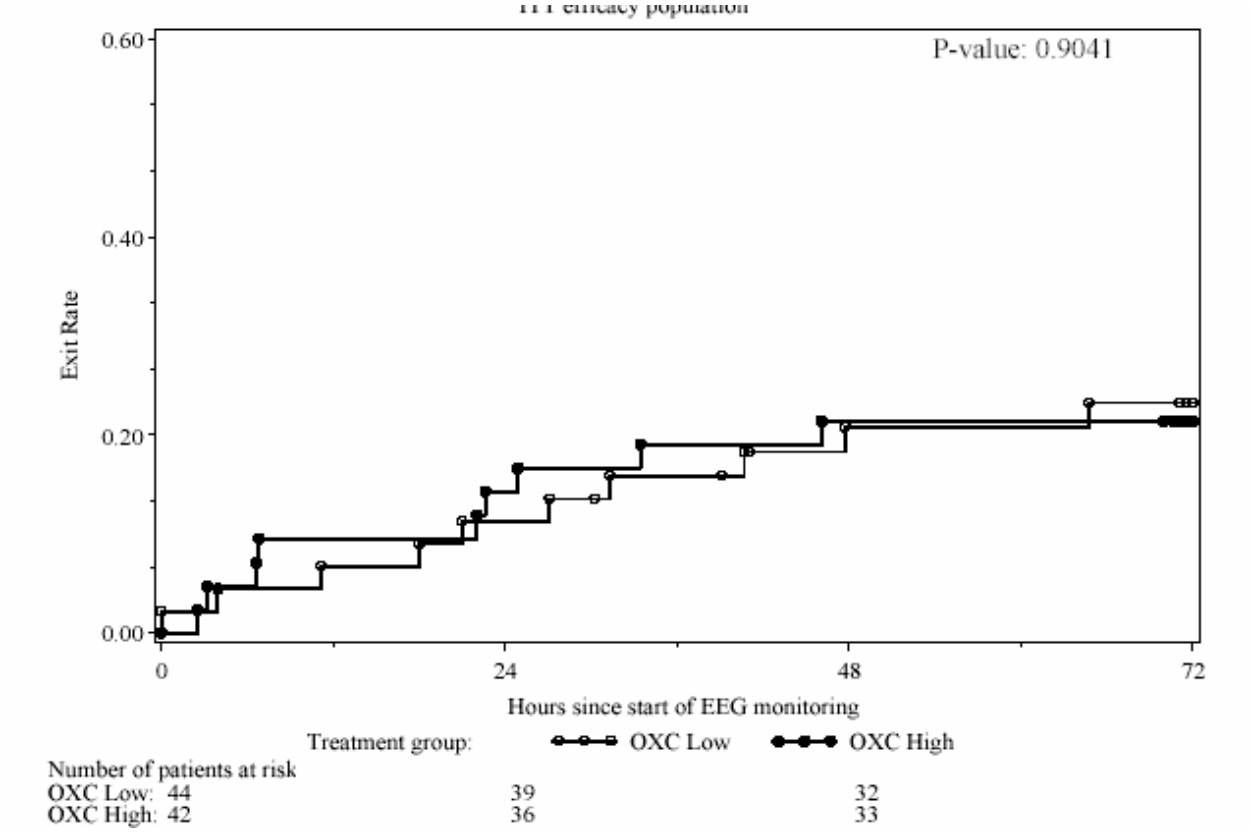
> In an effort to comply with the request for baseline seizure data we retrospectively collected this data from the clinical sites that participated in the TRI2339 study. We have compiled a list of data that was obtained from the investigator sites. The data that was obtained from the sites is not complete and is soft data as the sites were not required to collect this type of data for this study as indicated above. We are providing this data as an attachment for your

The information provided indicated that patients had a relatively low seizure frequency but were approximately equivalent with the low dose having a median of 4.5 seizures and the high dose having median number 3.0 seizures during 7 day pre-dose baseline period.

6.1.4.1.3 Efficacy Results

The figure below presents the time to meeting the exit criteria, the primary endpoint. Only a small percent of patients in both groups met these criteria. One patient in the low dose group discontinued the study immediately after electrode placement. There was little difference

between both groups with a p-value of 0.90 on the log rank test. This p-value was similar to other p-values obtained where the effects of age, gender and initiation of monotherapy (yes or no) were examined through Cox regression models. The Sponsor notes that the exit rates were "much lower particularly in the Low-dose OXC group than the assumed rates of 35% and 70%" for the low and high dose group respectively. As noted above, the predicted rates were based upon an adult monotherapy study that used a survival analysis to compare drug to placebo treatments.



The table below presents a comparison between the percent of patients meeting the exit criteria for each day of EEG evaluation. There was little numerical difference between both experimental groups for each day. No statistical difference[8] was apparent for the day five difference, a secondary endpoint. The p-value was similar to p-values obtained from Cox regression model where effects of age, gender and initiation of monotherapy (yes or no) were further investigated: i.e. none of these factors were identified as affecting the time to meet exit criteria.

8 Using Cochran-Mantel-Haenszel (CMH) test blocking on age groups.

Treatment	By Day 3 (1st day of EEG) n (%)	By Day 4 (1st - 2nd day of EEG) n (%)	By Day 5 (1st - 3rd day of EEG) n (%)
OXC Low (N=45)	5 (11.1)	9 (20.0)	10 (22.2)
OXC High (N=42)	6 (14.3)	9 (21.4)	9 (21.4)
p-value*			0.939

The table below presents total electrographic partial seizure frequency per 24 hours (SST1 + SST2) during the treatment phase, a secondary endpoint. While there is a slightly greater percent in the high dose treatment group it is small and not statistically significant. Half of the patients in both groups experienced no seizures, as indicted by a median of 0 seizures.

	OXC Low	OXC High
N	45	42
Mean	1.0	1.3
SD	2.16	4.33
Median	0.0	0.0
Minimum	0.0	0.0
Maximum	10.1	25.6
p-value*	0.371	

6.1.4.1.4 Summary of Statistical Review Analysis (performed by Dr. S Yan) by the FDA

The FDA statistical reviewer (Dr. S. Yan) concluded that the analysis of the primary endpoints performed by the Sponsor performed was correct.

6.1.4.1.5 Sponsors Efficacy Conclusions

The Sponsor notes that the results of little or no difference between treatment groups were unexpected. They anticipated, based upon an earlier adult placebo controlled pre-surgical study (study 004), that exit rates would be 35% and 70% for the High-dose OXC and Low-dose OXC groups, respectively. These unexpected results were thought to result from a number of factors as follows:

- The Sponsor points out that the low dose may have an unanticipated higher therapeutic effect then was anticipated. They note that from analysis that trough concentrations, in the low-dose group, ranged from 4.64 – 40.2 µmol/L (median 19.0 µmol/L). This is very close to concentrations (range: 1.5 – 41.9 µmol/L, median: 17.0 µmol/L) that were found to be therapeutic in adjunctive adults studies that examined a low dose (600 mg/day) to placebo. The Sponsor notes that the present sample n size was based upon a prior short term in-patient OXC study that compared placebo to an adjusted high dose of OXC (2400 mg/day). In this study over to 80% of patients on placebo meet exit criteria after 5 days. This compares to about 20% on drug. The efficacious low dose in this case may have reduced a difference in effect between the groups.
- The Sponsor also notes that the difference between the uses of historical information for entry criteria and clinical criteria in study for seizure definition may have overestimated expected exit rates in the study. In study seizure criteria required both EEG and behavioral correlate because of the difficulty of identifying seizures in the very young whereas entry criteria only required behavioral rates.
- The Sponsor notes a longer duration study may have allowed the presently designed study to discern differences between both treatment groups.

6.1.4.2 2340 (Adjunctive Therapy)

6.1.4.2.1 Patient Disposition

Patient disposition is presented in the table below. Of the 191 patients screened 63 were not randomized. Fifty four of those who were not randomized were rejected for not meeting the baseline criteria during the baseline monitoring. Of 128 patients randomized 115 completed the study and 13 prematurely discontinued. Five withdrew for reasons of adverse events with little difference between the low and high dose group.

Patient disposition	OXC Low n (%)	OXC High n (%)	Total n (%)
Screened*			191
Randomized	64 (100)	64 (100)	128 (100)
Completed	59 (92.2)	56 (87.5)	115 (89.8)
Prematurely Discontinued	5 (7.8)	8 (12.5)	13 (10.2)
Adverse Event(s)	2 (3.1)	3 (4.7)	5 (3.9)
Subject withdrew consent	2 (3.1)	2 (3.1)	4 (3.1)
Unsatisfactory therapeutic effect	1 (1.6)	3 (4.7)	4 (3.1)

A listing of protocol deviations/violations is presented in the table below. There was a large number such occurrences. The most common were a result of patients who were not stable on a dose of anticonvulsant. Similar rates occurred between both experimental groups. A total of 12 patients were missing a baseline and/or treatment video-EEG and were therefore excluded from the ITT and per-protocol analysis. These were the only patients who were excluded from the ITT analysis. In two cases, data was accidentally deleted by the investigator and in 5 cases patients prematurely discontinued prior to the final video-EEG analysis. An additional 11 patients had 0 seizures during baseline. This occurred more frequently in the high dose group. This disparity results in a more stringent threshold in demonstrating efficacy as patients with zero baseline seizures cannot, by definition, exhibit a post-treatment seizure reduction. These were analyzed in the ITT amended analysis that is described above but were excluded in the per-protocol analysis. A total 116 patients were analyzed in ITT population and 106 in the per-protocol.

	OXC Low N=64 n (%)	OXC High N=64 n (%)	Total N=128 n (%)
At least one protocol violation	21 (32.8)	22 (34.4)	43 (33.6)
Deviations from incl/excl. criteria	12 (18.8)	13 (20.3)	25 (19.5)
History hypersensitivity CBZ treatment	1 (1.6)	0 (0.0)	1 (0.8)
No focal discharges/abnormality on EEG	2 (3.1)	1 (1.6)	3 (2.3)
Not on stable dose of 1 or 2 AEDs	8 (12.5)	10 (15.6)	18 (14.1)
No previous CT or MRI	1 (1.6)	0 (0.0)	1 (0.8)
Did not have 24 hours continuous EEG	0 (0.0)	2 (3.1)	2 (1.6)
Deviations from study procedures	13 (20.3)	12 (18.8)	25 (19.5)
Only 1 SST1 seizure during baseline	2 (3.1)	0 (0.0)	2 (1.6)
Only 0 SST1 seizure during baseline	4 (6.3)	7 (10.9)	11 (8.6)
No baseline &/or treatment period v-EEG	7 (10.9)	5 (7.8)	12 (9.4)

6.1.4.2.2 Demographics

The table below presents general demographic variables for the safety population. As can be observed there was a similar age and sex distribution between both treatment groups. There was a somewhat greater preponderance of persons of “black” race in the high treatment group although the number of patients in this racial feature was small and likely did not influence the results to a large degree. There was also a preponderance of “other” race in the low treatment group. The significance of this is uncertain. The incidences of treatment types were similar between groups except for a slight preponderance of secondarily generalized seizures in the high dose group. Assuming that generalized seizures represent a more sever type of disorder, this disparity would only work against finding a significant effect of the drug.

	OXC Low N=64 n (%)	OXC High N=64 n (%)	Total N=128 n (%)
Baseline Age			
1 - <6 months	10 (15.6)	11 (17.2)	21 (16.4)
6 - <12 months	12 (18.8)	12 (18.8)	24 (18.8)
12 - <24 months	19 (29.7)	19 (29.7)	38 (29.7)
24 - <48 months	23 (35.9)	22 (34.4)	45 (35.2)
Sex			
Male	35 (54.7)	38 (59.4)	73 (57.0)
Female	29 (45.3)	26 (40.6)	55 (43.0)
Race			
Black	3 (4.7)	5 (7.8)	8 (6.3)
Caucasian	42 (65.6)	47 (73.4)	89 (69.5)
Other	19 (29.7)	12 (18.8)	31 (24.2)
ILAE Classification			
Simple partial seizures	20 (31.3)	23 (35.9)	43 (33.6)
Complex partial seizures	46 (71.9)	50 (78.1)	96 (75.0)
Partial seizures, secondarily generalized	24 (37.5)	35 (54.7)	59 (46.1)
Other seizures	18 (28.1)	22 (34.4)	40 (31.3)

Dose distributions between groups are presented in the table below. As noted above, while the target dose in the high dose groups was 60 mg/kg/day, dosage was allowed to downward titrate to tolerance. The doses, however, were to remain stable prior to and during study.

	OXC Low N=64	OXC High N=64
<=12 mg/Kg	62 (96.9%)	0 (0.0%)
>12 - 20 mg/kg	1 (1.6%)	1 (1.6%)
>20 - 37 mg/kg	1 (1.6%)	5 (7.8%)
>37 - 60 mg/kg	0 (0.0%)	50 (78.1%)
>60 mg/kg	0 (0.0%)	8 (12.5%)

This dosing resulted in a median trough MHD concentration[9] of 58.4 µmol/L (range 7.13 – 152 µmol/L) and 9.76 µmol/L (range– 36.6 µmol/L) for high and low dose groups respectively.

9 Measured 12 hours after the last dose administered on the last day of EEG monitoring.

Adjunctive agents present during the study are presented in the table below. Phenobarbital was the most commonly used agents and exhibited similar use across groups. Some agents exhibited some disparity of use between groups (e.g. topiramate) but on the whole the differences were not substantial. While the number of specific benzodiazepines use was different between experimental groups, total benzodiazepine use was similar between groups (low-dose 13 patient and high-dose 10 patients).

Preferred term	OXC Low N=64 n (%)	OXC High N=64 n (%)	Total N=128 n (%)
Phenobarbital	24 (37.5)	24 (37.5)	48 (37.5)
Valproate sodium, Valproate magnesium, Valproate semisodium[1]	8 (12.5)	14 (21.9)	22 (17.2)
Valproic acid	13 (20.3)	13 (20.3)	26 (20.3)
Carbamazepine	6 (9.4)	13 (20.3)	19 (14.8)
Levetiracetam	7 (10.9)	6 (9.4)	13 (10.2)
Topiramate	11 (17.2)	5 (7.8)	16 (12.5)
Vigabatrin	9 (14.1)	5 (7.8)	14 (10.9)
Clonazepam	4 (6.3)	5 (7.8)	9 (7.0)
Clobazam	3 (4.7)	5 (7.8)	8 (6.3)
Phenytoin, Phenytoin sodium [2]	2 (3.1)	5 (7.8)	7 (5.5)
Lamotrigine	6 (9.4)	4 (6.3)	10 (7.8)
Gabapentin	1 (1.6)	1 (1.6)	2 (1.6)
Levocarnitine	0 (0.0)	1 (1.6)	1 (0.8)
Sultiame	0 (0.0)	1 (1.6)	1 (0.8)
Zonisamide	1 (1.6)	1 (1.6)	2 (1.6)
Diazepam	3 (4.7)	0 (0.0)	3 (2.3)
Lorazepam	2 (3.1)	0 (0.0)	2 (1.6)
Ethosuximide	1 (1.6)	0 (0.0)	1 (0.8)
Nitrazepam	1 (1.6)	0 (0.0)	1 (0.8)
Stiripentol	1 (1.6)	0 (0.0)	1 (0.8)

6.1.4.2.3 Efficacy Results

6.1.4.2.3.1 Primary Endpoint

Mean and median changes in the absolute number of seizures from baseline to treatment periods are presented in the table below. A reduction in absolute seizure frequency can be observed. This proved statistically significant based on comparison for the median absolute change between the High-dose OXC group and the Low-dose OXC group from the Rank Analysis of Covariance Model stratifying by age groups with the SST1 seizure frequency per 24 hours at baseline as covariate.

	OXC Low N=57	OXC High N=59	P-value*
Baseline Mean (SD)	13.29 (22.34)	10.27 (17.82)	
Treatment Mean (SD)	10.50 (24.08)	2.67 (4.40)	
Absolute Change Mean (SD)	-2.79 (16.02)	-7.60 (17.38)	
Median Absolute Change	-1.37	-2.00	0.043

A similar result is observed for the per-protocol analysis, which excludes patients who had no seizures at baseline. These results are presented in the table below. The difference between the treatment groups were found to be statistically significant (p=0.044) using the same analysis as that used for the ITT population. As expected this slightly increased the difference between treatments groups as compared to the ITT analysis. This was because a larger number of patients were observed in the high dose treatment group with a zero seizure baseline and patients with a zero baseline are limited to no change or an increased seizures following treatment.

	Low Dose	High Dose
Baseline Seizures $\pm$ SD	14.3 $\pm$ 22.9	11.4 $\pm$ 18.5
Mean Change Mean $\pm$ SD	-3.0 $\pm$ 16.6	-8.5 $\pm$ 18.1
Median Change	-1.7	-2.8

6.1.4.2.3.2 Secondary Endpoints

Patients on high dose OXC exhibited a statistically[10] significant greater reduction in the percent change in seizures then those on low dose in both the ITT (p= 0.047, see table below) and per-protocol (p=0.030) populations. The effect appears more dramatic using each patient's baseline as the comparator for drug effect. This endpoint was the original primary endpoint but was made secondary because the need to obviate imputation. The effect on the percent change is a more commonly used endpoint.

10 Rank Analysis of Covariance model stratifying by age groups.

	OXC Low N=57	OXC High N=59	P-value*
Baseline Mean (SD)	13.29 (22.34)	10.27 (17.82)	
Treatment Mean (SD)	10.50 (24.08)	2.67 (4.40)	
Percent Change Mean (SD)	-12.80 (114.66)	-45.73 (90.36)	
Median Percent Change	-46.18	-83.33	0.047

There was also a statistically[11] greater reduction (in absolute numbers of electrographic seizures (SST1 + SST2) in the high dose group as compared to the low dose groups for the ITT population (see table below).

	OXC Low N=57	OXC High N=59	P-value*
Baseline Mean (SD)	14.03 (23.23)	10.82 (18.06)	
Treatment Mean (SD)	10.77 (24.11)	3.07 (5.11)	
Absolute Change Mean (SD)	-3.26 (16.78)	-7.76 (17.13)	
Median Absolute Change	-1.64	-2.32	0.020

Treatment response, determined by percentage seizure reduction in the ITT population, using various criteria are presented in the table below. While there was greater number of patients meeting all criteria in the high, as compared to the low dose, group, this difference was not statistical significant[12] for the $\geq$ 50 reduction analysis. Other reduction criteria were not evaluated.

	OXC Low N=57 n (%)	OXC High N=59 n (%)	P-value*
≥ 50% Reduction	27 (47.37)	38 (64.41)	0.088
≥ 75% Reduction	19 (33.33)	32 (54.24)	--
100% Reduction	10 (17.54)	19 (32.20)	--

6.1.4.2.4 Sponsors Conclusions

The Sponsor notes that the a superior statistically significant effect was identified in the high dose compared to low dose groups for the primary endpoint along with all secondary endpoint but one, the responder rate. In the latter case, although not statistically significant there was a distinctive trend that suggested a therapeutic effect.

The Sponsor compares the present results to the prior adjunctive pediatric study in an older pediatric population (study 011: 4-17 years old). The prior study examined the percent change in

11 Rank Analysis of Covariance model stratifying by age groups.

12 Cochran-Mantel-Haenszel (CMH) test.

seizure frequency placebo and a drug adjusted to an optimal dose (median daily dose 31 mg/kg/day). Placebo and drug produced a 9% and 35% reduction, respectively, in the prior study. Low and high dose groups exhibited a 46% and 83 %, respectively in the present study. This means that the low dose group (10 mg/kg) exhibited a greater percent reduction then the experimental dose (median 31 mg/kg) group in the prior study. The Sponsor concludes that, "that the low-dose OXC group appears to behave differently than a placebo-treatment group in a similar patient population and may have exerted some effect."

The Sponsor points out that the mean ± SD trough plasma concentrations in the low dose group (12.1 ± 8.7µmol/L) is lower then that observed for the trough (18.3 ± 7.3 µmol/L) in the lowest dose (600 mg daily) that was found effective in prior adjunctive adult studies.

The Sponsor concludes that this adequate evidence to demonstrate efficacy of OXC at the studied dosages as adjunctive treatment in the studied patient population.

6.1.4.2.5 Summary of Statistical Review Analysis (performed by Dr. S Yan) by the FDA

The statistical reviewer confirmed that the analyses of all primary and secondary endpoints performed by the by the Sponsor were correct. The statistician notes that there was a large seizure frequency baseline effect for the Rank Analysis of Covariance used to examine the primary endpoint; i.e. the larger baseline seizure frequency the larger the absolute change in seizure frequency during the experimental period. The statistical examination that demonstrated a therapeutic affect included a correction for this: i.e. examining the residual frequency following the consideration of the baseline effect.

Important information was gleaned from a subgroups age analysis of the primary endpoint performed by the statistician. The statistician noted that the reduction in absolute seizures frequency was dependent on resting baseline; i.e. as noted above, the greater seizure frequency baseline the greater the reduction from baseline to the experimental period. As different groups had very different resting baseline frequencies a comparison of residuals, based upon a regression model, was performed for age subgroup analysis. An analysis of uncorrected changes and corrected in the form of residuals are presented in the table below. The p-value in this table is based upon this correction. As is apparent from this table a nominally statistically significant result occurred only in the older (>24 month) group. A therapeutic effect in younger groups, based upon this residual, was not apparent based upon magnitude of effect and p-value (compare low and high dose residuals) statistically. An analysis of secondary endpoints yielded similar results.

SST1 Seizure Frequency by Age Group (Source: Reviewer's Analysis)

Age Group	Low Dose		High Dose		Nominal p-value
	Mean (SD)	Median	Mean (SD)	Median	
< 6 months					
n	7		10		
Baseline	21.32 (38.06)	6.70	13.56 (12.93)	11.04	
Final	9.57 (18.51)	1.06	4.94 (6.34)	2.68	
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		
Baseline	24.49 (33.51)	10.14	8.83 (8.78)	7.98	
Final	18.65 (33.60)	5.32	4.14 (5.28)	2.00	
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		
Baseline	9.34 (12.73)	3.03	11.25 (22.65)	4.50	
Final	9.42 (31.50)	0.40	1.32 (2.06)	0.62	
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		
Baseline	7.51 (8.51)	6.19	8.50 (19.90)	2.99	
Final	7.13 (9.87)	3.83	1.82 (3.80)	0.00	.
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

Additional subgroup analysis by sex failed to reveal a difference between sexes. Race subgroup analysis by the statistician revealed that the "Caucasian" analysis was similar to the population as a whole. While no effect was apparent in the "black" subgroup in terms of p-value and trends, the sample size (total n of 8) was too small to make any conclusions.

6.1.5 Clinical Microbiology

Not applicable.

6.1.6 Reviewer's Efficacy Conclusions

6.1.6.1 Monotherapy

In the planning for this study the determination of the n size depended upon results from a prior study (04) that examined patients who had been hospitalized for epilepsy surgery. This was a multicenter, double-blind, randomized, placebo-controlled, 2-arm parallel trial of monotherapy OXC. This study was a 10 day inpatient trial for subjects who were being evaluated for seizure surgery. Survival analysis criteria were similar for the present study as compared to this prior study. In the prior study, approximately 20 % of patients meet criteria in the drug group following 3d ays as compared to approximately 80 percent in the drug group. This compares to 20% for both groups in the present monotherapy study.

It should be noted that the difference between the present study and the 04 study cannot be explained by differences in concentrations achieved. Thus, median trough MHD levels calculated for the 04 study, calculated by Dr. Duan of the Clinical Pharmacology team, was lower (47.2µmol/L) then the median level in the present study (93.2 µmol/L). .

As noted above the Sponsor point out that this may have resulted from an underestimation of the anticonvulsant effect of the low does comparison group. Moreover, as the Sponsor points out, the anticipated exit rate was based upon historical criteria (patient's perception) that may have overestimated the survival criteria, based upon expert observation and EEG confirmation.

This reviewer would add that while the study was modeled after the prior in-patient monotherapy trial (04) the actual baseline seizure frequency difference between the populations used in these studies were likely very different. Thus although there was substantial overlap between entrance criteria seizure rate (2-10 seizures/ 2 days in the prior study and 2-30 seizures/ 7 days in the present study) this reviewer believes that given the difference in patients selection that the actual rates of seizures were likely quite different. Thus the present study included both patients with newly diagnosed epilepsy and patient being treated with a single anticonvulsant. Patients in the prior study were those being evaluated for intractable epilepsy and were likely to have a higher baseline rate. Indeed, patients in the present study had 7 day median seizure incidence of 3 and 4.5 seizures in both experimental groups whereas patients in the prior study exhibited a 2 day median incidence of 4.9 and 4.4 seizures. This is a greater then a 3 fold difference.

Another problem in the present study is that about half of patients were on concomitant medications prior to entry. The withdrawal phase was a short time prior to evaluation; i.e. a 2 day rapid withdrawal followed by a 3 day evaluation period. This meant that a number of patients may still have had significant drug levels present, at least on the first evaluation day. This may have decreased the differences between low and high dose survival rates. For instance, carbamazepine was the most commonly used prior anticonvulsant with 30% of low dose patients and 39 % of high dose patients on this medication. The half life of this drug is generally 12 to

17 hours.[13] This would mean that some medication would be present during the first day of video EEG monitoring period.

Ideally, this study may have been designed differently to increase the likelihood of the demonstration of an effect. There, however, a number of limitations, both technical and ethical that make an ideal pediatric monotherapy study difficult.

Thus, as pointed out by the Sponsor, the study may have been improved had had there been a longer observation period. This may have increased the difference between the low and high dose groups. Thus, in a prior low/high dose monotherapy study (026), which compared survival curves in a predominately adult population, the differences in patients exiting was not apparent until about 2 weeks after treatment was initiated. An important caveat, however, is that the exit criteria for the prior study was determined by a different formula then that used in the present pediatric study. However, the ethical propriety of maintaining children on sub-optimal treatment may be questioned. Moreover, it may also be technically difficult because of the need to evaluate young children with continuous video-EEG monitoring.

Alternatively differences may have more easily been discerned with a placebo control. There are obvious ethical reasons that this could not be done.

In view of the previous proven significant therapeutic effects in previous adjunctive treatment studies in children and adults and as monotherapy in adults, this reviewer believes that the lack of effect observed in the present study is a result of study design and not an absence of a therapeutic effect. There is no scientific reason to believe that this drug should not be effective in this population with the prior proven therapeutic spectrum of efficacy.

This reviewer therefore feels that monotherapy labeling should be permitted but a discussion of the present study should be included in the labeling in the labeling. Dosing should be based upon prior PK/PD analysis and not the present study. Like adjunctive treatment, dosing (see below) dosing should be indicated only down to 2 years of age.

6.1.6.2 Adjunctive Therapy

The present study suggests a therapeutic effect of OXC for the treatment of seizures of partial origin in patients less then 4 years of age.

13 But, as this drug is auto-induced patients who were recently started on the medication can have half lives of 25-65 hours

This reviewer (with assistance of Dr Duan of clinical pharmacology) constructed the following table comparing response rates for the prior adjunctive study (011) that examined patients between ages 4 and 17 years old with the present study that examined patients less then 4 years of age. As apparent, and as pointed out by the Sponsor, the low dose in the present study may have produced an effect different from the previous placebo. That is, the percent reduction in seizures with the low dose in the present study was numerically greater then the effect for the drug group in the previous study even though the dose was 3 fold lower. It, however, may not be completely justifiable to compare these two studies. Thus, the means of identifying seizures were different. The present study depended upon expert observation of video-EEG records for a short period of time whereas the prior study depended on patient diaries over a long period of time. Moreover, inclusion criteria where not completely identical: i.e. in one case they were dependent on a given minimal frequency of seizures measured by video-EEG over a short time period and in the other case they were dependent on a different minimal (lower then latter) frequency measured by patient diary.
Nonetheless, both studies indicate an effect of doses of 60 mg/kg/day and less.

	Study 011		Study 2340	
Median Dose (mg/kg/day)	0	31	9.8	58.4
Percent Seizure Reduction (%)	9%	35%	46%	83%

The failure to see a consistent effect in the adjunctive trial across all age groups is of some concern and may indicate a lower therapeutic effect in younger patients. This is consistent with the higher rate of seizures identified as an adverse event in younger patients (see Safety review). These results suggest to this reviewer that OXC should be labeled only for ages of 2 and above.

7 INTEGRATED REVIEW OF SAFETY

Methods and Findings

The summary of clinical safety presented by the Sponsor contains a total of 337 OXC treated patients (60% < 4 years old) with partial seizures who ranged in age from 1 month to <17 years old. These data were derived from a total of 8 completed plus one ongoing study (study 2340E1). These studies included the two randomized blinded low-dose controlled pivotal efficacy studies as well as 7 open label trials that are described in the two tables below, respectively. The Sponsor performed analyses on two overlapping safety groups: group 1 that included all patients exposed to OXC (n=337) and group 2 that included information of patients during the 2 pivotal efficacy trials (n=220). All adverse events were classified according to the MedDRA dictionary using both primary system organ class (PSOC) and preferred term (PT).

Study no.	Study design	Number of OXC-treated patients / ages	Treatment duration (days)	Oxcarbazepine (mg/kg/day)
[2339]	Randomized, multicenter, rater-blind, age-stratified, parallel-group, two doses of OXC monotherapy	92 1 month to <17 years	5	Low-dose OXC = 10 High-dose OXC = 40 to 60
[2340]	Randomized, multicenter, rater- blind, age-stratified, parallel-group, two doses of OXC adjunctive therapy	128 1 month to <4 years	Low-dose OXC = 9 High-dose OXC = 35	Low-dose OXC = 10 High-dose OXC = 60

Study no.	Study design	Number of OXC-treated patients / age range	Treatment duration	Oxcarbazepine (mg/kg/day)
[2337]	Open-label, randomized, active-control, multicenter, flexible dose, monotherapy	55 OXC patients / 6 to <17 yrs	6 months	Median: 19.25 Range: 2.3 to 32.2
[2338]	Open-label, age-stratified, tolerability and pharmacokinetics of ascending dose of OXC adjunctive and monotherapy	24 patients / 1 month to <4 yrs	≤30 days	10 to 60
[2338E1]	6-month open-label extension to [2338]	20 patients / 1 month to <4 yrs	6 months	Median: 44.68 Range: 8.2 to 56.6
[2339E1]	6-month open-label extension to [2339]	82 patients / 1 month to <17 yrs	6 months	Median: 37.5 Range: 1.7 to 90.8
[2340E1 [a]]	6-month open-label extension to [2340]	145 patients / 1 month to <4 yrs	6 months	Median: 37.1 Range: 7.9 to 67.9
[2341]	Open-label, age-stratified tolerability study, ascending dose of OXC monotherapy	4 patients / 1 month to <4 yrs	4 to 5 days	10 to 40
[2341E1]	6-month open-label extension to [2341]	4 patients / 1 month to <4 yrs	6 months	Median: 45.7 Range: 28.8 to 59.6

This division had previously reviewed pediatric data and determined that Trileptal was safe in the treatment of seizures for children of 4 years of age and older. These data were principally derived from studies using adjunctive treatment. This new safety information includes patients 1 month to <4 years old on adjunctive treatment and 1 month to < 17 years old on monotherapy. OXC is already approved, and safety data reviewed, for the use as adjunctive treatment in patients 4 years to < 17 years of age. Subset analysis is performed, as requested in a meeting with the FDA on 3/24/04, for groups <2 years of age, 2 to <4 years of age and >4 years of age.

A review of pediatric post marketing reporting for patients 1 month to <17 years of age is also included in the Sponsors summary.

7.1.1 Deaths

Five deaths were reported for patients in group 1 (patients in all new studies). A summary of these is found in the table below. Zero dose in this table alludes to the fact that two of these patients died after the medication was discontinued: one after only 2 days (0038/00005) and the other (0522/00001) after 8.5 months. Although not provided on the table, the latter was previously on a maximal dose of 78 mg/kg/day and the former was previously on a maximal

dose of 60 mg/kg/day (but subsequently titrated down). Full narrative reports of these cases are contained in Appendix D.

Deaths occurred in younger children with age ranging from 10 to 40 months and at doses that varied from 18 to 60 mg/kg/day with a majority being 60mg/kg/day. Deaths occurred in both male and female patients 1.5 to 8 months following the initiation of treatments.

	Serious adverse event preferred term(s)	Treatment [b], Duration	Sex, age	Investigator attribution	Comments
2339E1					
0522/00001	Disease Progression	0 mg/kg/day 1.5 months	Female 12 months	Not Suspected	Died 8.5 months after last dose
2340					
0038/00005	Convulsion, lung disorder	0 mg/kg/day 2 months	Male 10 months	Not Suspected	Died 2 days after last dose
2340E1 [a]					
0028/00005	Sudden death	18 mg/kg/day 5.5 months	Male 10 months	Not Suspected	Died while receiving study drug
0072/00001	Pneumonia	60 mg/kg/day 4.5 months	Male 22 months	Not Suspected	Died while receiving study drug
0072/00003	Convulsion	60 mg/kg/day 8 months	Female 40 Months	Not Suspected	Extension phase completed; died while receiving commercial OXC

A discussion of each individual death is described below:

- Death was very unlikely caused by medication in patient 0522/00001 considering the fact that the patient was not on OXC for 8.5 months. Although while on OXC the patient suffered a serious adverse event (viral syndrome, increased seizures, malnutrition, lethargy and dehydration), which resulted in drug discontinuation and the initiation of other anticonvulsants, these events appeared to completely resolve well before death. The death was finally attributed to "progression of her seizure disorder."

- Patient 0038/00005 died 2 days after treatment was discontinued and following a 2 month treatment. Prior to death but during OXC treatment (about 2 weeks into OXC treatment) the patients developed "pneumopathy secondary to an increase in seizures." No further description of this was found. The patient did have a prior history of "encephalopathy, lung infection and a subdural." This patient was also on clobazam, valproate and vigabatrin at the time of death. With a potential reasonable cause of death it is difficult to conclude causality attributed to drug.

- Another patient (0072/0001) was described to die as a result of "pneumonia" that lead to sepsis and death. This patient was on monotherapy at the time and had been on treatment for 4.5 months. The patient had a clinical history of influenza, pharyngitis and oral

Candida. An autopsy demonstrated bilateral pulmonary infiltrates. This reviewer sees no obvious linkage with OXC treatment.

- Patient 0028/00005 died of "sudden death" 2 ½ weeks following surgery (right frontal parietal cortical resection) for increase in seizures for seizures. The seizures appeared to cease following surgery. Patient's seizure disorder was likely secondary to cortical dysplasia and had a history of bronchitis. The patient had been on OXC for 5.5 months. The patient had OXC suspended for two days around the time of surgery. Concomitant medications included topiramate and valproic acid. No autopsy was performed. It is not obvious to this reviewer that the death was related to OXC.

- Patient 0072/0003 died following an episode of status epilepsia that consisted of a 4-hour seizure. The cause of death was noted to be "bronchoaspiration." The patient had been on OXC for 8 months and was also on valproic acid. The patient had a medical history of developmental delay, cerebral infarction, influenza and urinary tract infection. No autopsy was noted. There does not appear to be an obvious association with OXC to this reviewer.

In the examination of deaths as a whole there appears to be a predominance of deaths (n=3) that were in some way related to respiratory pathology: e.g. "pneumonia," "bronchoaspiration," and "pneumopathy secondary to an increase in seizures." Such patients were 10 to 40 months of age. Two of these cases appear to be related secondarily to episodes of severe seizures. It is noteworthy that a prospective study,[14] that followed patients for 20 years from childhood, demonstrated that pneumonia is a common cause of mortality. Thus, of 245 patients with seizures since childhood, pneumonia was one of the more common causes of death with 17 patients noted to have died as a result of this adverse event. The presence of an underling neurological disorder may make such children prone to aspiration and pneumonia following seizures.[15] In the present database 2 such patients had some underlying neuropathology that may have contributed in a similar way: e.g. encephalopathy" in one case and developmental delay and a history of cerebral infarction in the other case. For this reason it is difficult to definitively attribute deaths as dues to drug treatment.

One death occurred in the limited control database. This occurred in the high dose group but occurred 2 days following withdrawal from medication. This occurred in one of the cases of deaths attributed to pulmonary causes described above whom had what appeared as significant underling neurological disease and a prior history of pulmonary infections. Comparison of high dose control to low dose control is difficult because of the limited exposure in both groups (5 to 35 days) and the unbalanced nature of exposure in the adjunctive treatment study (i.e. low dose exposed for 9 days and high dose for 35 days). Prior comparisons in control data base that

14 Sillanpaa M et. al., Long Term Prognosis of Seizures with onset in childhood, New Eng. J Med. 338:1715-1722, 1998.
15 Breningstall G., Mortality in pediatric Epilepsy. Ped. Neurol. 25:9-16, 2001.

included studies in adult and pediatric population (>4 years old on adjunctive treatment) did not find a signal for increased deaths.

7.1.2 Other Serious Adverse Events

A total of 62 serious adverse events (in 18.4% patients) were reported for all patients who participated in the new studies (group 1). Overall the most common organ class affected were "nervous system disorders" (10.1 %) and ""infections and infestations." This relative incidence was reflective of the incidence of common adverse events regardless of the degree of seriousness (see below). A listing the serious AEs for group 1, by preferred term, is presented in the table below. The most common events included convulsions, status epilepticus and pneumonia. As is apparent from the table serious adverse events were more common in the younger age group when comparing <4 to >4 years of age and <2 with 2- < 4 years of age.

Preferred term	Age <2 yrs N=158 n (%)	Age 2-<4 yrs N=83 n (%)	Age <4 yrs N=241 n (%)	Age >=4 yrs N=96 n (%)	Total N=337 n (%)
Total patients with AEs	42(26.6)	13(15.7)	55(22.8)	7(7.3)	62(18.4)
Convulsion	15(9.5)	4(4.8)	19(7.9)	1(1.0)	20(5.9)
Status epilepticus	10(6.3)	2(2.4)	12(5.0)	1(1.0)	13(3.9)
Pneumonia	8(5.1)	2(2.4)	10(4.1)	0(0.0)	10(3.0)
Bronchiolitis	5(3.2)	0(0.0)	5(2.1)	0(0.0)	5(1.5)
Pyrexia	4(2.5)	1(1.2)	5(2.1)	0(0.0)	5(1.5)
Vomiting	3(1.9)	2(2.4)	5(2.1)	0(0.0)	5(1.5)
Dehydration	1(0.6)	2(2.4)	3(1.2)	0(0.0)	3(0.9)
Apnoea	2(1.3)	0(0.0)	2(0.8)	0(0.0)	2(0.6)
Bronchospasm	1(0.6)	1(1.2)	2(0.8)	0(0.0)	2(0.6)
Electroencephalogram abnormal	1(0.6)	0(0.0)	1(0.4)	1(1.0)	2(0.6)
Hyponatraemia	2(1.3)	0(0.0)	2(0.8)	0(0.0)	2(0.6)
Pneumonia aspiration	1(0.6)	1(1.2)	2(0.8)	0(0.0)	2(0.6)
Somnolence	2(1.3)	0(0.0)	2(0.8)	0(0.0)	2(0.6)
Urinary tract infection	2(1.3)	0(0.0)	2(0.8)	0(0.0)	2(0.6)
Varicella	0(0.0)	1(1.2)	1(0.4)	1(1.0)	2(0.6)
Acute respiratory distress syndrome	0(0.0)	1(1.2)	1(0.4)	0(0.0)	1(0.3)
Anaemia	0(0.0)	1(1.2)	1(0.4)	0(0.0)	1(0.3)
Arachnoid cyst	1(0.6)	0(0.0)	1(0.4)	0(0.0)	1(0.3)
Asthma	1(0.6)	0(0.0)	1(0.4)	0(0.0)	1(0.3)
Bradycardia	1(0.6)	0(0.0)	1(0.4)	0(0.0)	1(0.3)
Bronchitis	0(0.0)	1(1.2)	1(0.4)	0(0.0)	1(0.3)
Bronchopneumonia	1(0.6)	0(0.0)	1(0.4)	0(0.0)	1(0.3)
Cardiac arrest	1(0.6)	0(0.0)	1(0.4)	0(0.0)	1(0.3)
Concussion	0(0.0)	1(1.2)	1(0.4)	0(0.0)	1(0.3)
Croup infectious	1(0.6)	0(0.0)	1(0.4)	0(0.0)	1(0.3)
Ear infection	1(0.6)	0(0.0)	1(0.4)	0(0.0)	1(0.3)
Escherichia infection	1(0.6)	0(0.0)	1(0.4)	0(0.0)	1(0.3)
Exanthem	1(0.6)	0(0.0)	1(0.4)	0(0.0)	1(0.3)
Faecaloma	0(0.0)	1(1.2)	1(0.4)	0(0.0)	1(0.3)
Femur fracture	0(0.0)	0(0.0)	0(0.0)	1(1.0)	1(0.3)
Food aversion	1(0.6)	0(0.0)	1(0.4)	0(0.0)	1(0.3)
Gastroenteritis	1(0.6)	0(0.0)	1(0.4)	0(0.0)	1(0.3)
Gastroenteritis viral	1(0.6)	0(0.0)	1(0.4)	0(0.0)	1(0.3)
Headache	0(0.0)	0(0.0)	0(0.0)	1(1.0)	1(0.3)
Hip fracture	0(0.0)	0(0.0)	0(0.0)	1(1.0)	1(0.3)
Hyperhidrosis	0(0.0)	1(1.2)	1(0.4)	0(0.0)	1(0.3)
Hypernatraemia	1(0.6)	0(0.0)	1(0.4)	0(0.0)	1(0.3)
Hypertension	1(0.6)	0(0.0)	1(0.4)	0(0.0)	1(0.3)
Hyperthermia	1(0.6)	0(0.0)	1(0.4)	0(0.0)	1(0.3)
Intracranial pressure increased	1(0.6)	0(0.0)	1(0.4)	0(0.0)	1(0.3)
Lethargy	1(0.6)	0(0.0)	1(0.4)	0(0.0)	1(0.3)
Lymphadenitis	0(0.0)	0(0.0)	0(0.0)	1(1.0)	1(0.3)
Osteotomy	0(0.0)	0(0.0)	0(0.0)	1(1.0)	1(0.3)
Pharyngitis streptococcal	0(0.0)	1(1.2)	1(0.4)	0(0.0)	1(0.3)
Platelet count decreased	1(0.6)	0(0.0)	1(0.4)	0(0.0)	1(0.3)
Pleural effusion	0(0.0)	1(1.2)	1(0.4)	0(0.0)	1(0.3)
Pneumonia bacterial	0(0.0)	1(1.2)	1(0.4)	0(0.0)	1(0.3)
Pyelonephritis	1(0.6)	0(0.0)	1(0.4)	0(0.0)	1(0.3)
Respiratory distress	0(0.0)	1(1.2)	1(0.4)	0(0.0)	1(0.3)
Respiratory syncytial virus infection	0(0.0)	1(1.2)	1(0.4)	0(0.0)	1(0.3)
Sepsis	1(0.6)	0(0.0)	1(0.4)	0(0.0)	1(0.3)
Septic shock	0(0.0)	1(1.2)	1(0.4)	0(0.0)	1(0.3)
Shunt infection	1(0.6)	0(0.0)	1(0.4)	0(0.0)	1(0.3)
Sudden death	1(0.6)	0(0.0)	1(0.4)	0(0.0)	1(0.3)
Superinfection	1(0.6)	0(0.0)	1(0.4)	0(0.0)	1(0.3)
Tachypnoea	0(0.0)	1(1.2)	1(0.4)	0(0.0)	1(0.3)
Transaminases increased	1(0.6)	0(0.0)	1(0.4)	0(0.0)	1(0.3)
Viral infection	0(0.0)	1(1.2)	1(0.4)	0(0.0)	1(0.3)

The table below presents the most common (> 1% in any group) serious adverse events, by preferred term, for the different dosing groups in the pivotal trials (group 2). Of these status epilepticus and pneumonia were somewhat more commonly seen in the high dose group (≥ 1.8% difference between groups). A caveat for this and all subsequent group 2 analyses is that they involve an unbalanced comparison. 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). This may result in the appearance of a spurious dose effect.

	Low-dose OXC 10 mg/kg/day (N = 110)	High-dose OXC 40 to 60 mg/kg/day [a] (N = 110)	Total (N = 220)
	n (%)	n (%)	n (%)
Total patients with serious adverse events	6 (5.5)	12 (10.9)	18 (8.2)
Preferred term			
Status epilepticus	3 (2.7)	5 (4.5)	8 (3.6)
Pneumonia	0 (0.0)	3 (2.7)	3 (1.4)
Convulsion	1 (0.9)	1 (0.9)	2 (0.9)
Pyrexia	1 (0.9)	1 (0.9)	2 (0.9)
Somnolence	1 (0.9)	1 (0.9)	2 (0.9)
Vomiting	0 (0.0)	2 (1.8)	2 (0.9)

With regard to the most commonly observed serious adverse events, the incidence of status epilepticus and seizures are not unexpected in the present group 1 population of patients with epilepsy. Examination of the narratives revealed that the type of seizures experienced by patients described as a serious adverse event were generally types of seizures that would be expected from the underlying seizure disorder. The present database does not allow comparison to placebo group. Moreover, the group 2 comparison of high versus low dose is somewhat limited as the period of comparison constitutes a very short period of and exposures are not balanced. The slightly greater incidence of status epilepticus in the high, as compared to the low, dose group is therefore not unexpected and likely does not represent a signal. Moreover, convulsions were observed to be less frequent in the drug as compared to placebo groups in the original NDA submission that grouped adult and children.

Pneumonia was another very common serious adverse event. This is consistent with an increase risk of infections in the young. But, it is also likely a result of the increased likelihood of infections in young pediatric patients with epilepsy as previously discussed. This may be a result of increased risk of aspiration because of the seizures themselves and underlying co-morbid neurological disorders. This reviewer examined all the narratives that were described as pneumonia and bronchiolitis in group 1 to confirm this assumption. Many patients were noted to have significant co-morbid neurological disease and some were noted to have significant previous respiratory infections. Of all the cases examined only one (MEX/0072/00010 in study 2340) describes any white cell suppression. This patient had neutrophil counts that fluctuated throughout the study (MEX/0072/00010 in study 2340). At that time of this report counts were only borderline low (1,760/mm^3). This patient recovered from the pneumonia after antibiotic treatment and was subsequently enrolled in the extension trial. A relation to the borderline

reduction in neutrophils cannot be made. Issues of low neutrophile counts are discussed in greater details in the laboratory section below

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

Overall dropouts for any reason (administrative, adverse events, etc.) are not presented by the Sponsor, however, the reader is refereed to above efficacy analysis for drop out rates in individual controlled studies.

7.1.3.2 Adverse events associated with dropouts

In total 31 (or 9.2 %) patients in the group 1 analysis withdrew from the studies because of adverse events. This compares to a rate of 19% rate of discontinuation due to adverse events from the original NDA that includes predominately adult and some pediatric data. A table that classifies events by organ systems and preferred term is presented below. From this table it is apparent that patients less then 4 years old would more likely be withdrawn from studies because of adverse events then older patients. There was no additional obvious difference in rates between <4 year old subgroups. The difference between the two age groups was mostly the result of differences in CNS adverse events.

The most common category for withdrawal, under organ system, was "nervous system disorders." Convulsions (i.e. "convulsions," "status epilepticus," "infantile spasms" and "epilepsy") were the most common reason for withdrawal under this organ system. This differs from the original analysis where the rate of discontinuation for convulsions was not greater then 1%[16]. This adverse event were more common for patients <4 years old as compared to the older pediatric cohort. Without a placebo comparison it is difficult to determine the significance of this observation. It is of interest to note, however, that a subgroup analysis of controlled studies suggested a lower efficacy of OXC in patients <2 years of age. As noted above seizures generally appeared to be consistent with the underling seizure disorder. Ataxia was the second most common CNS reason fro withdrawal. Tremor, somnolence and ataxia were also almost exclusive reasons for withdrawal in the younger age group. Again, without a placebo comparison, it is difficult to determine if this truly represents an age group difference. It is, however, noteworthy that the rates withdrawal because of the CNS adverse event other then

16 Based upon the original safety review by Dr. Gerard Boehm 7/23/99.

convulsions where less then that observed in databases that where the subject of the original NDA review and included both adult and pediatric data[17].

The second highest rate among organ system adverse event resulting in withdrawal was that of skin. Skin related events appeared more common in younger patients (< 4 years old), but these differences are small and may not be clinically significant (1.7% of patients Vs 1.0 % of patients). These rates do not significantly differ, and in fact may be slightly lower, than rates observed in the previous NDA pediatric/adult database[18]. Skin reactions will be discussed in more detail in a latter section.

Withdrawal occurred because of reasons of abnormal clinical blood results in single isolated patients and included "alkaline phosphatase increase," "liver function abnormal" and "platelet count decreased." These deserve further discussion.

The case of platelet reduction was a 6-month old patient (AR/00005/00002) who was actually discontinued because of seizures, but his platelet count was noted to be decreased when he presented for increased seizures 2 months after treatment was initiated. Platelet count dropped to 64 X 10^9 /L (normal 220 X10^9 /L). Six month latter the patient was discontinued because of continued seizures. The drug is unlikely to have been the cause of the decreased platelet count as the drop resolved with continued treatment and the patient had a prior history of "decreased platelets."

The case of discontinuation because of elevated liver function tests involved a 5 month old (USA/051/00002) who presented 3 weeks after the initiation of OXC with GOT and GPT at 213 and 141, respectively, which is approximately 4 time the upper limit of normal. The patient was also on Phenobarbital. OXC was discontinued with a return of liver function tests to normal 1 month latter. The patient was not hospitalized. Bilirubin was not elevated. This case is discussed further below. Cases of elevated liver function have been reported in the previous NDA database and are presently noted in the Trileptal labeling under "laboratory abnormality" that states "Gamma-GT increased, hyperglycemia, hypocalcemia, hypoglycemia, hypokalemia, liver enzymes elevated, serum transaminase increased."

The case of elevated alkaline phosphatase involves a 5 month old (USA/0505/00004) who presented 6 months following the initiation of OXC with and Alkaline phosphatase of 3648 that further increased to 5122 U/L (reference 155 to 420 U/L). The patient was discontinued with resolution of the event. A causality attribution in this single case is difficult to make at the repent time. Concomitant medications included phenobarbital and nystatin. This case is discussed further below. "Colelithiasis" type events were reported in the original NDA database.

17 Based upon the original safety review by Dr. Gerard Boehm 7/23/99.
18 Based upon the original safety review by Dr. Gerard Boehm 7/23/99.

	Age				
	<2 yrs (N = 158)	2 to <4 yrs (N = 83)	<4 yrs (N = 241)	>=4 yrs (N = 96)	Total (N = 337)
	n (%)	n (%)	n (%)	n (%)	n (%)
Total patients disc. due to adverse events	18 (11.4)	9 (10.8)	27 (11.2)	4 (4.2)	31 (9.2)
Primary system organ class / Preferred term					
Gastrointestinal disorders	0 (0.0)	1 (1.2)	1 (0.4)	0 (0.0)	1 (0.3)
Vomiting	0 (0.0)	1 (1.2)	1 (0.4)	0 (0.0)	1 (0.3)
General disorders and administration site conditions	1 (0.6)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.3)
Fatigue	1 (0.6)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.3)
Investigations	3 (1.9)	0 (0.0)	3 (1.2)	1 (1.0)	4 (1.2)
Blood alkaline phosphatase increased	1 (0.6)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.3)
Electroencephalogram abnormal	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	1 (0.3)
Liver function test abnormal	1 (0.6)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.3)
Platelet count decreased	1 (0.6)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.3)
Musculoskeletal and connective tissue disorders	1 (0.6)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.3)
Muscle twitching	1 (0.6)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.3)
Nervous system disorders	12 (7.6)	8 (9.6)	20 (8.3)	2 (2.1)	22 (6.5)
Convulsions	6 (3.8)	3 (3.6)	9 (3.7)	1 (1.0)	10 (3.0)
Ataxia	1 (0.6)	2 (2.4)	3 (1.2)	0 (0.0)	3 (0.9)
Status epilepticus	2 (1.3)	1 (1.2)	3 (1.2)	0 (0.0)	3 (0.9)
Somnolence	1 (0.6)	1 (1.2)	2 (0.8)	0 (0.0)	2 (0.6)
Tremor	1 (0.6)	1 (1.2)	2 (0.8)	0 (0.0)	2 (0.6)
Epilepsy	1 (0.6)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.3)
Headache	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	1 (0.3)
Infantile spasms	1 (0.6)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.3)
Lethargy	0 (0.0)	1 (1.2)	1 (0.4)	0 (0.0)	1 (0.3)
Psychomotor hyperactivity	0 (0.0)	1 (1.2)	1 (0.4)	0 (0.0)	1 (0.3)
Psychiatric disorders	1 (0.6)	1 (1.2)	2 (0.8)	0 (0.0)	2 (0.6)
Insomnia	0 (0.0)	1 (1.2)	1 (0.4)	0 (0.0)	1 (0.3)
Irritability	1 (0.6)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.3)
Skin and subcutaneous tissue disorders	3 (1.9)	1 (1.2)	4 (1.7)	1 (1.0)	5 (1.5)
Exanthem	1 (0.6)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.3)
Rash	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	1 (0.3)
Rash maculopapular	0 (0.0)	1 (1.2)	1 (0.4)	0 (0.0)	1 (0.3)
Rash papular	1 (0.6)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.3)
Swelling face	1 (0.6)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.3)

7.1.3.3 Other significant adverse events

The Sponsor has performed additional more careful analyses of certain types of adverse events because of there known association with OXC and there description in the Warnings and Precautions labeling sections. These include central nervous system symptoms, hyponatremia, and dermatological reactions.

7.1.3.3.1 Central Nervous System Symptoms

The Sponsor examined the incidence of the adverse event for preferred terms that were thought to reflect cognitive dysfunction. These included "cognitive deterioration," "memory impairment," "affect liability" "amnesia," "disturbance of attention," dysarthria," and "mental status change." A total of 9 of 337 (2.7%) patients experienced such adverse events. Only one patient was observed for each such preferred term except "cognitive deterioration" and "memory impairment" for which 2 patients were observed. All such adverse events were classified as mild or moderate. There was a slightly greater incidence in older patients.

The Sponsor performed a separate study (2337) that examined the potential of OXC to influence cognitive function. This study was a three-arm parallel, multicenter, open label, active control randomized examination of patients, age 6 to <17 years old, with partial seizures and no previous treatment. Forty-seven patients on OXC monotherapy was compared to 26 patients on carbamazepine and 24 on valproic acid monotherapy. Dose was adjusted for an optimal treatment effect. The primary endpoint was to measure mental speed and attention using the "Computerized Visual Searching Task (CVST)" test. Secondary endpoints included Finger Tapping Task, Simple reaction-time measurement, Binary Choice Reaction Test, Recognition of words and figures, Rey Auditory Verbal-Learning Test. These endpoints were added to measure: 1) psychomotor speed and alertness, 2) mental information processing speed and attention, 3) memory and learning. No statistically significant difference was observed for the primary endpoint between OXC and the combined valproic acid/ carbamazepine groups although there was a very slight trend toward OXC superiority. Except for word recognition, there was no significant difference between OXC and other treatment groups for secondary endpoint evaluations. All tests of cognition showed a numerical improvement from baseline to the 6 month test period. This reviewer believes that while these findings are helpful and suggestive of no major difference in effect on cognition as compared to the other anticonvulsants studied, they are only tentative conclusions as it is beyond the scope of the present review to examine the power and sensitivity of such studies. The sponsor powered the study so as to pick up a difference of 4.5 seconds between both treatment groups. The clinical significance of this difference, however, is not discussed. Moreover, there is no placebo control, nor can a placebo controlled study be ethically justified. The control group contains patients on carbamazepine which is chemically and mechanistically similar to OXC and likely has a similar cognitive adverse event profile.

Adverse events associated with somnolence and fatigue were examined by searching under a number of preferred term (e.g. "somnolence," "fatigue," "lethargy," "sedation," "sleep disorder," etc). The grouped incidence was observed to be rather high, e.g. 25% of patients <4 years old and 26% of patients $\geq$ 4 years old. There did not appear to be age dependency when these groups are compared. These symptoms were generally reported most frequently in the age 2 to < 4 year group as compared to patients < 2 years and $\geq$ 4 years. Most symptoms were rated as mild to moderate but 1.2 % of patients had symptoms rated as severe. Some patients (n=4) had medication discontinued because of these symptoms. These rates did not very greatly with rates in somnolence observed in the original NDA(see Appendix F) review and are labeled in the "Warnings" section in the present label.

Coordination abnormalities were also examined by grouping preferred terms such as "ataxia," "gait abnormal balance disorder," "difficult walking" etc. When this was done 11% of patents <4 and 10 % of patients ≥ 4 years of age were noted to suffer from some from coordination abnormality. Collectively these symptoms were generally reported most frequently in the age 2 to < 4 year group as compared to patients < 2 years and ≥ 4 years. This class of adverse event was rated mild to moderate and 1.2 % of patients discontinued.

This reviewer would note that a prior analysis by this division[19] the incidence of ataxia was compared across three age groups from the experimental clinical data. These groups included <11 years old, 12 to 17 years old and ≥18 years old. The incidence of ataxia alone was 13.7%, 13% and 11.4%, respectively. When compared to the present results, there does not appear to be a significant difference for the various age groups amongst

This reviewer believes that the observation that the adverse events described above were generally reported in a higher incidence in the 2 to 4 year old group as compared to other groups may be a combination of increased sensitivity to younger patients and reduced ability to discern neurological changes in the very young patients. However, without an adequate placebo group for comparison a definitive conclusion is not possible.

7.1.3.3.2 Hyponatremia

The Sponsor notes that only 2 patients in the present safety database, or 0.6 %, had sodium values <125 mM. OXC was not discontinued in either patient. This incidence compares to 2.5% of patients in prior clinical studies. From this the Sponsor concludes that pediatric patients may be at a lower risk for developing hyponatremia. Both patients were <2 years old. Even if you use this smaller population to calculate incidence of hyponatremia of <125 mM, the value (1.27%) is lower in this very young population then in the prior predominately adult population. As noted above, however, there was a tendency for the very young to have a higher incidence of hyponatremia then the older pediatric patients. The previous NDA safety review by this division also noted in a comparisons of age groups, that adverse events identified as "hyponatremia" were less common in younger patients. (e.g. 1.4% in <11 years old, 1 % in 12 to 17 years old and 3.5% in and ≥18 years old). Moreover, if one examines adverse events recorded as hyponatremia in various age groups (see Appendix B) we see a slight increase in reporting rate for in the youngest age group (< 2 years of age). Thus, hyponatremia was reported as an AE in 4.4% of exposed patients < 4 years old as compared to 0 % in patients 2 to< 4 years of age and 1% in patients >4 years of age. These data may indicate that there may be a "U" shaped relation with hyponatremia with very young and older populations being at greater risk. Alternatively, this difference may be the result of sampling error.

19 Based upon the original safety review by Dr. Gerard Boehm 7/23/99.

7.1.3.3.3 Dermatological Reactions

The Sponsor has tabulated all dermatological preferred terms. This is presented in the table below. There were no patients described as having Stevens-Johnson syndrome, toxic epidermal necrolysis or erythema multiforme. Severity was almost exclusively described as mild to moderate. One patient was described as having a severe rash (papular). Five patients were discontinued because of the rash.

To determine relative incidence of potential drug induced rashes, this reviewer added up all rashes that were possibly caused by drug. Thus, all rashes below were added up except the following: eczema, dermatitis diaper, exanthema, dermatitis contact, dermatitis atopic, hand dermatitis, skin irritation and seborrhea dermatitis. In that case suspect rashes were observed in patient age groups of <2, 2 to <4 and ≥ 4, at a rate of 10%, 12% and 10 %. Thus there were very little obvious age differences amongst pediatric groups.

	Age				
	<2 yrs (N = 158) n (%)	2 - <4 yrs (N = 83) n (%)	<4 yrs (N = 241) n (%)	>=4 yrs (N = 96) n (%)	Total (N = 337) n (%)
Preferred term					
Rash	8 (5.1)	2 (2.4)	10 (4.1)	7 (7.3)	17 (5.0)
Eczema	3 (1.9)	0 (0.0)	3 (1.2)	2 (2.1)	5 (1.5)
Dermatitis diaper	2 (1.3)	2 (2.4)	4 (1.7)	0 (0.0)	4 (1.2)
Erythema	1 (0.6)	1 (1.2)	2 (0.8)	1 (1.0)	3 (0.9)
Exanthem	1 (0.6)	2 (2.4)	3 (1.2)	0 (0.0)	3 (0.9)
Pruritus	0 (0.0)	1 (1.2)	1 (0.4)	2 (2.1)	3 (0.9)
Rash maculo-papular	0 (0.0)	3 (3.6)	3 (1.2)	0 (0.0)	3 (0.9)
Dermatitis allergic	2 (1.3)	0 (0.0)	2 (0.8)	0 (0.0)	2 (0.6)
Dermatitis contact	2 (1.3)	0 (0.0)	2 (0.8)	0 (0.0)	2 (0.6)
Rash papular	2 (1.3)	0 (0.0)	2 (0.8)	0 (0.0)	2 (0.6)
Swelling face	1 (0.6)	1 (1.2)	2 (0.8)	0 (0.0)	2 (0.6)
Dermatitis atopic	1 (0.6)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.3)
Dermatitis medicamentosa	1 (0.6)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.3)
Dry skin	1 (0.6)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.3)
Hand dermatitis	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	1 (0.3)
Photosensitivity reaction	0 (0.0)	1 (1.2)	1 (0.4)	0 (0.0)	1 (0.3)
Rash generalized	1 (0.6)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.3)
Rash morbilliform	0 (0.0)	1 (1.2)	1 (0.4)	0 (0.0)	1 (0.3)
Seborrhoeic dermatitis	1 (0.6)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.3)
Skin Irritation	1 (0.6)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.3)

The prior review by this division compared rashes in different age groups. This was done by comparing all rashes listed as “rash,” rash maculo-papular” and rash erythematous. When this

was done age groups <11 years old, 12 to 17 years old and ≥18 years old demonstrated an incidence of 5.5%, 8%% and 5.9%, respectively. This can be compared to an incidence of the rash calculated in a similar fashion in the present age group. Thus, an incidence of 10%, 12% and 10 %for age groups <2 years old, 2-4 years old and >4 years old are observed. Internal comparison of groups supports a lack of an age dependent sensitivity with regard to rash. Comparison between the two databases, however, revealed some variability. The reason for this is unknown.

7.1.3.3.4 Cardiac Effects

The Sponsor performed a more careful analysis of cardiac adverse events because of a request by the division to include EKG analysis. This information was requested because of the general lack of such information in prior submission and not because there was any worrisome cardiac signals. The EKG analysis is described below in a separate section. A listing of cardiac adverse events by preferred terms is presented below. All adverse events were rated as mild to moderate except for one case which included "cardiac arrest and bradycardia." A requested narration of this case was received by e-mail on 5/27/05. This episode occurred after a crying spell. The patient had a history of cerebral palsy and liver failure. The patient was noted to "fully recover" in spite of what appears to be continued treatment. There were no discontinuations because of cardiac events. Few cardiac adverse events were reported. It is hard to associate his single case, particularly with recovery, to drug. Somewhat higher incidences of cardiovascular adverse events were reported for the older pediatric group. The significance of this is unknown.

The significance of the listed single isolated cardiac events is unknown and may represent background. It is difficult to determine such significance without substantial placebo control or background information.

Cardiac issues are discussed further in the section on EKG.

	Age				
	<2 yrs (N = 158)	2 - <4 yrs (N = 83)	<4 yrs (N = 241)	>=4 yrs (N = 96)	Total (N = 337)
	n (%)	n (%)	n (%)	n (%)	n (%)
Preferred term					
Electrocardiogram QT prolonged	1 (0.6)	0 (0.0)	1 (0.4)	2 (2.1)	3 (0.9)
Asthenia	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	1 (0.3)
Bradycardia	1 (0.6)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.3)
Cardiac arrest	1 (0.6)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.3)
Chest pain	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	1 (0.3)
Electrocardiogram abnormal	1 (0.6)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.3)
Heart rate irregular	0 (0.0)	1 (1.2)	1 (0.4)	0 (0.0)	1 (0.3)
Hypertension	1 (0.6)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.3)
Palpitations	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	1 (0.3)
Sinus tachycardia	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	1 (0.3)
Tachycardia	0 (0.0)	1 (1.2)	1 (0.4)	0 (0.0)	1 (0.3)

7.1.4 Other Search Strategies

See above section “Other Significant Adverse Events.”

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

All adverse events, whether volunteered by the patient, volunteered by the parent/caregiver, discovered by investigator questioning, or detected through physical examination, laboratory test or other means, were collected and recorded on the Adverse Event Case Report Forms and followed as appropriate. Abnormal laboratory values or test results constituted adverse events only if they induced clinical signs or symptoms or required therapy.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

Investigator reported terms for adverse events were standardized by coding of the events according to the MedDRA dictionary, providing both primary system organ class (PSOC) and preferred term (PT). The pooling of adverse event data necessitated re-coding of some data using the most recent version of the MedDRA dictionary.

MedDRA is a conventional dictionary accepted by the FDA. Examination of various narratives from serious adverse events revealed that the use of preferred term were generally appropriate.

7.1.5.3 Incidence of common adverse events

Adverse events for all studied patients (group 1) classified by organ system are presented in the table below. The table includes all patients studied and patients classified according to age. The most common observations are higher-most in the listings here and all subsequent tables in this section. Patients younger then 4 years had a mildly higher incidence in total AEs. The most common AEs, by organ systems, were infections, nervous systems disorders, GI disorders, general disorders and administrative site conditions, respiratory disorders, psychiatric disorders and skin and subcutaneous disorders. Except for “infections and infestations” and “respiratory thoracic and mediastinal disorders” affect on organ system where similar in patients less then and greater then 4 years of age. In these cases the younger group at a higher incidence. The incidence of organ systems involved in AEs where similar in groups <2 and 2-<4 years old with the exception of injury, poisoning and procedural complications, in which case it was more common in the younger group.

	Age				
	<2 yrs (N = 158)	2 - <4 yrs (N = 83)	<4 yrs (N = 241)	>=4 yrs (N = 96)	Total (N = 337)
	n (%)	n (%)	n (%)	n (%)	n (%)
Total patients with adverse events	134 (84.8)	72 (86.7)	206 (85.5)	71 (74.0)	277 (82.2)
Primary system organ class					
Infections and infestations	102 (64.6)	49 (59.0)	151 (62.7)	30 (31.3)	181 (53.7)
Nervous system disorders	66 (41.8)	31 (37.3)	97 (40.2)	39 (40.6)	136 (40.4)
Gastrointestinal disorders	51 (32.3)	33 (39.8)	84 (34.9)	23 (24.0)	107 (31.8)
General disorders and administration site conditions	52 (32.9)	22 (26.5)	74 (30.7)	25 (26.0)	99 (29.4)
Respiratory, thoracic and mediastinal disorders	39 (24.7)	25 (30.1)	64 (26.6)	5 (5.2)	69 (20.5)
Psychiatric disorders	30 (19.0)	18 (21.7)	48 (19.9)	14 (14.6)	62 (18.4)
Skin and subcutaneous tissue disorders	28 (17.7)	13 (15.7)	41 (17.0)	14 (14.6)	55 (16.3)
Metabolism and nutrition disorders	21 (13.3)	9 (10.8)	30 (12.4)	10 (10.4)	40 (11.9)
Investigations	15 (9.5)	9 (10.8)	24 (10.0)	4 (4.2)	28 (8.3)
Injury, poisoning and procedural complications	7 (4.4)	14 (16.9)	21 (8.7)	6 (6.3)	27 (8.0)
Eye disorders	4 (2.5)	4 (4.8)	8 (3.3)	9 (9.4)	17 (5.0)
Blood and lymphatic system disorders	4 (2.5)	3 (3.6)	7 (2.9)	2 (2.1)	9 (2.7)
Musculoskeletal and connective tissue disorders	2 (1.3)	2 (2.4)	4 (1.7)	1 (1.0)	5 (1.5)
Cardiac disorders	1 (0.6)	1 (1.2)	2 (0.8)	2 (2.1)	4 (1.2)
Ear and labyrinth disorders	0 (0.0)	1 (1.2)	1 (0.4)	3 (3.1)	4 (1.2)
Immune system disorders	3 (1.9)	0 (0.0)	3 (1.2)	1 (1.0)	4 (1.2)
Renal and urinary disorders	2 (1.3)	0 (0.0)	2 (0.8)	2 (2.1)	4 (1.2)
Vascular disorders	2 (1.3)	1 (1.2)	3 (1.2)	1 (1.0)	4 (1.2)
Reproductive system and breast disorders	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.1)	2 (0.6)
Surgical and medical procedures	0 (0.0)	1 (1.2)	1 (0.4)	1 (1.0)	2 (0.6)

Adverse events by organ systems for group 2, which allows comparison between high and low dose groups, in the two pivotal trials are presented in the table below. It should be remembered that reporting for this group constituted a very short time period and in general the reporting period for the high dose is longer because of the extended titration period for high dose in study 2440. There was a higher incidence of reported AEs in the higher dose groups. This was most pronounced for nervous system disorders but was also observed for gastrointestinal disorders, infections, general disorders and perhaps psychiatric disorders. Because of the unbalanced nature of exposures, dose dependency of these effects cannot, therefore, be assumed.

	Low-Dose OXC 10 mg/kg/day (N = 110)	High-Dose OXC 40 to 60 mg/kg/day (N = 110)	Total (N = 220)
	n (%)	n (%)	n (%)
Total patients with adverse events	48 (43.6)	75 (68.2)	123 (55.9)
Primary system organ class			
Nervous system disorders	9 (8.2)	43 (39.1)	52 (23.6)
Gastrointestinal disorders	15 (13.6)	27 (24.5)	42 (19.1)
Infections and infestations	12 (10.9)	26 (23.6)	38 (17.3)
General disorders and administration site conditions	10 (9.1)	18 (16.4)	28 (12.7)
Respiratory, thoracic and mediastinal disorders	8 (7.3)	10 (9.1)	18 (8.2)
Skin and subcutaneous tissue disorders	9 (8.2)	5 (4.5)	14 (6.4)
Psychiatric disorders	4 (3.6)	9 (8.2)	13 (5.9)
Investigations	5 (4.5)	5 (4.5)	10 (4.5)
Metabolism and nutrition disorders	4 (3.6)	4 (3.6)	8 (3.6)
Eye disorders	0 (0.0)	3 (2.7)	3 (1.4)
Injury, poisoning and procedural complications	1 (0.9)	2 (1.8)	3 (1.4)
Cardiac disorders	1 (0.9)	1 (0.9)	2 (0.9)
Vascular disorders	0 (0.0)	2 (1.8)	2 (0.9)
Blood and lymphatic system disorders	0 (0.0)	1 (0.9)	1 (0.5)
Renal and urinary disorders	1 (0.9)	0 (0.0)	1 (0.5)

The most common adverse events (≥5% of patients in any age group), by preferred term, for all patients receiving OXC is presented in the table below. The most common adverse events in these grouping are those related to infection (e.g. pyrexia, upper respiratory infection and nasopharyngitis), vomiting and somnolence.

All types of infection processes were far more common in the <4 then >4 year old group. The Sponsor suggests that this is consistent with increased incidence of infections in the young. This reviewer concurs with this conclusion. As noted, above this may also be consistent with the high rate of pulmonary infections leading to mortality in the pediatric population. It also does not appear to be related to decreases in white cell count (see discussion of serious event above and clinical labs below). It is noteworthy that the rate of pneumonia for pediatric patients >4 years of age in the present studies (0%) is lower then pediatric patients >4 years old in previous controlled studies (study 011: placebo1% and drug 2%: see Appendix A). Presumably the high rate in the younger population (8.7%) is, as noted, a result of increased risk of infection in the young seizure patient.

Examination of the risk of the very common two AEs of vomiting and somnolence observed in the present study are less common then previously reviewed pediatric data. This can be observed in this divisions analysis for common adverse events in all patients in prior studies that by age (see Appendix F) as well as patients from previous controlled adjunctive studies that are described in the present labeling (see Appendix A). The present study has approximately a 2

fold lower incidence. This may be a result of the prior pediatric population consisting of predominately patients on adjunctive treatment whereas the present study consists of many patients on monotherapy. Moreover, it may result form differing exposures.

Many of the other less common adverse events described in the table below are also less frequent in the present study report then prior ones (e.g. headache, rash, ataxia. And dizziness).

Adverse events that required symptom reporting by patients, including headache, dizziness and nausea, were more common in older children (>4 years of age). This difference likely is a result of differences in the patient reporting capacity.

Of interest is the fact that the incidence of convulsions reported as AEs appeared to be generally inversely proportional to age. The Sponsor suggests that this may be related to the increased incidence of infections in the younger patients and the association with increased seizures in patients with epilepsy during infections. Although speculative, it remains a possibility, that this may also result from a lower efficacy in the very younger population (<2 years). This observation is supported by this divisions analysis that failed to demonstrate a statistically significant reduction in seizures for children <2 year of age but demonstrated an effect for children > 2 years of age in the new adjunctive trial (2440).

	Age				
	<2 yrs (N = 158)	2 to <4 yrs (N = 83)	<4 yrs (N = 241)	>=4 yrs (N = 96)	Total (N = 337)
	n (%)	n (%)	n (%)	n (%)	n (%)
Total patients with adverse events	134 (84.8)	72 (86.7)	206 (85.5)	71 (74.0)	277 (82.2)
Preferred term					
Pyrexia	45 (28.5)	19 (22.9)	64 (26.6)	9 (9.4)	73 (21.7)
Vomiting	24 (15.2)	16 (19.3)	40 (16.6)	10 (10.4)	50 (14.8)
Somnolence	21 (13.3)	13 (15.7)	34 (14.1)	13 (13.5)	47 (13.9)
Upper Respiratory tract infection	30 (19.0)	11 (13.3)	41 (17.0)	2 (2.1)	43 (12.8)
Convulsions	25 (15.8)	9 (10.8)	34 (14.1)	4 (4.2)	38 (11.3)
Nasopharyngitis	17 (10.8)	15 (18.1)	32 (13.3)	5 (5.2)	37 (11.0)
Cough	17 (10.8)	11 (13.3)	28 (11.6)	2 (2.1)	30 (8.9)
Otitis Media	18 (11.4)	7 (8.4)	25 (10.4)	1 (1.0)	26 (7.7)
Ear infection	16 (10.1)	8 (9.6)	24 (10.0)	1 (1.0)	25 (7.4)
Diarrhea	13 (8.2)	8 (9.6)	21 (8.7)	3 (3.1)	24 (7.1)
Irritability	14 (8.9)	6 (7.2)	20 (8.3)	1 (1.0)	21 (6.2)
Nasal congestion	15 (9.5)	6 (7.2)	21 (8.7)	0 (0.0)	21 (6.2)
Pneumonia	17 (10.8)	4 (4.8)	21 (8.7)	0 (0.0)	21 (6.2)
Ataxia	7 (4.4)	9 (10.8)	16 (6.6)	4 (4.2)	20 (5.9)
Bronchitis	9 (5.7)	7 (8.4)	16 (6.6)	3 (3.1)	19 (5.6)
Constipation	9 (5.7)	5 (6.0)	14 (5.8)	3 (3.1)	17 (5.0)
Rash	8 (5.1)	2 (2.4)	10 (4.1)	7 (7.3)	17 (5.0)
Headache	1 (0.6)	4 (4.8)	5 (2.1)	11 (11.5)	16 (4.7)
Influenza	9 (5.7)	5 (6.0)	14 (5.8)	2 (2.1)	16 (4.7)
Dizziness	1 (0.6)	1 (1.2)	2 (0.8)	13 (13.5)	15 (4.5)
Decreased appetite	6 (3.8)	2 (2.4)	8 (3.3)	6 (6.3)	14 (4.2)
Fatigue	3 (1.9)	1 (1.2)	4 (1.7)	10 (10.4)	14 (4.2)
Status epilepticus	10 (6.3)	3 (3.6)	13 (5.4)	1 (1.0)	14 (4.2)
Nausea	4 (2.5)	3 (3.6)	7 (2.9)	6 (6.3)	13 (3.9)
Insomnia	6 (3.8)	5 (6.0)	11 (4.6)	1 (1.0)	12 (3.6)
Rhinorrhea	4 (2.5)	6 (7.2)	10 (4.1)	2 (2.1)	12 (3.6)
Teething	10 (6.3)	0 (0.0)	10 (4.1)	0 (0.0)	10 (3.0)
Urinary tract infection	8 (5.1)	1 (1.2)	9 (3.7)	1 (1.0)	10 (3.0)
Bronchiolitis	9 (5.7)	0 (0.0)	9 (3.7)	0 (0.0)	9 (2.7)

A more expanded tabulation for adverse events by preferred term for patients overall down to 1% of patients can be found in Appendix B. Most notable in this expanded tabulation is the fact that hyponatremia may be more common in children <2 years of age. Thus, it occurred in 4.4% of exposed patients in this population as compared to 0 % in patients 2 to< 4 years of age and 1% in patients >4 years of age. These differences are discussed in detail in the section on hypponatremia in "Other Significant Adverse Events."

Information of incidence of common (≥ 5% of patients) AE in the pivotal low/high dose controlled studies (Group 2) are presented in the table below. Adverse events that were more common in the high dose groups with a greater then 5% difference from the low dose group

include somnolence, convulsions, ataxia, dizziness, and nausea. Except for convulsions, these symptoms are already noted in the labeling as occurring more frequently in drug as compared to the placebo group in prior adjunctive studies. It should, however, be recalled that the high and low dose comparisons are not balanced. Thus, patients receiving high dose in study 2440 was on medication for a substantially longer time then those in the low dose group. This would result in higher background rate in the high dose group making any comparison to low dose for reasons of determining dose dependency and causality difficult. Such decisions should be left to the prior adjunctive placebo control study that is already described in the labeling.

	Low-dose OXC 10 mg/kg/day (N = 110)	High-dose OXC 40 to 60 mg/kg/day (N = 110)	Total (N = 220)
	n (%)	n (%)	n (%)
Total patients with adverse events	48 (43.6)	75 (68.2)	123 (55.9)
Preferred term			
Somnolence	3 (2.7)	19 (17.3)	22 (10.0)
Pyrexia	8 (7.3)	12 (10.9)	20 (9.1)
Vomiting	7 (6.4)	11 (10.0)	18 (8.2)
Convulsions	2 (1.8)	8 (7.3)	10 (4.5)
Status epilepticus	3 (2.7)	6 (5.5)	9 (4.1)
Cough	2 (1.8)	6 (5.5)	8 (3.6)
Ataxia	0 (0.0)	7 (6.4)	7 (3.2)
Dizziness	0 (0.0)	6 (5.5)	6 (2.7)
Nausea	0 (0.0)	6 (5.5)	6 (2.7)

A more expanded tabulation of adverse events for the group 2 analysis is presented in Appendix C; i.e., events occurring in at least 1% of patients in either group. In addition to the above observations it can be gleaned from these tables that other AEs that were minimally greater in the high dose group (>2% and <5% from low dose). These include tremor, diarrhea, pneumonia, otitis media, nasal congestion, and urinary tract infections. Pneumonia was also more common in the high dose group (4% high and 0 % low), but like seizures, little can be concluded from this disparity because of the unbalanced nature of groups.

Common ($\geq$ 5% of patients overall) adverse events by severity are presented in the table below. For almost all categories most events were mild with some being moderate. The exception to this included ataxia, pneumonia and convulsions, where moderate and/or severe events were as or more common then mild events.

	Adverse event severity			
	Mild (N = 337) n (%)	Moderate (N = 337) n (%)	Severe (N = 337) n (%)	Overall (N = 337) n (%)
Preferred term				
Pyrexia	59 (17.5)	8 (2.4)	6 (1.8)	73 (21.7)
Vomiting	39 (11.6)	9 (2.7)	2 (0.6)	50 (14.8)
Somnolence	35 (10.4)	9 (2.7)	3 (0.9)	47 (13.9)
Upper respiratory tract infection	36 (10.7)	6 (1.8)	1 (0.3)	43 (12.8)
Convulsion	9 (2.7)	19 (5.6)	10 (3.0)	38 (11.3)
Nasopharyngitis	34 (10.1)	3 (0.9)	0 (0.0)	37 (11.0)
Cough	26 (7.7)	4 (1.2)	0 (0.0)	30 (8.9)
Otitis media	17 (5.0)	7 (2.1)	2 (0.6)	26 (7.7)
Ear infection	20 (5.9)	5 (1.5)	0 (0.0)	25 (7.4)
Diarrhea	20 (5.9)	4 (1.2)	0 (0.0)	24 (7.1)
Irritability	18 (5.3)	3 (0.9)	0 (0.0)	21 (6.2)
Nasal congestion	17 (5.0)	4 (1.2)	0 (0.0)	21 (6.2)
Pneumonia	6 (1.8)	8 (2.4)	7 (2.1)	21 (6.2)
Ataxia	9 (2.7)	10 (3.0)	1 (0.3)	20 (5.9)
Bronchitis	14 (4.2)	5 (1.5)	0 (0.0)	19 (5.6)
Constipation	14 (4.2)	3 (0.9)	0 (0.0)	17 (5.0)
Rash	15 (4.5)	2 (0.6)	0 (0.0)	17 (5.0)

7.1.5.4 Common adverse event tables

See above section (“Incidence of Common adverse Events”).

7.1.5.5 Identifying common and drug-related adverse events

The best analysis of for the determination of drug related adverse events would come from placebo controlled studies. Low dose controlled studies are helpful, but the unbalanced design of the present study complicates their impetration. As a whole there was no evidence in the present studies that would suggest a different profile of common, treatment-emergent, adverse events as has already been described and are included in the present labeling (see Appendix A). For a comparison between the present study with prior study the reader is referred to the above section on "Incidence of Common Adverse Events."

7.1.5.6 Additional analyses and explorations

The Sponsor tabulated events in all patients (group 1) less then 4 years old based upon mean daily dose. A tabulation of these data for "most frequent adverse events) (i.e. with occurrence of $\geq$ 10% in any subgroup) is presented below. Little can be said for the >60 mg/kg/day group because so few patients are included. Comparison of the < 20 with the 20-60 mg/kg/day doses indicates more common adverse events were observed with the high dose. Many of these common adverse events that are observed at a higher are at greater doses are symptoms associated with infections (e.g. pyrexia, cough, etc.). Convulsions are again seen to occur more commonly in the high dose groups. These conclusions are similar to the group 2 analysis described above. There is however a caveat; the data is unbalanced for period of exposure. Thus, low dose groups likely predominately include data from the short pivotal trials (patients who did not go on to the extended trials) and high dose data would include patients from these as well as long term extension trials. It is therefore difficult to conclude causality and dose dependency from this data.

	Mean daily dose			
	<20 mg/kg/day (N = 60)	20 to 60 mg/kg/day (N = 169)	>60 mg/kg/day (N = 12)	Total (N = 241)
	n (%)	n (%)	n (%)	n (%)
Total patients with adverse events	45 (75.0)	151 (89.3)	10 (83.3)	206 (85.5)
Preferred term				
Pyrexia	9 (15.0)	52 (30.8)	3 (25.0)	64 (26.6)
Upper respiratory tract infection	8 (13.3)	31 (18.3)	2 (16.7)	41 (17.0)
Vomiting	7 (11.7)	29 (17.2)	4 (33.3)	40 (16.6)
Convulsion	3 (5.0)	29 (17.2)	2 (16.7)	34 (14.1)
Somnolence	6 (10.0)	27 (16.0)	1 (8.3)	34 (14.1)
Nasopharyngitis	6 (10.0)	26 (15.4)	0 (0.0)	32 (13.3)
Cough	3 (5.0)	25 (14.8)	0 (0.0)	28 (11.6)
Otitis media	2 (3.3)	23 (13.6)	0 (0.0)	25 (10.4)
Ear infection	6 (10.0)	18 (10.7)	0 (0.0)	24 (10.0)
Diarrhea	4 (6.7)	15 (8.9)	2 (16.7)	21 (8.7)
Nasal congestion	3 (5.0)	18 (10.7)	0 (0.0)	21 (8.7)
Pneumonia	3 (5.0)	18 (10.7)	0 (0.0)	21 (8.7)

Common adverse event incidence was examined by preferred terms and organ class for different periods following treatment. The table below presents this tabulation by preferred term. Many of the common adverse events (e.g. somnolence, vomiting ataxia, dizziness, irritability, etc), particularly those related to a CNS effect, exhibited a greater incidence in the early phase of treatment and subsequently declined. These data are very rough as they have not been corrected for differences in exposure time between the various bins. Moreover it is difficult to determine from this data as to whether this simply represents habituation or drop out.

Preferred term	Onset < 1 mo n (%)	Onset 1-<3 mos n (%)	Onset 3-<6 mos n (%)	Onset >=6 mos n (%)
Total patients at risk	337	304	248	163
Total patients with AEs	207 (61.4)	182 (59.9)	128 (51.6)	40 (24.5)
Pyrexia	35 (10.4)	27 (8.9)	21 (8.5)	11 (6.7)
Somnolence	33 (9.8)	13 (4.3)	7 (2.8)	1 (0.6)
Vomiting	30 (8.9)	13 (4.3)	16 (6.5)	4 (2.5)
Upper respiratory tract infection	16 (4.7)	18 (5.9)	17 (6.9)	4 (2.5)
Ataxia	15 (4.5)	5 (1.6)	0 (0.0)	1 (0.6)
Convulsion	14 (4.2)	16 (5.3)	14 (5.6)	2 (1.2)
Cough	14 (4.2)	14 (4.6)	4 (1.6)	4 (2.5)
Irritability	14 (4.2)	5 (1.6)	3 (1.2)	0 (0.0)
Diarrhoea	13 (3.9)	5 (1.6)	9 (3.6)	1 (0.6)
Rash	12 (3.6)	6 (2.0)	0 (0.0)	0 (0.0)
Dizziness	11 (3.3)	4 (1.3)	3 (1.2)	0 (0.0)
Nasopharyngitis	11 (3.3)	15 (4.9)	12 (4.8)	3 (1.8)
Status epilepticus	11 (3.3)	4 (1.3)	3 (1.2)	0 (0.0)
Nasal congestion	10 (3.0)	6 (2.0)	5 (2.0)	5 (3.1)
Fatigue	9 (2.7)	1 (0.3)	2 (0.8)	0 (0.0)
Constipation	8 (2.4)	6 (2.0)	3 (1.2)	0 (0.0)
Headache	8 (2.4)	6 (2.0)	4 (1.6)	2 (1.2)
Influenza	8 (2.4)	9 (3.0)	4 (1.6)	1 (0.6)
Decreased appetite	7 (2.1)	5 (1.6)	2 (0.8)	0 (0.0)
Nausea	7 (2.1)	2 (0.7)	6 (2.4)	0 (0.0)

The Sponsor performed an in depth subgroup analysis for gender, race and age in patients < 4 years old. This age range was examined because previous studies were performed in and the drug is labeled (for adjunctive treatment) for an older pediatric patient population.

The Sponsor examined gender differences for all adverse events for patients included in all new trials (Group 1). Female patients appeared to show a slightly greater incidence of adverse event occurrence. Thus 88% of female suffered AEs as compared to 83% of males. A table presenting the most common adverse events (≥ 5% of any gender group) is included in the table below. There was a trend for a greater incidence of adverse events in females. These differences were, however, small in magnitude. Thus, except for influenza, there was a less then 5% difference. There were also notable exceptions (e.g. ataxia and status epilepticus was more common in males). Without background incidences it is difficult to determine if such small difference are related to a gender/drug interaction.

	Gender		
	Male (N = 132)	Female (N = 109)	Total (N = 241)
	n (%)	n (%)	n (%)
Total patients with adverse events	110 (83.3)	96 (88.1)	206 (85.5)
Preferred term			
Pyrexia	32 (24.2)	32 (29.4)	64 (26.6)
Upper respiratory tract infection	21 (15.9)	20 (18.3)	41 (17.0)
Vomiting	19 (14.4)	21 (19.3)	40 (16.6)
Convulsion	17 (12.9)	17 (15.6)	34 (14.1)
Somnolence	17 (12.9)	17 (15.6)	34 (14.1)
Nasopharyngitis	18 (13.6)	14 (12.8)	32 (13.3)
Cough	17 (12.9)	11 (10.1)	28 (11.6)
Otitis media	14 (10.6)	11 (10.1)	25 (10.4)
Ear infection	13 (9.8)	11 (10.1)	24 (10.0)
Diarrhea	10 (7.6)	11 (10.1)	21 (8.7)
Nasal congestion	9 (6.8)	12 (11.0)	21 (8.7)
Pneumonia	12 (9.1)	9 (8.3)	21 (8.7)
Irritability	9 (6.8)	11 (10.1)	20 (8.3)
Ataxia	10 (7.6)	6 (5.5)	16 (6.6)
Bronchitis	9 (6.8)	7 (6.4)	16 (6.6)
Constipation	6 (4.5)	8 (7.3)	14 (5.8)
Influenza	4 (3.0)	10 (9.2)	14 (5.8)
Status epilepticus	9 (6.8)	4 (3.7)	13 (5.4)
Rash	4 (3.0)	6 (5.5)	10 (4.1)
Dehydration	2 (1.5)	7 (6.4)	9 (3.7)
Urinary tract infection	2 (1.5)	7 (6.4)	9 (3.7)

Of 337 patients included in the group 1 database 237 were Caucasian, 33 were black, 1 was Asian and 66 were other. For analysis of relative rates of adverse events the single Asian

patients was included under the category of other. The numbers of patients experiencing adverse events across all groups were 82.1% for Blacks; 86.0% for Caucasians; 85.7% for "Other." There were differences in the incidence of a variety of specific adverse events between these different racial groups. These differences were at times large. Tabulation of some of the more common adverse events by racial groups is presented in Appendix E. As to whether these differences drug related differences in sensitivity are beyond the power of the data (very few blacks were included in the data base).

Age differences are discussed in the sections above.

Disease related factors were not explored by the Sponsor nor was the safety profile, based upon concomitant medication.

7.1.6 Less Common Adverse Events

See above.

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

The following laboratories were routinely obtained in the reported studies:

- Hematology: hemoglobin, hematocrit, complete blood cell count with differential and platelet count.
- Serum chemistry: serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), alkaline phosphatase, lactate dehydrogenase (LDH), blood urea nitrogen (BUN), bilirubin (total and direct), creatinine, sodium, potassium, chloride, calcium, uric acid, total protein, albumin and glucose.
- Urinalysis: protein (albumin), glucose, bilirubin, white blood cell count (WBC) and red blood cell count.

Populations analyzed are from the same studies as those described above for adverse events. Laboratories were generally analyzed in a central lab.

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

Data were collected from studies that are noted above for adverse event analysis except only a group 1 analysis was performed. The Sponsor justifies this by noting that the data from patients in dose controlled studies (Group 2) is similar to that observed for all OXC-treated patients (Group 1). The present labeling, which includes adult and pediatric (< 4 years old), was in part a result of comparative placebo/drug analysis of collective data (pediatric and adults).

7.1.7.3 Standard analyses and explorations of laboratory data

Data were analyzed in terms of: 1) number and percent of patients with lab values above or below clinically notable values at any visit and at 2 or more consecutive visits, (the table below presents such criteria), 2) Changes from baseline to final visits, 3) shift table from baseline to final visit in laboratory results (i.e. shift from normal, low or high to normal low or high values).

	Less Than	Greater Than
Hematology		
RBC		
<6 months	2.9 m/mm3	6.8 m/mm3
≥6 months	3.3 m/mm3	6.8 m/mm3
Hemoglobin		
<6 months	8.7 g/dL	20 g/dL
≥6 months	10 g/dL	20 g/dL
Hematocrit		
<6 months	25%	60%
≥6 months	30%	60%
Platelet Count		
<2 years	220 k/mm3	620 k/mm3
≥ 2 years	100 k/mm3	600 k/mm3
WBC	3.0 k/mm3	16.2 k/mm3
Neutrophils		
<2 years	14%	69%
≥ 2 years	30%	90%
Basophils	0%	6%
Eosinophils	0%	10%
Lymphocytes		
<6 months	30%	70%
≥ 6 months	10%	60%
Monocytes	0%	20%
Chemistry		
Glucose	50 mg/dL	200 mg/dL
Sodium[1]	125 mEq/L	150 mEq/L
Potassium	3.5 mEq/L	5.0 mEq/L
Chloride	85 mEq/L	119 mEq/L
Calcium	7.5 mg/dL	11.6 mg/dL
BUN	2 mg/dL	30 mg/dL
Uric Acid	1.5 mg/dL	10 mg/dL
Alkaline Phosphatate		
<11 years	0	420 U/L
≥11 years	0	700 U/L
Albumin	2.5 g/dL	6.0 g/dL
Creatinine	0.2 mg/dL	1.6 mg/dL
AST (SGOT)	0 U/L	100 U/L
ALT (SGPT)	0 U/L	100 U/L
LDH	0 U/L	500 U/L
Total Bilirubin	0.1 mg/dL	1.2 mg/dL
Direct Bilirubin	0 mg/dL	0.4 mg/dL
Total Protein	4 g/dL	9.5 g/dL
Urinalysis		
Glucose		+
Bilirubin		+
Protein		+
RBC		>5
WBC		>5

[1] In addition, treatment emergent sodium values <135 mEq/L are also summarized.

7.1.7.3.1 Analyses focused on measures of central tendency

7.1.7.3.1.1 Hematology

The table below presents central trend data (mean and median) of selected hematological values for group 1 patients. Cell indices, except the differential counts, are in terms of absolute count. The differential is in terms of percent (and not absolute values). This does not include the complete analysis (e.g. Hgb percent, basophiles etc.), but the data not presented is non-contributory. There was little clinically significant change in RBC and HCT which is consistent with lack of evidence from outlier based upon "notable laboratory" criteria.

Despite the large number of patients with increased WBC values in the "notable laboratory" analysis there were small reductions in measures of central tendency for WBCs (see below) and small increases in percent neutrophils and decreases in percent lymphocytes. These likely are probably clinically insignificant, suppression of cell count. Similar effects have been observed for other anticonvulants. There was generally no notable patients with notable reductions in "WBC" count. There were cases of decreased neutrophils absolute count. For a discussion of these the reader is referred to below. Analysis of central tendency for changes of WBCs and neutrophils in previous NDA submission did not indicate a significant reduction in placebo-control comparisons.

	Patients <4 years old		Patients ≥ 4 years old	
	Mean Baseline	Change at final visit Mean (Median)	Baseline	Change at final visit Mean (Median)
RBC	4.48	0.03 (0.0)	4.73	-0.06 (-0.10)
HCT	0.38	0.005 (0.0)	0.40	-0.001 (0.0)
Platelets	374.9	-19.7 (-15.5)	310	-9.8 (-9.5)
WBC	9.99	-0.55 (-0.50)	6.93	-0.21 (-0.20)
% neutrophils	34.9	2.3 (2.0)	50.4	0.1 (0.5)
% lymphocytes	54.2	-2.6 (-3.0)	37.7	-0.5 (0.0)

7.1.7.3.1.2 Clinical Chemistry

The table below presents mean and median changes in the clinical laboratories in patients divided into two age groups. As can be observed no clinically significant mean alterations in chemistries are obvious. Differences between the age groups were small. There may be a slight propensity for greater, but likely clinically insignificant, increases in GOT and GPT in younger patients. This observation was supported by outlier evaluation below. A similar very slight increased propensity for sodium decreases may occur in the younger pediatric patients. This is also supported by outlier evaluation (see below). The differences of the mean values are very small.

	< 4 years old		≥ 4 years old	
	Mean Baseline	Change at final visit mean (median)	Mean Baseline	Change at final visit mean (median)
glucose (mM)	4.89	-0.15 (-0.20)	4.77	0.28 (0.30)
Na (mM)	139.7	-1.7 (-1.0)	139	0.1 (0.0)
K (mM)	4.58	-0.08 (0.0)	4.26	-0.02 (0.0)
Cl (mM)	104.0	-1.7 (-1.0)	103.8	-0.5 (0.0)
Ca (mM)	2.49	-0.01 (-0.01)	2.41	-.02 (-.02)
Urea (mM)	3.91	0.21 (0.0)	4.68	-0.13 (0.0)
Uric Acid (mM)	0.207	-0.024 (-0.03)	0.233	-.026 (-.030)
Alk Phos (U/L)	303	13 (-6)	291	11 (-2)
GOT (U/L)	36.3	1.8 (1.0)	26.5	-2.0 (-1.0)
GPT (U/L)	23.0	3.2 (1.0)	19.6	-2.0 (0.0)
LDH (U/L)	288	-11 (-2)	209	13 (7)
Bilirubin total (uM)	2.7	-0.3 (0.0)	5.9	-1.8 (-2.0)
Bilirubin direct (uM)	0.4	0.0 (0.0)	1.4	-0.5 (0.0)
Creatinine (uM)	25.7	1.0 (0.0)	55.9	-1.0 (0.0)
Albumen (g/L)	43.17	0.24 (0.0)	44.58	0.04 (0.0)
Total Protein	67.6	0.7 (1.0)	72.5	-1.3 (-0.5)

7.1.7.3.2 Analyses focused on outliers or shifts from normal to abnormal

7.1.7.3.2.1 Hematology

Number (and percent) of patients (group 1) with notable post-baseline alterations (high and low) in hematological indices are presented in the table below. The Sponsor notes that the most salient change is the number of patients with increased lymphocytes (41.3% of all patients) and the number of patients with decreased neutrophils (18.1 % of all patients). The incidences for these outliers were substantially more common in patients younger then 4 years old and in the case of lymphocyte changes, were even more common in the very young (<2 years old). The Sponsor suggests that both changes may be linked to the increased incidence of viral infections. Such an effect may be a direct bone marrow effect from resulting infection.[20] But, it should also be noted that the low/high criteria was based upon percent of total WBC and a general lymphocytosis resulting from a viral infection may numerically reduce the percent of neutrophils of total WBCs . For this reason the Sponsor was asked to provide this reviewer with means in terms of absolute neutrophil and lymphocyte counts. Absolute outlier data were provided by the Sponsor on a 6/10/05 e-mail following a request on 6/3/05. The table below presents outlier data for patient with lymphocyte and neutrophile counts less then 1,000/mm^3 in 269 patients from the

20 Neutropenia is known to occur transiently with viral or bacterial infections because of increase margination or bone marrow suppression.

total database patients where absolute counts were available. As apparent from this table, only one patient was noted to have low lymphocyte count < 1,000/mm^3. Twelve patients, however, were observed to have a low neutrophile counts <1,000/mm^3. Most of these were in the <2 years old group and all were <4 years old. Five of these patients had low neutrophile values at the visit prior to administration of study drug with values ranging from 840 to 1470/mm^3. The Sponsor also notes that five of the 12 patients had absolute neutrophil counts below 1000/mm^3 during the study, but remained on study drug and the absolute neutrophil counts returned to normal values. The Sponsor notes that one of these patients (CTRI676E2340 0038-00003) met the definition of "neutropenia" with counts <500/mm^3 (460 /mm^3). The neutrophile count in this patient, however, returned to normal with continued treatment. One additional patient is described as having a low absolute neutrophil count at the final study visit. Examination of this data indicates large fluctuation in neutrophile with a basline neutrophile count of 1,960/mm^3 and low platelet count of 980/mm^3. This subsequently returned to normal and in fact in further follow-up with the Sponor on 6/13/04 level returned to 2,110 /mm^3 on the last day on record. One patient had neutrophil counts that fluctuated throughout the study (MEX/0072/00010 in study 2340). This patient is described below as part of a serious adverse event, pneumonia. At that time of the report of pneumonia the counts were only borderline low (1,760/mm^3). These data appear to indicate that low neutrophile counts are more common in younger patients. Off note, no patients were discontinued for reasons of neutropenia. It appears that these data may result from a combination of factores that might include a mild myelosuppressive effect, increased incidence of infections in the younger population and the tendency toward lower norms. Count supreesion is ferqeuntly transient. These do not appear as part of a more serious agranulocytosis or aplastic anemia.

	<2 years	2-4 years	>4 years	Total
n	148	81	40	269
Number (%) of patients with <1,000 /mm^3 neutrophiles	9 (6.1%)	3 (3.7%)	0.0 (0.0%)	16 (5.9%)
Number (%) of patients with <1,000 /mm^3 lymphocytes	0 (0.0%)	1 (1.2%)	1 (0.4)	1 (0.4%)

Changes in platelet count were also observed with decreases (in 9.8% of patients) and increases (7 % of patients) occurring at about the same rate. Larger proportions of patients were noted to have reductions in platelets in the very young (2 years). The Sponsor feels this age difference may result from the difference criteria used for older and younger patients. Thus, the Sponsor notes that the criteria in the <2 year age group (100) was defined conservatively by "lower limit of the normal range" as the expanded clinically notable values were not known for this young

population." Nonetheless, the mean reduction in platelet count for younger patients was larger (see central tendencies, above). Such an effect may be a true, but its significance is unknown.

Total WBCs were notably elevated with a greater frequency occurring in younger groups. This is likely a result of the observed changes noted in lymphocytes with a higher incidence of infections in this group.

To help determine the significance of some of these hematological changes one can examine the incidence of notable results in 2 or more consecutive examinations. The comparison to single value incidence reveals substantially lower rates, indicating that many of these shifts may be transient in nature. An examination of this data reveals a similar age dependency of the lymphocytosis with 0% in ages >4 years old, 3.7 % in ages 2-4 years old and 29% at <2 years old. This speaks to the fact that this likely represents a true age difference but does not address whether this is drug related. As the Sponsor suggests, this may simply represent differences in infection rate between age groups. Substantially fewer patients had lower neutrophils counts then observed in the above single observation analysis with no patients >4 years old experiencing this, but 11.1% and 3.4 % experiencing notably low neutrophils in ages <2 and 2-4 years old, respectively. Very few consecutive shifts were noted in platelets; all cases were observed in the <2 year old group (3.4%).

Table 5-2 Patients with clinically notable hematology values at any visit post-baseline by age: Group 1 – all OXC-treated patients

		Age				
		<2 yrs n (%)	2 to <4 yrs n (%)	<4 yrs n (%)	>=4 yrs n (%)	Total n (%)
Basophils	N	148	81	229	86	315
	Low	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	High	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Eosinophils	N	148	81	229	86	315
	Low	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	High	3 (2.0)	4 (4.9)	7 (3.1)	3 (3.5)	10 (3.2)
Hematocrit	N	148	81	229	87	316
	Low	2 (1.4)	0 (0.0)	2 (0.9)	0 (0.0)	2 (0.6)
	High	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hemoglobin	N	148	81	229	89	318
	Low	9 (6.1)	3 (3.7)	12 (5.2)	0 (0.0)	12 (3.8)
	High	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Lymphocytes	N	148	81	229	86	315
	Low	0 (0.0)	3 (3.7)	3 (1.3)	1 (1.2)	4 (1.3)
	High	102 (68.9)	22 (27.2)	124 (54.1)	6 (7.0)	130 (41.3)
Monocytes	N	148	81	229	86	315
	Low	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	High	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Neutrophils	N	148	81	229	86	315
	Low	31 (20.9)	22 (27.2)	53 (23.1)	4 (4.7)	57 (18.1)
	High	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Platelet count (direct)	N	148	81	229	86	315
	Low	31 (20.9)	0 (0.0)	31 (13.5)	0 (0.0)	31 (9.8)
	High	15 (10.1)	5 (6.2)	20 (8.7)	2 (2.3)	22 (7.0)
RBC	N	148	81	229	87	316
	Low	1 (0.7)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.3)
	High	1 (0.7)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.3)
WBC	N	148	81	229	87	316
	Low	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	High	24 (16.2)	4 (4.9)	28 (12.2)	1 (1.1)	29 (9.2)

7.1.7.3.2.2 Clinical Chemistry

Notable clinical chemistries, by age, are presented in the table below. The most frequent notable laboratory changes were increased alkaline phosphatase, increased serum potassium and reduced sodium.

The increased alkaline phosphatase appeared to be inversely related to age. The Sponsor speculates that this elevation is related to the relation of elevated alkaline phosphatase and growth in children.

The elevated potassium also appeared to be inversely related to age. The Sponsor suggests that this change may be related to an increased incidence of sample hemolysis that is common with blood collection techniques in young children.

As apparent from the table hyponatremia was more common in the younger pediatric patents. However, as previously discussed (see section on hyponatremia) when comparing certain outlier data, hyponatremia appeared more common in adults. Using marked outlier criteria (<125 mM) younger pediatric patients (< 2years) had similar risk for hyponatremia as adults.

A small number of patients exhibited increase in direct and total bilirubin, 3 and 1 respectively. All children were less then 4 years old. Some children also exhibited increases in GOT and GPT (15 and 11, respectively). These changes in LFTs were solely observed in younger patients. This reviwer requested additional information including transaminase and alkaline phosphatase for these 3 cases of increased bilirubin from the Sponsor on 6/2/05. The Sponsor provided this information on 6/10/05. The table below presents bilirubin levels with associated transaminase and alkaline phosphates. In this table asterisk denotes abnormal values. The data is somewhat confusing in that the total bilirubin in two cases are greater then the direct. In one case (0516/00002) bilirubin is not associated with transaminase elevation and was transient and borderline. In the another case (0516/00005) while the direct bilirubin is elevated about three fold to normal limits the transaminases are not elevated. Moreover, in this case direct bilirubin was elevated before drug, but to a lesser extent and remained so throughout treatment. In this case there was a mild alkaline phosphates elevation that preexisted drug administration. The last case of elevation was associated with significant elevation of alkaline phosphates and examination for the tables provided by the Sponsor indicates the elevation was transient with continued treatment. These data do not provide evidence fro hepatotoxicity.

	Total Bilirubin uM/L	Direct Bilirubun umol/L	GOT U/L	GPT U/L	Alkaline Phosphatase U/L
USA/0503/00005	6	30*	212*	67*	713*
USA/0516/00002	3	11*	28	10	251
USA/0528/00005	22*	17*	27	20	483*

		Age				
		<2 yrs n (%)	2 to <4 yrs n (%)	<4 yrs n (%)	>=4 yrs n (%)	Total n (%)
Albumin	N	149	82	231	90	321
	Low	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	High	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Alkaline phosphatase	N	149	82	231	90	321
	Low	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	High	28 (18.8)	11 (13.4)	39 (16.9)	3 (3.3)	42 (13.1)
Bilirubin (direct)	N	149	82	231	90	321
	Low	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	High	2 (1.3)	1 (1.2)	3 (1.3)	0 (0.0)	3 (0.9)
Bilirubin (total)	N	149	82	231	90	321
	Low	20 (13.4)	12 (14.6)	32 (13.9)	2 (2.2)	34 (10.6)
	High	0 (0.0)	1 (1.2)	1 (0.4)	0 (0.0)	1 (0.3)
Calcium	N	149	82	231	90	321
	Low	1 (0.7)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.3)
	High	4 (2.7)	0 (0.0)	4 (1.7)	0 (0.0)	4 (1.2)
Chloride	N	149	82	231	90	321
	Low	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	High	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Creatinine	N	149	82	231	90	321
	Low	12 (8.1)	4 (4.9)	16 (6.9)	0 (0.0)	16 (5.0)
	High	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Glucose	N	149	82	231	40	271
	Low	4 (2.7)	0 (0.0)	4 (1.7)	1 (2.5)	5 (1.8)
	High	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
LDH	N	149	82	231	90	321
	Low	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	High	13 (8.7)	3 (3.7)	16 (6.9)	2 (2.2)	18 (5.6)
Potassium	N	149	82	231	90	321
	Low	2 (1.3)	3 (3.7)	5 (2.2)	3 (3.3)	8 (2.5)
	High	68 (45.6)	11 (13.4)	79 (34.2)	3 (3.3)	82 (25.5)
SGOT (AST)	N	149	82	231	90	321
	Low	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	High	11 (7.4)	4 (4.9)	15 (6.5)	0 (0.0)	15 (4.7)
SGPT (ALT)	N	149	82	231	90	321
	Low	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	High	8 (5.4)	3 (3.7)	11 (4.8)	0 (0.0)	11 (3.4)
Sodium	N	149	82	231	90	321
(<125 mEq/L)	Low	2 (1.3)	0 (0.0)	2 (0.9)	0 (0.0)	2 (0.6)
(<135 mEq/L)	Low	45 (30.2)	20 (24.4)	65 (28.1)	9 (10.0)	74 (23.1)
	High	3 (2.0)	3 (3.7)	6 (2.6)	2 (2.2)	8 (2.5)
Total Protein	N	149	82	231	90	321
	Low	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	High	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Urea	N	149	82	231	90	321
	Low	1 (0.7)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.3)
	High	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Uric Acid	N	149	82	231	90	321
	Low	14 (9.4)	7 (8.5)	21 (9.1)	1 (1.1)	22 (6.9)
	High	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

7.1.7.3.2.3 Urinalysis

Information on clinically notable changes in the urinalysis, by age, is presented in the table below. The most common abnormalities included the presence of WBCs and protein in urine. Although WBCs were seen in a total of 31 patients, only 4 of these had consecutive urinalyses with WBCs. Although the presence of WBCs did not appear to be dependent on age, the presence of protein was more common in younger patients. Although not commented on by the Sponsor the presence of protein likely represents the normal transient "physiological proteinuria" seen in children that is inversely proportional to age. Supporting this is the observation that no patients had two consecutive incidences of proteinurea. The frequent infections may have also contributed to this. The Sponsor does not comment on the cause of WBCs but they were likely largely the result of previously noted urinary tract infections. A few patients exhibited RBCs in urine. Although not commented on by Sponsor, this may be largely related to the presence of urinary tract infections. Because there is no placebo comparison, absolute significance of these baseline abnormalities are difficult to determine in a definitive fashion. Previous examination of adult and pediatric placebo controlled data from the original NDA submission failed to recognize a signal from the urinalysis data.

		Age				
		<2 yrs n (%)	2 to <4 yrs n (%)	<4 yrs n (%)	>=4 yrs n (%)	Total n (%)
Bilirubin	N	140	77	217	39	256
	Low	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	High	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Glucose	N	140	77	217	39	256
	Low	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	High	1 (0.7)	0 (0.0)	1 (0.5)	1 (2.6)	2 (0.8)
Protein	N	140	77	217	39	256
	Low	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	High	20 (14.3)	6 (7.8)	26 (12.0)	1 (2.6)	27 (10.5)
RBC/HPF (Red Blood Cells)	N	140	77	217	39	256
	Low	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	High	7 (5.0)	2 (2.6)	9 (4.1)	2 (5.1)	11 (4.3)
UWBC	N	140	77	217	39	256
	Low	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	High	20 (14.3)	6 (7.8)	26 (12.0)	5 (12.8)	31 (12.1)

7.1.7.3.3 Marked outliers and dropouts for laboratory abnormalities

The Sponsor did not perform a formal analysis of marked laboratory outliers. They noted that no patients discontinued because "a primary cause of laboratory abnormalities." The Sponsor notes

that "some patients were discontinued due to a primary cause of adverse events involving laboratory abnormalities."

These narratives examined by this revwier. Of note, and already discussed in serious adverse event section, one patient (MEX/0072/00010 in study 2340) was noted to have a neutropenia associated with pneumonia. Cross referencing this narrative with information provided in an e-mail from the Sponsor (6/10/05), neutrophile count had dropped to 1,760 /mm^3 from a pres-drug baseline of 2,270 /mm^3. The patient was also on also on valproic acid and topiramate at the time of the adverse event. This patient recovered from the pneumonia after antibiotic treatment and was subsequently enrolled in the extension trial. ~~Presumably this represented a small transient neutropenia.~~ Neutrophile count varied during the follow-up period with all but one count being below 1,830 /mm^3. One count was 960 /mm^3 and another 6,860 /mm^3. The variability, and low basline, of these counts do not suggest a definitive drug effect. For more definitive discussion of white counts the reader is refered to the outlier section above.

Three cases of elevated liver function tests were noted in the narratives. These are described in the Table below. As can be seen one involved elevation in alkaline phosphates with no mention of transaminase or bilirubin. Another patient experienced a transient increase in liver function tests with resolution in spite of continuation of OXC. The third patient experienced a moderate increase in transaminase. There is no mention of changes in bilirubin in this narrative. This patient was discontinued with resolution of transaminase elevation. No definitive conclusions can be drawn regarding hepatotoxicity from these cases. Transaminase increases are mild to moderate and ~~no mention is made of changes in bilirubin~~bilirubin was normal.

Patient #	Age	Dose	LFTs	Comments
FR/0037/ 00002	11 month	60 mg/kg/day	GOT=78 GPT=83	The event occurred 2 month after OXC started and was associated with the serious adverse event of increased seizures. Increase LFTs resolved within 1 month with treatment continuation. ~~No mention of bilirubin change.~~Bilirubin was normal. Concomitant medication included clobazam and Phenytoin.
USA/0501 /00002	5 month	55.9 mg/kg/day	GOT=213 GPT-141	The event occurred 3 weeks after OXC started. The patient was hospitalized for this event. Bilirubin was normal. Concomitant anticonvulsants were phenobarbital. The patient was discontinued because of this event and LFTs completely recovered in about 1 month latter.
USA/0505/ 0004	5 month	18 mg/kg/day	Alk Phos=5122	The event occurred 6 month after OXC was started. Bilirubin was normal. The patient was discontinued from the study and alkaline phosphatase returned to normal in 1 month.

				Concomitant medications included phenobarbital and nystatin. No mention of bilirubin or

Three narratives were noted that describe hyponatremia. These are described in the table below. It is noteworthy that all are less then 2 years of age. As noted above this population may be more at risk then older children, but similar to that of adults. The presentation is s within 3 months of drug initiation and may be associated with alterations of mental status or seizures. The information contained in the present labeling adequately describes this information.

Patient #	Age	Dose	Sodium Level	Comments
USA/0504/ 0404	6 month	60 mg/kg/day	131	Admitted for convulsions about 1 month following OXC start. Sodium noted to be reduced. OXC dose slowly reduced to 30 mg/kg/day with resolution of hyponatremia
US/0507/ 00002	23 month	30.5 mg/kg/day	126-129	Over a period of 4 months the patient was admitted 2 times for the following reasons: 1) "altered" mental status, 2) lethargy, sensory loss fatigue, floppy infant, paralysis. Patient was treated with saline bolus and noted to recover. A last time patient presented with respiratory syncytial virus infection and noted to have hyponatremia (129). The infection was treated and patient recovered. This time patient's hyponatremia resolved with fluid restriction.
US/0507/ 00005	13 month	57 mg/kg/day	132	This patient was admitted for pneumonia and the sodium was coincidentally noted to be low2 months after OXC was initiated. Investigators did not believe that hyponatremia treatment needed to be initiated. Pneumonia resolved with treatment. The dose of OXC remained the same and 6 months latter sodium levels returned to normal.

Absolute neutrophils and lymphocytes marked outlier data are discussed in the section on outlier data above.

7.1.7.4 Additional analyses and explorations

The reader is referred to the analysis described in prior sections.

7.1.7.5 Special assessments

The reader is referred to the analysis described in prior sections.

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

Vital signs data were analyzed for all OXC-treated patients in the Group 1 population. Analysis included a separate analysis of ages <4 years old and ≥ 4 years old. The <4 year-old group was further analyzed by two age subgroups, <2 and 2 to <4 years of age. Analysis concentrated on the evaluation of incidences for outlier data. The age dependent criteria for outliers are presented in the table below.

Vital sign	Age group	Criteria
Heart Rate	<4 years	>160 bpm and increase from Baseline by 15 (high) <80 bpm and decrease from Baseline by 15 (low)
	4 - <12 years	>130 bpm and increase from Baseline by 15 (high) <70 bpm and decrease from Baseline by 15 (low)
	≥12 years	>120 bpm and increase from Baseline by 15 (high) <50 bpm and decrease from Baseline by 15 (low)
Systolic Blood Pressure	<4 years	>112 mmHg and increase from Baseline by 20 (high) <70 mmHg and decrease from Baseline by 20 (low)
	4 - <12 years	>125 mmHg and increase from Baseline by 20 (high) <70 mmHg and decrease from Baseline by 20 (low)
	≥12 years	>180 mmHg and increase from Baseline by 20 (high) <90 mmHg and decrease from Baseline by 20 (low)
Diastolic Blood Pressure	<4 years	>74 mmHg and increase from Baseline by 15 (high) <40 mmHg and decrease from Baseline by 15 (low)
	4 - <12 years	>85 mmHg and increase from Baseline by 15 (high) <40 mmHg and decrease from Baseline by 15 (low)
	≥12 years	>105 mmHg and increase from Baseline by 15 (high) <50 mmHg and decrease from Baseline by 15 (low)
Weight		≥7% decrease from Baseline weight (low)

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

All studies described for adverse events were utilized for these analyses. Only a group 1 type analysis was performed.

7.1.8.3 Standard analyses and explorations of vital signs data

7.1.8.3.1 Analyses focused on measures of central tendencies

The Sponsor did not perform this analysis.

7.1.8.3.2 Analyses focused on outliers or shifts from normal to abnormal

The table below presents the Sponsor's outlier analysis for vital signs and weight. The most common outlier observation was the elevation in systolic and diastolic blood pressures. These values were greatest for patients < 4 years old. The significance of this data is difficult to determine without a control comparison. The previous NDA review compared vital signs in experimental and placebo groups for pediatric patients greater and less then 12 years old. There appeared to be little or no difference when placebo and drug groups were compared in both age groups.

Vital Sign	Result	Age				Total n (%)
		<2 yrs n (%)	2 to <4 yrs n (%)	<4 yrs n (%)	>=4 yrs n (%)	
Diastolic BP (mmHg)	N	140	77	217	90	307
	Low	16 (11.4)	3 (3.9)	19 (8.8)	0 (0.0)	19 (6.2)
	High	27 (19.3)	17 (22.1)	44 (20.3)	3 (3.3)	47 (15.3)
Systolic BP (mmHg)	N	140	77	217	90	307
	Low	7 (5.0)	3 (3.9)	10 (4.6)	1 (1.1)	11 (3.6)
	High	38 (27.1)	13 (16.9)	51 (23.5)	9 (10.0)	60 (19.5)
Pulse (bpm)	N	147	79	226	91	317
	Low	9 (6.1)	9 (11.4)	18 (8.0)	8 (8.8)	26 (8.2)
	High	15 (10.2)	1 (1.3)	16 (7.1)	3 (3.3)	19 (6.0)
Weight (kg)	N	108	51	159	90	249
	Low	6 (5.6)	5 (9.8)	11 (6.9)	8 (8.9)	19 (7.6)

7.1.8.3.3 Marked outliers and dropouts for vital sign abnormalities

The Sponsor did not perform such an analysis.

7.1.8.4 Additional analyses and explorations

None were performed.

7.1.9 Electrocardiograms (ECGs)

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

No special EKG analysis study was performed. The EKG evaluation was obtained from routine EKGs included in the course of the clinical trials. This is described below.

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

Routine EKG monitoring was performed as part of all study protocols with the exception of 2337. As part of these protocols, EKG analyses were to be examined by on site investigators and clinically significant changes were to be reported in the CRFs. As a result of meeting with this division (3/24/04) the Sponsor was asked to perform a careful interval analysis. The Sponsor has subsequently performed an outlier evaluation. These were performed by a central reader. As Trileptal has been approved for older children, only patients < 4 years old were examined. EKG was generally performed at baseline and at the end of the studies. EKGs were not generally performed at a time synchronized to dosing. Both central and categorical analyses were performed for the group 1 and group 2 analysis populations.

7.1.9.3 Standard analyses and explorations of ECG data

7.1.9.3.1 Analyses focused on measures of central tendency

Central tendency, dose dependency, was examined for change from baseline to the final on-drug evaluation for group 2 children <4 years (low/high dose controlled pivotal studies). The table below summarizes results of this analysis. Little or no differences can be observed for the changes from baseline for the different measures. No dose dependent QT prolongation is apparent. If anything, there may be a slight shortening that is likely not clinically significant. These data, however, are not well controlled and must be interpreted with caution.

	QTcB (msec) Mean (median)	QTcF (msec) Mean (median)	PR (msec) Mean (median)	QRS (msec) Mean (median)	Rate – BPM Mean (median)
Low Dose (n=90)	-0.03 (-4.00)	0.10 (-1.00)	0.07 (0.0)	0.54 (0.0)	-0.69 (-3.0)
High Dose (n=89)	-5.60 (-7.50)	-4.6 (-5.50)	4.53 (4.0)	-121 (0.0)	-0.48 (-30)

7.1.9.3.2 Analyses focused on outliers or shifts from normal to abnormal

Outlier analysis was performed using endpoint outlier criteria presented in the table below.

ECG interval parameter	Criteria
QT	> 500 ms
QTcB (Bazett)	> 500 ms
QTcF (Fridericia)	> 500 ms
PR	> 200 ms
QRS	> 110ms
HR	<50 or >120

As part of the group 1 analysis a total of 207 patients were examined in two separate two age groups, <2 years (n=135) and ≥ 2 years to 4 years (n= 72) of age. No patients in any group were observed with a QTcB, QTcF PR or QRS interval fulfilling the outlier criteria during control or post dose final visit period. No patients during baseline or the final visit in any age group experienced heart rates of <50 BPM. While patients during baseline period and final treatment period exhibited increases in heart rate greater the 120 BPM, these changes were not consistent; i.e. there were similar rates of change for patients with decreasing rates from 120 to less then 120 when going from baseline to final visit as there were patients with increasing rates. No obvious abnormal EKG signal was therefore identified.

7.1.9.3.3 Marked outliers and dropouts for ECG abnormalities

Newly or worsening EKG were to be identified by investigator or on site cardiologist. Two such EKGs were identified, but were not reported as adverse events. The two are described below:

- Patient 0010/00012 in study 2340 had a normal QTc at baseline (QTc = 420) and a prolonged QTc at the completion visit of the Treatment Phase on Day 41 (QTc = 500). The type of correction was not noted. This value analyzed on site was not confirmed when read by the central reader. This patient entered the extension study and approximately 3 weeks later the patient's QTc value had returned to normal (QTc = 409). The return to normal values despite continued treatment would suggest that this may have been spurious measure (but were things controlled). This finding appears spurious as it was not confirmed with repeat EKG was normal.
- A second patient, 0507/00005 study 2340 had sinus bradycardia, sinus arrhythmia, and left axis deviation at baseline, and on study day 34 the ECG results showed a new abnormality (sinus tachycardia) and a worsening abnormality (right axis deviation). The significance of this isolated report and the potential of drug causality is difficult to determine.

Two additional events of EKG abnormalities were reported as adverse events. Both of these involved prolongation of the QT interval. Note the type of correction is not noted.

- Patient 0501/00001 in study 2339 had a prolonged QT interval (QTc = 529), right axis deviation, incomplete right bundle branch block, possible right ventricular hypertrophy, and nonspecific T wave abnormality on Day 6 of the Treatment Phase of the core study value analyzed and not confirmed when read by the central reader. The patient entered the Extension Phase of the study and approximately 3 weeks later the QT prolongation resolved on Day 28 (QTc = 455). The QT interval prolongation was not suspected to be related to study drug by the investigator. The lack of confirmation of this prolonged interval and the return to normal would suggest that it may not be clinically relevant.
- Patient 0501/00002 in study 2339 had a prolonged QT interval (QTc = 502) on Day 6 of the Treatment phase of the core study with sinus bradycardia and ST abnormality. The prolongation was analyzed locally but the significant QTc prolongation was not confirmed when read by the central reader. The patient entered the Extension Phase of the study and the QT prolongation resolved approximately 2 weeks later on Day 20 (QTc = 398). The prolonged QT interval was suspected by the investigator to be related to study drug.

The issue is then raised whether the QT prolongation identified in the above three patients is significant. In all cases the degree of QT prolongation, was not confirmed by the central reader. Moreover, the prolongation appeared to be at least partly resolved upon continued treatment. The problem, however, is this is not controlled data. No comparisons are made to placebo nor are these carefully collected EKG (multiple reading, controlled for time of day, time from treatment etc). Although no worrisome signal is raised a definitive conclusion cannot be made.

7.1.9.4 Additional analyses and explorations

No further analysis of this data was performed.

7.1.10 Immunogenicity

Not applicable.

7.1.11 Human Carcinogenicity

Not performed.

7.1.12 Special Safety Studies

See "Central Nervous System Symptom" section under "Other Significant Adverse Events."

7.1.13 Withdrawal Phenomena and/or Abuse Potential

Drug abuse potential was not studied. This drug is presently on the market. Withdrawal was not studied in this or prior development programs. There was one case of a "withdrawal syndrome" with epilepsy. The label presently contains information in "Warnings" regarding the risk of seizure with withdrawal of the medication.

7.1.14 Human Reproduction and Pregnancy Data

There were no pregnancies in these studies.

7.1.15 Assessment of Effect on Growth

Height measurements were not included in the present studies, nor was it requested as part of the pediatric written request. Data from weight analysis is included in the section on "Vital Signs." A small number of low weight outliers were noted but without control the significance of this is unknown.

7.1.16 Overdose Experience

The Sponsor notes that the clinical studies were not designed to explore doses above the therapeutic dose and that no new cases of overdose were observed in the present development program.

7.1.17 Postmarketing Experience

See "Postmarketing Experience" in the section "Description of Secondary Clinical Data Sources Used to Evaluate Safety" below.

Adequacy of Patient Exposure and Safety Assessments

This drug is presently approved for the use as adjunctive treatment in patients with epilepsy of partial origin at ages of 4 years old and above. Additional data is included on this demographic subgroup (patients older then 4 years old) of patients as monotherapy. Included with this is additional safety data on patients 1 month to 4 years old. Information on exposure (dose and duration) is included in the section below on demographics. While the number is not large, these data adequately compliment the already existing data on pediatric safety. Study safety monitoring was generally adequate. Types of safety monitoring (e.g. laboratories) were adequate. The only caveat is that the lack of placebo controls and the unbalanced design of some control studies (see above) make definitive conclusions regarding adverse event causality difficult at times. The present data with the previous large double-blind and open label database, however, allows for adequate review.

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

This information is contained in Section 4 in the subsections "Source of Clinical Data" and "Tables of Clinical Studies."

7.1.18.1 Study type and design/patient enumeration

This information is contained in Section 4 in the subsections "Source of Clinical Data" and "Tables of Clinical Studies."

7.1.18.2 Demographics

Basic demographics characteristics of the two study populations (see above) are presented in the table below. There is a satisfactory distribution across age and sex. While racial differences in

the study population are apparent this reviewer believes that these proportions are generally representative of the general study population.

Variable	Group 1 - all OXC-treated patients (N = 337)	Group 2 - OXC-treated patients in dose-controlled studies (N = 220)
Age		
1 to <6 months	38 (11.3%)	29 (13.2%)
6 to <12 months	50 (14.8%)	37 (16.8%)
12 to <24 months	70 (20.8%)	50 (22.7%)
24 to <48 months	83 (24.6%)	63 (28.6%)
4 to <8 years	32 (9.5%)	21 (9.6%)
8 to <16 years	60 (17.8%)	18 (8.2%)
16 years	4 (1.2%)	2 (0.9%)
Sex		
Male	176 (52.2%)	122 (55.5%)
Female	161 (47.8%)	98 (44.6%)
Race		
Caucasian	237 (70.3%)	145 (65.9%)
Black	33 (9.8%)	20 (9.1%)
Oriental	1 (0.3%)	0 (0.0%)
"Other"	66 (19.6%)	55 (25.0%)

Additional racial and ethnic were retrospectively collected because of a request of Office of Counter-terrorism and Pediatric Drug Development. These data are presented in the table below. The Sponsor notes that these data are similar but not completely consistent with the data above. This was attributed as "due to the differences in the description of races" in FDA's request as compared to the fashion data was prospectively collected.

Variable	Group 1 - all OXC-treated patients (N = 337)	Group 2 - OXC-treated patients in dose-controlled studies (N = 220)
Race		
American Indian or Alaska Native	18 (5.3%)	17 (7.7%)
Asian	5 (1.5%)	4 (1.8%)
Black or African American	35 (10.4%)	21 (9.6%)
White	251 (74.5%)	157 (71.4%)
"Other"	27 (8.0%)	20 (9.1%)
Unknown	1 (0.3%)	1 (0.5%)
Ethnicity		
Hispanic/Latino	94 (27.9%)	61 (27.7%)
Not Hispanic/Latino	202 (59.9%)	131 (59.6%)
Chinese	1 (0.3%)	1 (0.5%)
Indian/India subcontinent	3 (0.9%)	2 (0.9%)
"Other"	198 (58.8%)	128 (58.2%)
Unknown	41 (12.2%)	28 (12.7%)

7.1.18.3 Extent of exposure (dose/duration)

The number (and percent) of patients with various duration of exposures, divided by epochs and cumulative exposure, are presented in the table below. Descriptive statistics for exposures are also presented in this table. Greater then 60% of 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. It is noteworthy then the database for the initial submission of this NDA, which led to its approval, contained a total of 581 patients between the ages of 6 and 17 and 21 patients younger than 6 years old.[21]

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

	Age <2 yrs N=158	Age 2 to <4 yrs N=83	Age <4 yrs N=241	Age >=4 yrs N=96	Total N=337
Cumulative exposure (days)					
≥1 day	158 (100.0%)	83 (100.0%)	241 (100.0%)	96 (100.0%)	337 (100.0%)
≥30 days	136 (86.1%)	78 (94.0%)	214 (88.8%)	90 (93.8%)	304 (90.2%)
≥90 days	103 (65.2%)	64 (77.1%)	167 (69.3%)	81 (84.4%)	248 (73.6%)
≥180 days	69 (43.7%)	47 (56.6%)	116 (48.1%)	47 (49.0%)	163 (48.4%)
Duration of exposure (months)					
<1 month	22 (13.9%)	5 (6.0%)	27 (11.2%)	6 (6.3%)	33 (9.8%)
1 to <3 months	33 (20.9%)	14 (16.9%)	47 (19.5%)	9 (9.4%)	56 (16.6%)
3 to <6 months	34 (21.5%)	17 (20.5%)	51 (21.2%)	34 (35.4%)	85 (25.2%)
≥6 months	69 (43.7%)	47 (56.6%)	116 (48.1%)	47 (49.0%)	163 (48.4%)
Summary statistics (months)					
Mean	4.55	5.21	4.78	5.30	4.93
SD	2.738	2.533	2.683	1.831	2.479
Median	5.18	6.27	5.63	5.88	5.83
Min	0.07	0.07	0.07	0.17	0.07
Max	13.60	10.73	13.60	7.20	13.60

Because this submission principally focused on younger pediatric patients the Sponsor provided a breakdown of exposure by dose for patients < 4 years old. This is presented in the table below. As is apparent, most patients were exposed to doses of 20 to 60 mg/kg day. Except for the lower dose groups a majority of patients in the various age groups had exposures for greater then 6 months

Duration of exposure	Mean daily dose			Total N = 241
	<20 mg/kg/day N = 60	20 to 60 mg/kg/day N = 169	>60 mg/kg/day N = 12	
By frequency interval				
<1 months	20 (33.3 %)	6 (3.6%)	1 (8.3%)	27 (11.2%)
1 to <3 months	11 (18.3%)	34 (20.1%)	2 (16.7%)	47 (19.5%)
3 to <6 months	13 (21.7%)	36 (21.3%)	2 (16.7%)	51 (21.2%)
≥6 months	16 (26.7%)	93 (55.0%)	7 (58.3%)	116 (48.1%)
Summary Statistics (months)				
Mean ± SD	3.18 ± 2.581	5.27 ± 2.469	5.91 ± 3.014	4.78 ± 2.683
Median	2.72	6.2	6.28	5.63
Range	0.07 – 7.93	0.17 – 13.6	0.5 – 10.13	0.07 – 13.6

For the 96 patients older then 4 years 31 of 65 patients receiving 20-60 mg/kg/day groups and 2 of 5 receiving ≥60 mg/kg/day were treated for a period of greater then 6 month.

7.1.19 Description of Secondary Clinical Data Sources Used to Evaluate Safety

7.1.19.1 Other studies

The Sponsor briefly describes 6 worldwide phase 4 local epilepsy studies performed from the dates of 5/31/99 (time of approval) to 6/30/04. In total, 4 serious adverse events were observed in these studies. The Sponsor briefly describes only 2 where drug causality was suspected. No causality was suspected in the other two. These cases are described as follows: 1) epilepsy worsening (PHHO2002FR02653), 2) hyperthermia, scarletiform rash, epileptic seizures, and withdrawal reaction (PHHO2002FR03321). No deaths were reported.

Also a number of extension trials were ongoing during the time period that included some pediatric patient of 5/31/99 to 6/30/04. In these trials no serious events or deaths were reported for patients in the pediatric age group.

7.1.19.2 Postmarketing experience

As Trileptal has been approved for a number of years, post marketing adverse event data is available. The Sponsor performed a search in thier database for such data between the period of 5/31/99 to 6/30/04 in patients <17 years of age. A total of 970 patients with 1808 adverse events were identified.

Five fatalities were noted in this database. These were briefly described in the submission and are presented below:

- PHNU1998DE01112: An 11 year old male with systemic lupus erythematosus. Cause of death was not given. This was thought to be not drug induced lupus by reporters (negative dechallenge of several months). Phenytoin and phenobarbital were co-suspect medications.
- PHNU2000DE07848: A 10 year old male with rhabdomyolysis secondary to prolonged status epilepticus. Propofol was co-suspect.
- PHEH2000US06835: An 11 year old male with cause of death ascribed to seizure and asphyxiation.
- PHRM2001FR02260: A 9 year old male with sudden unexplained death in epilepsy. This patient was taking oxcarbazepine and valproate.
- PHBS2002BR03292: A 4 year-old male with a history of feeding difficulty. The patient underwent gastrostomy placement with subsequent complications including perforation, hemorrhage and multi-organ failure.

The Sponsor believes that all cases of death were a result of a secondary condition or the underlying seizure disorder. There is presently no reason to believe otherwise.

Included in the submission is a table presenting the frequency of adverse events by preferred terms. This reviewer examined this table and identified one worrisome case of "liver failure." To further investigate this the reviewer examined the AERS data base (AERS Datamart) using the key word of "hepatic failure." Three children were identified. One case was liver failure associated with the "DRESS syndrome." It should be noted that this is synonymous with the multi-organ hypersensitivity syndrome for which labeling has recently been added in precautions. Another case was liver failure, which resolved, that associated with a viral infection. A third case was liver failure as a result of "shock liver" that apparently resulted from a concomitant pneumopathy. These data do not indicate that a change in labeling is required.

The Sponsor discuses the most frequent reported events by primary system organ class. These included nervous system disorders (360 adverse events, 19.9%), skin and subcutaneous tissue disorders (219 adverse events, 12.1%), general disorders and administration site conditions (209 adverse events, 11.6%), investigations (177 adverse events, 9.8%), gastrointestinal disorders (173 adverse events, 9.6%), psychiatric disorders (136 adverse events, 7.5%), respiratory, thoracic and mediastinal disorders (98 adverse events, 5.4%) and infections and infestations (91 adverse events, 5.0%). A more careful discussion of the preferred term within this classification indicated this information does not indicate a change in the pediatric labeling.

7.1.19.3 Literature

Using Medline, the Sponsor performed a literature search for the period of time for articles describing Trileptal associated adverse events in the pediatric population from 5/31/99 to 6/30/04. A number of reports were identified. But, following the elimination of the reports that described data that originated from Novartis' program, six new reports were identified that the Sponsor felt were germane to safety issues. These articles are briefly described below:

- Chapman, Holland, Erenberg (2003) studied seizure exacerbation associated with oxcarbazepine in idiopathic focal epilepsy of childhood. This was a single case report and additional information may be required before an association can be made.
- Disabato, Levisohn, Laoprasert (2003) studied oxcarbazepine-related hyponatremia in pediatric patients. Brain tumors are a risk factor. Authors reviewed charts of two pediatric patients with hyponatremia and remote histories of brain tumors. Only two patients were reported, one of whom was successfully treated by an increase in sodium supplementation and continued OXC treatment.
- Kwon, et al (2004) evaluated QT intervals in 152 children (age 1 month to 18.9 years) with epilepsy on a number of different antiepileptic drugs compared with 26 age matched controls and found no significant difference between the two groups. The difference between the QTcF in the drug as compared to age matched control was made. The only

analysis performed specifically to evaluate OXC was the use of a 42 patient group who was on either OXC or carbamazepine (n=34). This group did not differ from control. This was not a well controlled QTc study and because of this it is this reviewer's opinion that this report lends little light on the effect of OXC on the QT interval.

- Vainionpaa, et al (2004) studied thyroid function in 78 girls, 8-18 years of age, on valproate, carbamazepine and oxcarbazepine. This publication indicated a small mean reduction in both free-T4 and T4 levels but no significant change in TSH in patients on CBZ and OXC. Sixty-seven percent of patients on OXC had an abnormally low T4 and/or FT4. Patients were clinically euthyroid without developmental anomalies. Upon follow up thyroid function tests of patients who had discontinued OXC (n=10) and CBZ (n=10) were noted to have normalized. The authors note that the present results were not worrisome as patients were euthyroid. This reviewer has previously reviewed this finding as part of an annual report (21014, 2-0005) and noted "this reviewer agrees with the investigators that this likely does not represent a medically significant effect." Some minor issues were raised, but they are presently under review by this division.
- Vaisleib, et al (2003) concluded children with intellectual disabilities may be at greater risk of developing status epilepticus when treated with oxcarbazepine. This conclusion was based upon a chart review of 20 patients in which 3 developed status epilepticus "when OXC was added" (time not specified). One patient had a prior history of status epilepticus. This was published in abstract form alone and in the opinion of this reviewer can only be considered preliminary.

The Sponsor believes that there is "no new relevant safety information." This reviewer generally agrees.

7.1.20 Adequacy of Overall Clinical Experience

With the inclusion of prior database in the original NDA review (7/23/99) the present submission contains a generally adequate database for examining the safety of OXC treatment in the pediatric population of 1 month and above. One complicating factor is the nature of the control database. Thus, this database was not placebo controlled but a low/high dose comparisons of

very short duration. Moreover and perhaps more important, exposures between groups in this control database were unbalanced: i.e. low dose exposure on average was of longer duration then high dose exposure. The present data, complimented by prior data and open label experience, probably allows for generally adequate experience. ,

7.1.21 Adequacy of Special Animal and/or In Vitro Testing

See previous reviews by Pharm/Tox.

7.1.22 Adequacy of Routine Clinical Testing

As previously noted these were adequate.

7.1.23 Adequacy of Metabolic, Clearance, and Interaction Workup

The reader is referred to the Clinical Pharmacology review.

7.1.24 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

The present study used adequate monitoring for a variety of adverse events.

7.1.25 Assessment of Quality and Completeness of Data

The submission was generally complete. At times this reviewer requested additional information from the Sponsor (see sections above). The Sponsor adequately answered this reviewer's requests.

7.1.26 Additional Submissions, Including Safety Update

Data from the December 13 submission reviewed in this submission utilized a cut-off date of 6/30/04. The Sponsor provided a safety update on 4/12/05. This safety update includes additional data for 46 pediatric patients with partial seizures, age 1 month to <4 years, from an extension study (2340-E1) that was newly completed. The original submission contained a preliminary report of this study. In addition, the Sponsor has provided post-marketing experience and other safety data pertaining to pediatric patients with epilepsy (<17 years of age) that occurred between 7/1/04 and 1/31/05. The inclusion of these data meant that 15 more patients were exposed for period of $\geq$ 3 months and 43 more patients for $\geq$ 6 months. The Sponsor has provided information for review based upon requested additional information or analysis (see above).

No new deaths were observed in the safety update for study 2340-E1. There were no new discontinuations because of serious adverse events or laboratory abnormalities. Three new serious adverse events were reported. These are briefly summarized as follows:

- Patient BR/0028/00009, a 13-month-old, female on 50 mg/kg/day of oxcarbazepine, was hospitalized for seizures approximately 3 ½ months after beginning treatment.
- Patient Mex/0072/00010, a 31 month old male on 57.4 mg/kg/day of oxcarbazepine, developed "uncontrolled seizures," 6 months after beginning treatment. The patient was admitted to the hospital and noted to have pharyngitis and also diagnosed with "epileptic encephalopathy." The patient was treated with antibiotic and fully recovered.
- Patient Mex/0072/00011, a 39 month old male on 57.9 mg/kg/day, was hospitalized for dengue fever 4 ½ months after beginning treatment. The patient was treated and recovered. The investigator noted that this may be related to an epidemic.

This new information in the safety update is similar to that described in the original submission and does not change conclusions on the safety profile of oxcarbazepine in the present population.

The Sponsor described pediatric patient's results from worldwide local Phase IV clinical studies and for other clinical studies that were ongoing during the interim time period of interest. Four serious adverse events were noted. The Sponsor only briefly describes 2 of the 4 cases were there was a suspected relation to drug. These cases are described as: 1) "status epilepticus, convulsion, hyponatremia, viral infection, nausea, diplopia and vomiting", 2) "rash pyrexia." Such reports do not obviously alter the adverse event profile already described in this submission.

One new pertinent article was identified in the world literature that described a case report of a 4 year old male who developed epileptic drop attacks following oxcarbazepine initiation. These resolved when the drug was discontinued.

New interim (01-Jul-2004 to 31-Jan-2005) pediatric postmarketing reports were identified and discussed by the Sponsor. Ninety two cases were identified. There were no deaths among these cases. The general adverse event profile amongst post-marketing reports did not differ from that described in the original submission.

The Sponsor notes that the additional data presented in the safety update was similar to that in the primary submission and indicated no new safety concerns. This reviewer agrees.

Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

This is described in above sections. To summarize those sections, the absence of placebo control data makes a definitive attribution difficult at times. However, comparison of previous pediatric studies with the present does not indicate that any labeling change is required.

General Methodology

7.1.27 Pooling Data Across Studies to Estimate and Compare Incidence

7.1.27.1 Pooled data vs. individual study data

Data were pooled for two group comparisons (group 1 and group 2) as noted above. Other important strategies of pooling that were performed, and which are discussed in prior sections, include grouping by age. This reviewer at times compared the analysis obtained from the present study to prior pediatric studies.

7.1.28 Explorations for Predictive Factors

Factors explored, which are discussed above, include age and dose.

8 ADDITIONAL CLINICAL ISSUES

Dosing Regimen and Administration

Drug dosage is described in the PK section and the review by Dr. Duan. Genearly the product should be labeled according to the target doses used in the present study.

Drug-Drug Interactions

This was not an important aspect of the present submission.

Special Populations

This was not a subject of the present submission.

Pediatrics

This application is a response to a Pediatric Written Request.

Advisory Committee Meeting

Not applicable.

Literature Review

See previous sections.

Postmarketing Risk Management Plan

None submitted.

Other Relevant Materials

Not applicable.

9 OVERALL ASSESSMENT

Conclusions

See next section on "Recommendation on Regulatory Action."

Recommendation on Regulatory Action

Trileptal is approvable based upon the following:

- 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 resulting because of ethical considerations. 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 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

9.1.1 Risk Management Activity

No specific recommendations are made.

9.1.2 Required Phase 4 Commitments

No specific recommendation are made.

9.1.3 Other Phase 4 Requests

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

Labeling Review

Labeling was reviewed by this reviewer in conjunction with Dr. Feeney, Team Leader, and Dr. Katz, division Director. The reader should refer to the approvable letter for recommendations.

10 APPENDICES

Appendix A: AE Pediatric report from protocol 011 in present label.

Table 6
Treatment-Emergent Adverse Event Incidence in Controlled Clinical Studies of Adjunctive Therapy/ Monotherapy in Pediatric Patients Previously Treated with Other AEDs (Events in at least 2% of patients treated with Trileptal and numerically more frequent than in the placebo group)

Body System/ Adverse Event	Oxcarbazepine N=171 %	Placebo N=139 %
Body as a Whole		
Fatigue	13	9
Allergy	2	0
Asthenia	2	1
Digestive System		
Vomiting	33	14
Nausea	19	5
Constipation	4	1
Dyspepsia	2	0
Nervous System		
Headache	31	19
Somnolence	31	13
Dizziness	28	8
Ataxia	13	4
Nystagmus	9	1
Emotional Lability	8	4
Gait Abnormal	8	3
Tremor	6	4
Speech Disorder	3	1
Concentration Impaired	2	1
Convulsions	2	1
Muscle Contractions Involuntary	2	1
Respiratory System		
Rhinitis	10	9
Pneumonia	2	1
Skin and Appendages		
Bruising	4	2
Sweating Increased	3	0
Special Senses		
Diplopia	17	1
Vision Abnormal	13	1
Vertigo	2	0

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Appendix B: Tabulation of Group 1 patients tabulation for patients experiencing adverse events in 1% of patients or higher.

Preferred term	Age <2 yrs N=158 n (%)	Age 2-<4 yrs N=83 n (%)	Age <4 yrs N=241 n (%)	Age >=4 yrs N=96 n (%)	Total N=337 n (%)
Total patients with AEs	134(84.8)	72(86.7)	206(85.5)	71(74.0)	277(82.2)
Pyrexia	45(28.5)	19(22.9)	64(26.6)	9(9.4)	73(21.7)
Vomiting	24(15.2)	16(19.3)	40(16.6)	10(10.4)	50(14.8)
Somnolence	21(13.3)	13(15.7)	34(14.1)	13(13.5)	47(13.9)
Upper respiratory tract infection	30(19.0)	11(13.3)	41(17.0)	2(2.1)	43(12.8)
Convulsion	25(15.8)	9(10.8)	34(14.1)	4(4.2)	38(11.3)
Nasopharyngitis	17(10.8)	15(18.1)	32(13.3)	5(5.2)	37(11.0)
Cough	17(10.8)	11(13.3)	28(11.6)	2(2.1)	30(8.9)
Otitis media	18(11.4)	7(8.4)	25(10.4)	1(1.0)	26(7.7)
Ear infection	16(10.1)	8(9.6)	24(10.0)	1(1.0)	25(7.4)
Diarrhoea	13(8.2)	8(9.6)	21(8.7)	3(3.1)	24(7.1)
Irritability	14(8.9)	6(7.2)	20(8.3)	1(1.0)	21(6.2)
Nasal congestion	15(9.5)	6(7.2)	21(8.7)	0(0.0)	21(6.2)
Pneumonia	17(10.8)	4(4.8)	21(8.7)	0(0.0)	21(6.2)
Ataxia	7(4.4)	9(10.8)	16(6.6)	4(4.2)	20(5.9)
Bronchitis	9(5.7)	7(8.4)	16(6.6)	3(3.1)	19(5.6)
Constipation	9(5.7)	5(6.0)	14(5.8)	3(3.1)	17(5.0)
Rash	8(5.1)	2(2.4)	10(4.1)	7(7.3)	17(5.0)
Headache	1(0.6)	4(4.8)	5(2.1)	11(11.5)	16(4.7)
Influenza	9(5.7)	5(6.0)	14(5.8)	2(2.1)	16(4.7)
Dizziness	1(0.6)	1(1.2)	2(0.8)	13(13.5)	15(4.5)
Decreased appetite	6(3.8)	2(2.4)	8(3.3)	6(6.3)	14(4.2)
Fatigue	3(1.9)	1(1.2)	4(1.7)	10(10.4)	14(4.2)

Preferred term	Age <2 yrs N=158 n (%)	Age 2-<4 yrs N=83 n (%)	Age <4 yrs N=241 n (%)	Age >=4 yrs N=96 n (%)	Total N=337 n (%)
Status epilepticus	10(6.3)	3(3.6)	13(5.4)	1(1.0)	14(4.2)
Nausea	4(2.5)	3(3.6)	7(2.9)	6(6.3)	13(3.9)
Insomnia	6(3.8)	5(6.0)	11(4.6)	1(1.0)	12(3.6)
Rhinorrhoea	4(2.5)	6(7.2)	10(4.1)	2(2.1)	12(3.6)
Lethargy	7(4.4)	4(4.8)	11(4.6)	0(0.0)	11(3.3)
Teething	10(6.3)	0(0.0)	10(4.1)	0(0.0)	10(3.0)
Urinary tract infection	8(5.1)	1(1.2)	9(3.7)	1(1.0)	10(3.0)
Bronchiolitis	9(5.7)	0(0.0)	9(3.7)	0(0.0)	9(2.7)
Dehydration	5(3.2)	4(4.8)	9(3.7)	0(0.0)	9(2.7)
Pharyngitis	3(1.9)	4(4.8)	7(2.9)	2(2.1)	9(2.7)
Hyponatraemia	7(4.4)	0(0.0)	7(2.9)	1(1.0)	8(2.4)
Abdominal pain upper	0(0.0)	3(3.6)	3(1.2)	4(4.2)	7(2.1)
Gastroenteritis viral	3(1.9)	4(4.8)	7(2.9)	0(0.0)	7(2.1)
Viral infection	3(1.9)	3(3.6)	6(2.5)	1(1.0)	7(2.1)
Anaemia	4(2.5)	2(2.4)	6(2.5)	0(0.0)	6(1.8)
Respiratory tract infection	3(1.9)	2(2.4)	5(2.1)	1(1.0)	6(1.8)
Upper respiratory tract congestion	4(2.5)	2(2.4)	6(2.5)	0(0.0)	6(1.8)
Agitation	4(2.5)	0(0.0)	4(1.7)	1(1.0)	5(1.5)
Asthma	3(1.9)	2(2.4)	5(2.1)	0(0.0)	5(1.5)
Bronchospasm	3(1.9)	2(2.4)	5(2.1)	0(0.0)	5(1.5)
Conjunctivitis	1(0.6)	3(3.6)	4(1.7)	1(1.0)	5(1.5)
Eczema	3(1.9)	0(0.0)	3(1.2)	2(2.1)	5(1.5)
Gait abnormal	2(1.3)	0(0.0)	2(0.8)	3(3.1)	5(1.5)
Gastroenteritis	2(1.3)	1(1.2)	3(1.2)	2(2.1)	5(1.5)

Preferred term	Age <2 yrs N=158 n (%)	Age 2-<4 yrs N=83 n (%)	Age <4 yrs N=241 n (%)	Age >=4 yrs N=96 n (%)	Total N=337 n (%)
Nystagmus	2(1.3)	2(2.4)	4(1.7)	1(1.0)	5(1.5)
Rhinitis	3(1.9)	1(1.2)	4(1.7)	1(1.0)	5(1.5)
Sinusitis	1(0.6)	2(2.4)	3(1.2)	2(2.1)	5(1.5)
Tremor	1(0.6)	4(4.8)	5(2.1)	0(0.0)	5(1.5)
Viral upper respiratory tract infection	2(1.3)	1(1.2)	3(1.2)	2(2.1)	5(1.5)
Wheezing	3(1.9)	2(2.4)	5(2.1)	0(0.0)	5(1.5)
Abdominal pain	2(1.3)	1(1.2)	3(1.2)	1(1.0)	4(1.2)
Blood lactate dehydrogenase increased	3(1.9)	0(0.0)	3(1.2)	1(1.0)	4(1.2)
Dermatitis diaper	2(1.3)	2(2.4)	4(1.7)	0(0.0)	4(1.2)
Diplopia	0(0.0)	0(0.0)	0(0.0)	4(4.2)	4(1.2)
Epistaxis	1(0.6)	2(2.4)	3(1.2)	1(1.0)	4(1.2)
Fluid intake reduced	2(1.3)	2(2.4)	4(1.7)	0(0.0)	4(1.2)
Gastrooesophageal reflux disease	4(2.5)	0(0.0)	4(1.7)	0(0.0)	4(1.2)
Loose stools	2(1.3)	1(1.2)	3(1.2)	1(1.0)	4(1.2)
Pharyngitis streptococcal	1(0.6)	1(1.2)	2(0.8)	2(2.1)	4(1.2)
Sedation	4(2.5)	0(0.0)	4(1.7)	0(0.0)	4(1.2)
Tonsillitis	0(0.0)	3(3.6)	3(1.2)	1(1.0)	4(1.2)

Appendix C: Incidence tabulation for adverse events observed in patients for group 2 (pivotal trail) analyses for patients with at least a 1% incidence in any group.

Preferred term	Low Dose (10 mg/kg/day) N=110 n (%)	High Dose (60 mg/kg/day) N=110 n (%)	Total N=220 n (%)
Total patients with AEs	48(43.6)	75(68.2)	123(55.9)
Somnolence	3(2.7)	19(17.3)	22(10.0)
Pyrexia	8(7.3)	12(10.9)	20(9.1)
Vomiting	7(6.4)	11(10.0)	18(8.2)
Convulsion	2(1.8)	8(7.3)	10(4.5)
Status epilepticus	3(2.7)	6(5.5)	9(4.1)
Cough	2(1.8)	6(5.5)	8(3.6)
Ataxia	0(0.0)	7(6.4)	7(3.2)
Constipation	3(2.7)	3(2.7)	6(2.7)
Dizziness	0(0.0)	6(5.5)	6(2.7)
Irritability	3(2.7)	3(2.7)	6(2.7)
Nasopharyngitis	3(2.7)	3(2.7)	6(2.7)
Nausea	0(0.0)	6(5.5)	6(2.7)
Diarrhoea	2(1.8)	3(2.7)	5(2.3)
Otitis media	1(0.9)	4(3.6)	5(2.3)
Headache	1(0.9)	3(2.7)	4(1.8)
Pneumonia	0(0.0)	4(3.6)	4(1.8)
Rash	3(2.7)	1(0.9)	4(1.8)
Rhinorrhoea	3(2.7)	1(0.9)	4(1.8)
Abdominal pain upper	2(1.8)	1(0.9)	3(1.4)
Agitation	1(0.9)	2(1.8)	3(1.4)
Nasal congestion	0(0.0)	3(2.7)	3(1.4)
Tremor	0(0.0)	3(2.7)	3(1.4)
Upper respiratory tract infection	2(1.8)	1(0.9)	3(1.4)
Urinary tract infection	0(0.0)	3(2.7)	3(1.4)
Viral infection	0(0.0)	3(2.7)	3(1.4)
Abdominal pain	0(0.0)	2(1.8)	2(0.9)
Bronchiolitis	2(1.8)	0(0.0)	2(0.9)
Bronchitis	0(0.0)	2(1.8)	2(0.9)
Decreased appetite	2(1.8)	0(0.0)	2(0.9)
Electrocardiogram QT prolonged	2(1.8)	0(0.0)	2(0.9)
Erythema	1(0.9)	1(0.9)	2(0.9)
Gait abnormal	0(0.0)	2(1.8)	2(0.9)
Influenza	0(0.0)	2(1.8)	2(0.9)
Insomnia	0(0.0)	2(1.8)	2(0.9)
Loose stools	0(0.0)	2(1.8)	2(0.9)
Nystagmus	0(0.0)	2(1.8)	2(0.9)
Pruritus	2(1.8)	0(0.0)	2(0.9)
Respiratory tract infection	0(0.0)	2(1.8)	2(0.9)
Rhinitis	0(0.0)	2(1.8)	2(0.9)
Stomach discomfort	1(0.9)	1(0.9)	2(0.9)
Teething	0(0.0)	2(1.8)	2(0.9)
Upper respiratory tract congestion	0(0.0)	2(1.8)	2(0.9)

Appendix D: Full narratives of deaths.

0522/00001:

This 13-month-old, female child entered study 2330 with a diagnosis of partial seizures that were being treated with topiramate upon entry into the Treatment Phase. The patient's significant medical history included poor appetite, constipation, reflux disease, intractable seizure syndrome, developmental delay, hypotonia, and static encephalopathy. During the Treatment Phase, the patient was randomized to the low-dose group and received her first dose of oxcarbazepine on 01-Oct-2002. The patient completed the Treatment Phase and entered the Extension Phase on 04-Oct-2002.

On (b) (6) approximately (b) (6) days after beginning treatment with oxcarbazepine, the patient experienced increased seizures and a viral syndrome with malnutrition, dehydration, decreased weight and lethargy. The patient was hospitalized (b) (6) The oxcarbazepine dose at the time of the SAE was 78 mg/kg/day. No other concomitant antiepileptic medication was taken. The patient was receiving ranitidine and Trivox, a vitamin supplement, as concomitant medications at the time of the SAE. Blood chemistries count was normal. The patient was treated with lorazepam, levetiracetam and fosphenytoin. Study medication was permanently discontinued (b) (6) within 4 days of the onset of the SAE, the patient was discharged from the hospital with the following sequelae: seizure disorder and high risk for dehydration (secondary to seizure disorder). The patient's condition was noted to improve on discharge, as she had not experienced seizure activity for the last 24 hours of hospitalization. The investigator did not suspect a relationship between the SAE and oxcarbazepine but considered the SAE may have been related to lack of therapeutic effect.

On (b) (6) approximately (b) (6) months after discontinuing treatment with oxcarbazepine, the patient died due to progression of her seizure disorder. The investigator did not suspect a relationship between the death and previous treatment with oxcarbazepine but indicated that the patient became weakened over the course of time and was no longer able to sustain life.

0038/00005

This 10-month-old, male child entered the study with a diagnosis of partial seizures and was taking topiramate, valproate and vigabatrin to control his seizures. The patient's significant medical history included encephalopathy, lung infection and a subdural hematoma. The patient was randomized to the high dose group (maximal dose approximately 60 kg/daily) and received his first dose of oxcarbazepine on 16-Jan-2004, and finished the Treatment Phase of the study on 20-Feb-2004 (maximal dose of approximately 60 mg/kg/day, but was titrated to lower doses). The patient did not enter the Open-label Extension Phase. Study drug was tapered and the patient received his last dose of oxcarbazepine on 22-Mar-2004. On (b) (6) the patient died due to pneumopathy. Prior to the death (b) (6) the patient developed pneumopathy secondary

to an increase in seizures. The patient had a prior history of recurrent lung infections and thus this event was not reported as an adverse event by the Investigator. At the time of death the patient was not taking oxcarbazepine. Concomitant medications taken at the time of the death were clobazam, valproate sodium and vigabatrin. The investigator did not suspect a relationship between the patient's death and oxcarbazepine, indicating that this event was due to the progression of the patient's underlying epilepsy.
(Can't find much about pneumopathy in the CRF- what do they mean pneumonia??)

APPEARS THIS WAY ON ORIGINAL

0028/00005:

This 10-month-old, male child entered the study with a diagnosis of partial seizures and was being treated with topiramate and valproic acid upon entry into the Treatment Phase. The patient's significant medical history included bronchitis and cortical resection due to dysplasia. During the Treatment Phase, the patient was randomized to the low-dose group and received his first dose of oxcarbazepine on 15-Aug-2003. The patient completed the Treatment Phase and entered the Extension Phase on 26-Sep-2003 and continued being treated with topiramate and valproic acid for seizure control. 1. On (b) (6), approximately (b) (6) months after beginning treatment with oxcarbazepine, the patient experienced dehydration and vomiting and was hospitalized. The oxcarbazepine dose at the time of the SAE was 13.3 mg/kg/day. The patient's concomitant medications included: ferrous sulfate, topiramate and valproic acid which was increased prior to hospitalization (b) (6) from 1 mL to 1.5 mL bid to control increased seizures. The patient was treated with sodium chloride for vomiting. On (b) (6) within (b) (6) days of the onset of the SAE, the patient was fully recovered and discharged from the hospital. The investigator did not suspect a relationship between the SAE and oxcarbazepine.

On (b) (6) approximately (b) (6) months after beginning treatment with oxcarbazepine, the patient was hospitalized for elective surgery (right frontal parietal cortical resection) due to worsening of seizure activity (considered characteristic of the patient's disease). Oxcarbazepine was temporarily suspended and restarted on the second post-operative day (b) (6) The patients concomitant medications included: topiramate and valproic acid. Following the surgery the patient was seizure free. On (b) (6) while still hospitalized, the patient experienced sudden death. The oxcarbazepine dose at the time of the death was 18 mg/kg/day. An autopsy was not performed. The investigator did not suspect a relationship between the death and oxcarbazepine.

0072/00001:

This 22-month-old, male child entered the study with a diagnosis of partial seizures and was being treated with valproic acid and clonazepam upon entry into the Treatment Phase. The patient's significant medical history included: influenza, pharyngitis and oral candidiasis. During the Treatment Phase, the patient was randomized to the high-dose group and received his first dose of oxcarbazepine on 13-Aug-2003. The patient completed the Treatment Phase and entered

the Extension Phase on 15-Sep-2003 and continued being treated with valproic acid and lonazepam for seizure control. On (b) (6) approximately (b) (6) months after beginning treatment with oxcarbazepine, the patient was hospitalized and diagnosed with pneumonia. Prior to hospitalization on (b) (6) the patient had experienced pharyngitis, cough, rhinorrhea and fever. The oxcarbazepine dose at the time of the SAE was 60.0 mg/kg/day. Approximately (b) (6) months prior to the occurrence of the SAE (b) (6), the patient's valproic acid medication was stopped and at the time of the SAE the patient was not taking any concomitant medication. Diagnostic evaluations included: respiration frequency (38), heart rate (130), temperature (38.3 degrees Celsius), blood pressure 100/60, normal hydration state and a Glasgow scale assessment 13 to 15. The patient was initially treated with ampicillin which was interrupted due to hypotension and then was treated with cefotaxime. The patient subsequently suffered a decrease in neurological status (Glasgow scale assessment 13 to 11), oxygen saturation 79% without oxygen and 80% with oxygen) and required mechanical ventilation. The patient's cardiac frequency and arterial tension decreased and the patient died (b) (6) due to pneumonia and sepsis. The patient was also treated with: ranitidine, midazolam, vecuronium and lidocaine hydrochloride. An autopsy revealed bilateral pulmonary infiltrate. The investigator did not suspect a relationship between the death and oxcarbazepine.

0072/00003:

This 40-month-old, female child entered the study with a diagnosis of partial seizures and was being treated with valproic acid upon entry into the Treatment Phase. The patient's significant medical history included developmental delay, cerebral infarction, urinary tract infection and influenza. During the Treatment Phase, the patient was randomized to the high-dose group and received her first dose of oxcarbazepine on 20-Sep-2003. The patient completed the Treatment Phase and entered the Extension Phase on 1-Nov-2003 and continued being treated with valproic acid for seizure control. On 30-Apr-2004 the patient completed the Extension Phase of the study.

On (b) (6) approximately (b) (6) after completing the Extension Phase and (b) (6) months after beginning treatment with oxcarbazepine, the patient had a 4-hour seizure, and died due to brochoaspiration (reason for death was confirmed with investigator) at home the same day. Concomitant medication taken at the time of the SAE included valproic acid. At the time of death the patient was taking 60 mg/kg/day oxcarbazepine commercially.

The investigator did not suspect a relationship between oxcarbazepine and the SAE.

Appendix E: Racial differences in the incidence of common adverse events (>2% for all patients) by preferred term.

Preferred term	Black N=28 n (%)	Caucasian N=157 n (%)	Other N=56 n (%)	Total N=241 n (%)
Total patients with AEs	23(82.1)	135(86.0)	48(85.7)	206(85.5)
Pyrexia	8(28.6)	44(28.0)	12(21.4)	64(26.6)
Upper respiratory tract infection	7(25.0)	28(17.8)	6(10.7)	41(17.0)
Vomiting	2(7.1)	32(20.4)	6(10.7)	40(16.6)
Convulsion	5(17.9)	21(13.4)	8(14.3)	34(14.1)
Somnolence	3(10.7)	27(17.2)	4(7.1)	34(14.1)
Nasopharyngitis	4(14.3)	21(13.4)	7(12.5)	32(13.3)
Cough	8(28.6)	15(9.6)	5(8.9)	28(11.6)
Otitis media	1(3.6)	22(14.0)	2(3.6)	25(10.4)
Ear infection	3(10.7)	18(11.5)	3(5.4)	24(10.0)
Diarrhoea	2(7.1)	14(8.9)	5(8.9)	21(8.7)
Nasal congestion	2(7.1)	15(9.6)	4(7.1)	21(8.7)
Pneumonia	4(14.3)	12(7.6)	5(8.9)	21(8.7)
Irritability	4(14.3)	15(9.6)	1(1.8)	20(8.3)
Ataxia	1(3.6)	14(8.9)	1(1.8)	16(6.6)
Bronchitis	1(3.6)	13(8.3)	2(3.6)	16(6.6)
Constipation	2(7.1)	10(6.4)	2(3.6)	14(5.8)
Influenza	0(0.0)	7(4.5)	7(12.5)	14(5.8)
Status epilepticus	0(0.0)	7(4.5)	6(10.7)	13(5.4)
Insomnia	3(10.7)	6(3.8)	2(3.6)	11(4.6)
Lethargy	4(14.3)	5(3.2)	2(3.6)	11(4.6)
Rash	2(7.1)	7(4.5)	1(1.8)	10(4.1)
Rhinorrhoea	2(7.1)	7(4.5)	1(1.8)	10(4.1)
Teething	1(3.6)	8(5.1)	1(1.8)	10(4.1)
Bronchiolitis	3(10.7)	4(2.5)	2(3.6)	9(3.7)
Dehydration	2(7.1)	7(4.5)	0(0.0)	9(3.7)
Urinary tract infection	0(0.0)	4(2.5)	5(8.9)	9(3.7)
Decreased appetite	2(7.1)	6(3.8)	0(0.0)	8(3.3)
Gastroenteritis viral	2(7.1)	4(2.5)	1(1.8)	7(2.9)
Hyponatraemia	2(7.1)	4(2.5)	1(1.8)	7(2.9)
Nausea	0(0.0)	3(1.9)	4(7.1)	7(2.9)
Pharyngitis	0(0.0)	4(2.5)	3(5.4)	7(2.9)
Anaemia	0(0.0)	5(3.2)	1(1.8)	6(2.5)
Upper respiratory tract congestion	3(10.7)	3(1.9)	0(0.0)	6(2.5)
Viral infection	0(0.0)	6(3.8)	0(0.0)	6(2.5)
Asthma	2(7.1)	3(1.9)	0(0.0)	5(2.1)
Bronchospasm	0(0.0)	5(3.2)	0(0.0)	5(2.1)
Headache	0(0.0)	4(2.5)	1(1.8)	5(2.1)
Respiratory tract infection	0(0.0)	3(1.9)	2(3.6)	5(2.1)
Tremor	0(0.0)	4(2.5)	1(1.8)	5(2.1)
Wheezing	2(7.1)	3(1.9)	0(0.0)	5(2.1)

Appendix F: Common adverse event risk by age in monotherapy and adjunctive therapy studies from the original NDAS review performed by Dr. Gerard Boehm (7/23/99)

	≤11 years old			12 to 17 years old			≥18 years old		
	Oxc	PBO	RR	Oxc	PBO	RR	Oxc	PBO	RR
	n=73	n=67		n=99	n=72		n=1100	n=214	
Event									
Fatigue	9.5%	8.9%	1.1	15%	8.3%	1.8	14.2%	5.6%	2.5
Vomiting	32.8%	19.4%	1.7	33%	8.3%	4.0	14.8%	4.7%	3.2
Hyponatremia	1.4%	0	-	1%	0	-	3.5%	0.4%	7.4
Ataxia	13.7%	7.5%	1.8	13%	1.4%	9.3	11.4%	4.2%	2.7
Dizziness	21.9%	10.4%	2.1	32%	5.6%	5.7	27.2%	12.6%	2.2
Emot lability	6.8%	1.5%	4.5	9%	5.6%	1.6	1.9%	0.9%	2.0
Headache	34.2%	16.4%	2.1	28%	22%	1.3	28.5%	21.9%	1.3
Nervousness	4.1%	7.4%	0.6	5%	2.8%	1.8	3.2%	0.9%	3.4
Somnolence	32.8%	16.4%	2.0	29%	9.7%	3.0	25.8%	9.3%	2.8
Rash*	5.5%	7.5%	0.7	8%	4.2%	1.9	5.9%	1.9%	3.2
Diplopia	19.2%	1.5%	12.8	16%	0	-	18%	3.7%	4.8
Vision abnl	11%	1.5%	7.3	15%	1.4%	10.7	9.4%	3.2%	2.9

* Combines the preferred terms rash, rash erythematous, and rash maculopapular

Appendix G: Pediatric Exclusivity Determination Template (distributed to the Pediatric Exclusivity Board for meeting on 3/2/05).

Pediatric Exclusivity Determination Template

Written Request Items	Information Submitted/ Sponsor's response
Types of studies/ Study Design: Studies should be listed exactly as written in the WR. Study 1: Pediatric Efficacy and Safety Study (1 month to 4 years) for adjunctive treatment. Study 2: Pediatric Efficacy and Safety Study (1 month to 16 years) for monotherapy treatment. Study 3: Pediatric Safety Study (1 month to 4 year) Study 4: Pharmacokinetic Study (1 month to 16 years) *{Any optional studies should be listed}*	**Types of studies:** *This section should list the studies actually performed. Please boldface the information that differs from what was asked for in the WR.* Study 1: Novartis' response to this request was to conduct Study 2340 (adjunctive safety and efficacy study), A multicenter, rater-blind, randomized, age-stratified, parallel-group study comparing two doses of oxcarbazepine as adjunctive therapy in pediatric patients (1 month to < 4 years) with inadequately-controlled partial seizures. Study 2: Novartis' response to this request was to conduct Study 2339 (monotherapy safety and efficacy study), A multicenter, rater-blind, randomized, age-stratified, parallel-group study comparing two doses of oxcarbazepine as monotherapy in pediatric patients (1 month to < 17 years) with inadequately-controlled partial seizures. Study 3: Long-term open label safety extensions were incorporated into all studies (2338, 2339, 2340 and 2341) to fulfill this aspect of the Written Request. Safety information from study 2337 (EU cognitive function study) is also included in the supplemental NDA. Study 4- A. Study 2338: An open-label, age-stratified pilot-study to assess the tolerability and pharmacokinetics of ascending doses of oxcarbazepine oral suspension as adjunctive therapy

	in pediatric patients (1 month to < 4 years of age) with inadequately-controlled partial seizures. A supplemental pharmacokinetic report for study 2338 is located in the Human Pharmacokinetics and Biopharmaceutics section of the supplemental NDA. This study served as a pilot study for justification of the titration and dosing schedule for the adjunctive therapy Study 2340. B. Study 2341: An open-label, age-stratified pilot-study to assess the tolerability and pharmacokinetics of ascending doses of oxcarbazepine oral suspension as monotherapy in pediatric patients (1 month to <17 years of age) with inadequately-controlled partial seizures. This study served as a pilot study for study for justification of the titration and dosing schedule for the monotherapy Study 2339. C. A random PK sampling procedure was employed in studies 2339 and 2340 in order to obtain plasma concentrations to be used in constructing a population pharmacokinetic model.
Indication(s) to be studied: **Study 1: To establish efficacy and short-term safety of oxcarbazepine as adjunctive therapy in the treatment of partial seizures in pediatric patients ages 1 month to 4 years.** Study 2: To establish efficacy and short-term safety of oxcarbazepine as monotherapy in the treatment of partial seizures in pediatric patients ages 1 month to 16 years. Study 3: To determine the long-term safety (duration of a minimum of 6 months) of oxcarbazepine as monotherapy or adjunctive therapy in the treatment of partial seizures in pediatric patients ages 1 month to 4 years. Study 4: To determine the steady state PK in	**Indication(s) studied:** Study 1: Study 2340 was designed and conducted to investigate the efficacy and short-term safety of oxcarbazepine as adjunctive therapy in the treatment of partial seizures in pediatric patients ages 1 month to <4 years. Study 2: Study 2339 was designed and conducted to investigate the efficacy and short-term safety of oxcarbazepine as monotherapy in the treatment of partial seizures in pediatric patients ages 1 month to <17 years. Study 3: Long-term open label safety extensions were incorporated into all studies (2338, 2339, 2340 and 2341) to collect 6-month plus safety data in patients 1 month to <4 years old being treated with oxcarbazepine as adjunctive therapy and in patients 1 month to <4 years (as well as patients 4 to 17 years) treated with oxcarbazepine as monotherapy. Safety data from study 2337 (EU cognitive function study) is also incorporated in the Summary of Clinical Safety.

pediatric subjects aged 1 month to 16 years.	Study 4- The pharmacokinetics was explored in the pilot studies 2338 and 2341. In addition a random PK sampling procedure was employed in studies 2339 and 2340 in order to obtain plasma concentrations (steady state) to be used in constructing a population pharmacokinetic model.
Age group and population in which study will be performed: Study 1 : 1 month to 4 years Study 2: 1 month to 16 years Study 3: 1 month to 4 years Study 4: 1 month to 16 years	Age group and population in which study was performed: Study 1 : Studies 2340 fulfilled this request. Study 2: Studies 2339 fulfilled this request Study3: Studies 2338 and 2340 included patients 1 month to 4 years while studies 2339 and 2341 included this range while encompassing a broader range of 1 month to < 17 years of age. Study4:

	<table><tr><th>Demographic Variable</th><th>Study 2338 N=23</th><th>Study 2339 N=81</th><th>Study 2340 N=111</th><th>Study 2341 N=3</th><th>All studies N=218</th></tr><tr><td>Sex</td><td></td><td></td><td></td><td></td><td></td></tr><tr><td>Male</td><td>13 (56.52%)</td><td>43 (53.09%)</td><td>63 (56.76%)</td><td>1 (33.33%)</td><td>120 (55.05%)</td></tr><tr><td>Female</td><td>10 (43.48%)</td><td>38 (46.91%)</td><td>48 (43.24%)</td><td>2 (66.67%)</td><td>98 (44.95%)</td></tr><tr><td>Race</td><td></td><td></td><td></td><td></td><td></td></tr><tr><td>Caucasian</td><td>14 (60.87%)</td><td>53 (65.43%)</td><td>77 (69.37%)</td><td>3 (100.00%)</td><td>147 (67.43%)</td></tr><tr><td>Black</td><td>6(26.09%)</td><td>11 (13.58%)</td><td>7 (6.31%)</td><td>0 (0.00%)</td><td>24 (11.01%)</td></tr><tr><td>Other</td><td>3 (13.04%)</td><td>17 (20.99%)</td><td>27 (24.32%)</td><td>0 (0.00%)</td><td>47 (21.56%)</td></tr><tr><td>Age (years)</td><td></td><td></td><td></td><td></td><td></td></tr><tr><td>1 month -<1 year</td><td>7 (30.43%)</td><td>15 (18.52%)</td><td>38 (34.23%)</td><td>2 (66.67%)</td><td>62 (28.44%)</td></tr><tr><td>1 year to <2 years</td><td>8 (34.78%)</td><td>11 (13.58%)</td><td>31 (27.93%)</td><td>0 (0.00%)</td><td>50 (22.94%)</td></tr><tr><td>2 years -<3 years</td><td>3 (13.04%)</td><td>7 (8.64%)</td><td>21 (18.92%)</td><td>1 (33.33%)</td><td>32 (14.68%)</td></tr><tr><td>3 years -<4 years</td><td>5 (21.74%)</td><td>8 (9.88%)</td><td>21 (18.92%)</td><td>0 (0.00%)</td><td>34 (15.60%)</td></tr><tr><td>≥4 years</td><td>0 (0.00%)</td><td>40 (49.38%)</td><td>0 (0.00%)</td><td>0 (0.00%)</td><td>40 (18.35%)</td></tr></table> *If there were specifics (such as number of patients aged birth to 6 months, 7 mos to 1 year, etc), please provide this breakdown.*
Number of patients to be studied or power of study to be achieved: **Study 1: Assessment of the between group difference on a standard measure of partial seizure frequency by a statistical methodology appropriate to the data generated and descriptive analysis of safety data. A sufficient number of pediatric patients to be able to detect a statistically significant difference between treatment and control should be included.** Study 2: Analyses appropriate to the design of the study. Study 3: Descriptive analysis of the safety.	**Number of patients studied or power achieved:** *Please list for each study separately. If there were specifics (such as number of females: males, or ethnic groups), please provide this demographic breakdown.* Study 4-Data were pooled from four studies: 2338, 2339, 2340, and 2341 to explore the population pharmacokinetics/pharmacodynamics of Trileptal® at doses up to 60 mg/kg/day as oral suspension as monotherapy or adjunctive therapy in pediatric patients 1 month to <17years of age with partial seizures. Data are presented in the report titled Population pharmacokinetic/pharmacodynamic analysis for Trileptal® in patients 1 month to < 17 years of age with partial seizures. Number of subjects evaluable for pharmacokinetic assessments: Overall 218 patients, 23 patients from study 2338, 81 patients from study 2339, 111 patients from study 2340, and 3 patients from study 2341 were used for the population pharmacokinetic and pharmacodynamic modeling. A descriptive assessment of the effect of age on pharmacokinetic

Study 4: Descriptive assessment of the effect of age on pharmacokinetic parameters.	parameters is presented in the submission. The population analysis includes pharmacokinetic/pharmacodynamic analyses to show the exposure-response relationship is also submitted. This information is summarized in Section 3 of the Clinical Overview, and in the Summary of Clinical Pharmacology, with a complete report in the combined Population PK/PD Report for Trileptal Pediatric Studies, which summarizes data from studies 2338, 2339, 2340, 2341 and their respective extension phases.
Written Request Items	Information Submitted/ Sponsor's response
Entry criteria:	Entry criteria used:
Clinical endpoints: Study 1 and 2: A single standard measure of seizure frequency should be chosen as the primary outcome measure, and standard measures of safety (clinical-including signs and symptoms-and laboratory). Study 3: Appropriately frequent standard measures of safety (clinical-including signs and symptoms-and laboratory). Study 4: Pharmacokinetic measurements as appropriate	**Clinical endpoints used:** Study 1 and 2: For the purposes of the Pediatric submission Novartis' approach to the efficacy analyses was discussed with FDA at the Pre-NDA (New Drug Application) meeting of 24-Mar-2004. The following agency recommendations were incorporated into the dossier by the Company: **Study 1:** Protocol Amendment 3 to Study 2340 changed the primary efficacy variable from "percent change in Study Seizure Type 1 (SST1) seizure frequency" to "absolute change in SST1 seizure frequency." Absolute change was chosen as the primary variable in order to avoid the use of imputation. Analysis by percent change can only include randomized patients with zero seizures at Baseline if imputed seizure data are used. The use of imputed data may lead to increased variability within the study. Analysis by absolute change will eliminate the use of imputed data and thus eliminate a potential source of additional variability. The percent change which uses the imputation for patients with zero seizures at baseline is considered as the secondary efficacy variable. Protocol Amendment 3 to Study 2340 also included clarification of the analysis populations, to define the per-protocol population which is used in the sensitivity analyses and clarification of the response-to-treatment variable for patients with zero seizures at baseline. **Study 2:** The primary outcome in study 2339 was the time to meeting exit criteria, as assessed by the Central Reader. The exit criteria were defined as: 1) three SST1 seizures with or without generalization or 2) prolonged SST1 seizure.

	Study 3: For the purposes of the Pediatric submission, the Company's approach to the safety analyses was discussed with FDA at the Pre-sNDA meeting of 24-Mar-2004. The following agency recommendations were incorporated into the dossier by the Company: • Long-term safety (6 months) in a minimum of 75-80 patients (1 month to <4 years of age). • Safety analysis is provided for two age groups, <4 years of age and ≥ 4 years of age. The <4 year-old group had safety data analyzed by two age subgroups, <2 years of age and 2 to <4 years of age as agreed with the FDA at the 24-Mar-2004 pre-sNDA meeting • ECG interval data, including QTc analysis is provided along with other pertinent intervals. To comply with this request ECG data was collected retrospectively from ECGs conducted during the studies. A central reader analyzed and interpreted all of the ECGs. Study 4-Steady state concentrations of MHD were summarized and population pharmacokinetic parameters were estimated including CL/F, V/F, KA and the variabilities. The age related covariates such as BSA and Height were included in the model.
Timing of assessments: if appropriate-N/A *i.e., Pre-clinical studies requested or conducting a PK study prior to efficacy study*	**Timing of assessments:**
Drug specific safety concerns: Hepatic, hematologic and skin hypersensitivity reactions, and hyponatremia.	**Drug specific safety concerns evaluated:** Hepatic, hematologic and skin hypersensitivity reactions were assessed by monitoring and recording all adverse events and serious adverse events, monitoring of hematology, chemistry and

	urine values, measurement of vital signs, ECGs and the performance of physical examinations.
Drug information: ***Dosage Form:*** Oral tablet and other formulation as appropriate for younger patients. ***Route of Administration:*** Oral ***Regimen:*** To be determined by the development plan	**Drug information:** • **Route of administration:** po • **Dosage:** *Monotherapy:* Initiate at 8-10 mg/kg/day (BID) titration to 60 mg/kg/day. *Adjunctive:* Initiate at 8-10 mg/kg (BID) titrate to 60 mg/kg (BID). • **Regimen:** BID. • **Formulation:** Tablets (150, 300 600 mg) and Suspension (60mg/ml).
Statistical information (statistical analyses of the data to be performed): **Study 1: Assessment of the between group difference on a standard measure of partial seizure frequency by a statistical methodology appropriate to the data generated and descriptive analysis of safety data. A sufficient number of pediatric patients to be able to detect a statistically significant difference between treatment and control should be included.** Study 2: Analyses appropriate to the design of the study. Study 3: Descriptive analysis of the safety. Study 4 : Descriptive assessment of the effect of age on pharmacokinetic parameters.	**Statistical information (statistical analyses of the data to be performed):** *What tests did the Sponsor use, did they follow the WR?* Study 1: Statistical methods: *Primary endpoint analysis:* The primary efficacy variable for Study 2340 was the absolute change in video-EEG confirmed seizure frequency per 24 hours. This was compared between the treatment groups using the Rank Analysis of Covariance. *Secondary endpoints analyses:* The first two secondary variables also were compared between the treatment groups using the Rank Analysis of Covariance: (1) percentage change in SST1 seizure frequency per 24 hours; and (2) absolute change in SST1 + SST2 seizure frequency per 24 hours. The third secondary efficacy variable was response to treatment, characterized by at least a 50%, 75%, or 100% reduction in SST1 seizure frequency per 24 hours; the Cochran-Mantel-Haenszel (CMH) test was used. Based upon discussion with the FDA at the May 22, 2003 meeting, it was agreed that a minimum power of 80% should be applied; 114 patients would be needed for the adjunctive therapy study (Study 2340). *Number of patients:* Planned – 128; Randomized – 128 (64 in each group); Analyzed for efficacy – 116 total (59 High-dose OXC, 57 Low-dose OXC); Analyzed for safety – total 128 (64

	High-dose OXC, 64 Low-dose OXC). *Safety analyses:* Safety was assessed using descriptive summaries of adverse events frequencies, laboratory and vital sign values that fell outside of pre-specified ranges, and clinically significant ECG abnormalities. Study 2: *Primary endpoint analysis:* The time to meeting exit criteria was tested for equality between the two groups (ITT efficacy population) using a log-rank test with evaluable video-EEG data. *Secondary endpoints analyses*: The percentage of patients meeting exit criteria based on SST1 seizure data was compared between the two dose groups using Cochran-Mantel-Haenszel (CMH) test blocking on age groups. Electrographic partial seizure frequency (SST1+SST2) per 24-hours during the Treatment Phase was compared between treatment groups using the Rank Analysis of Covariance with age as the covariate. Based upon discussion with the FDA at the May 22, 2003 meeting, it was agreed that a minimum power of 80% should be applied; 80 patients would be needed for the adjunctive therapy study (Study 2339). *Number of patients:* Planned – 80; Randomized – 92; Analyzed for efficacy – 87 total (42 High-dose OXC, 45 Low-dose OXC); Analyzed for safety – total 92 (46 High-dose OXC, 46 Low-dose OXC) *Safety analysis*: Safety was assessed using descriptive summaries of adverse events frequencies, laboratory and vital sign values that fell outside of pre-specified ranges, and clinically significant ECG abnormalities. Study 3 (Safety Analyses): The Summary of Clinical Safety contains data from a total of 337 pediatric patients 1 month to <17 years of age with partial seizures, from a total of eight completed studies (2338, 2338E1, 2339, 2339E1, 2340, 2341, 2341E1 and the EU cognitive function study 2337) and one ongoing extension study (2340E1). These nine studies are presented in Tables 1-1 and 1-2 of the Summary

	of Clinical Safety and were all conducted specifically in pediatric and adolescent patients. The cutoff date for inclusion of data for the one ongoing study was 30- Jun-2004 (i.e. any events or visits that occurred up to and including 30-Jun-2004) and the data are included in the interim CSR and in this summary document. Long term safety-at weeks 2, 6, 10, 18, and 26 after entering the extension Phase, safety assessments consisted of monitoring and recording all adverse events and serious adverse events, monitoring of hematology, blood chemistry and urine values, measurement of vital signs, ECGs and the performance of physical examinations. Post-marketing experience and other safety data pertaining to pediatric patients (1 month to <17 years) is described in Section 10 of the Summary of Clinical Safety. Study 4-Data were pooled from four studies: 2338, 2339, 2340, and 2341 to explore the population pharmacokinetics/pharmacodynamics of Trileptal® at doses up to 60 mg/kg/day as oral suspension as monotherapy or adjunctive therapy in pediatric patients 1 month to <17years of age with partial seizures. Data are presented in the report titled Population pharmacokinetic/pharmacodynamic analysis for Trileptal® in patients 1 month to < 17 years of age with partial seizures. Number of subjects evaluable for pharmacokinetic assessments: Overall 218 patients, 23 patients from study 2338, 81 patients from study 2339, 111 patients from study 2340, and 3 patients from study 2341 were used for the population pharmacokinetic and

	pharmacodynamic modeling. A descriptive assessment of the effect of age on pharmacokinetic parameters is presented in the submission. The population analysis includes pharmacokinetic/pharmacodynamic analyses to show the exposure-response relationship is also submitted. This information is summarized in Section 3 of the Clinical Overview, and in the Summary of Clinical Pharmacology, with a complete report in the combined Population PK/PD Report for Trileptal Pediatric Studies, which summarizes data from studies 2338, 2339, 2340, 2341 and their respective extension phases.
Labeling that may result from the studies: Appropriate sections of the label may be changed to incorporate the findings of the studies.	Did the sponsor submit proposed labeling? Yes: Draft labeling with proposed prescribing information for Trileptal for use as adjunctive therapy or monotherapy in the treatment of partial seizures in children with epilepsy aged 1 month and above. An annotated draft label is included in the Summary section of the electronic NDA. The Labeling section of the application includes copies of the approved PI, the current PI, the proposed PI and a review of the labeling history for Trileptal.
Format of reports to be submitted: Full study reports not previously submitted to the Agency addressing the issues outlined in this request with full analysis, assessment, and interpretation.	**Format of reports submitted:** Full reports are included except for 1 extension trial(2349E1) which will be included in a 3 month update. This was previously agreed to by this division. This constitutes a small number of additional patients and the division has agreed to this.
Timeframe for submitting reports of the studies: Reports of the above studies must be submitted to the Agency on or before January 14, 2005. Please remember that pediatric exclusivity extends only existing patent protection or exclusivity that has not expired or been previously extended at the time you submit your reports of studies in response to this Written Request.	Date study reports were submitted: Letter date was 12/13/04.
Additional Information:	

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Appendix H: Review of Individual Study Reports

See integrated summary of efficacy.

Appendix I: Line-by-Line Labeling Review

Include a detailed line-by-line review of labeling here (if performed). For clarity, underlined text for recommended additions to the applicant's proposed text and strike-through text for recommended deletions should be used.

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/s/

Norman Hershkowitz
6/14/05 04:34:27 PM
MEDICAL OFFICER

John Feeney
6/14/05 05:14:46 PM
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Concur