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*APPLICATION NUMBER:*  
**21-014/S-003**

**MEDICAL REVIEW**

## MEMORANDUM

DATE: August 5, 2003

FROM: Director  
Division of Neuropharmacological Drug Products/HFD-120

TO: File, NDA 21-014/S-003

SUBJECT: Action Memo for NDA 21-014/S-003, for the use of Trileptal (oxcarbazepine) tablets as monotherapy in the treatment of pediatric patients with partial seizures

NDA 21-014/S-003, for the use of Trileptal (oxcarbazepine) tablets as monotherapy in the treatment of pediatric patients with partial seizures, was submitted by Novartis Pharmaceuticals Corporation on 2/9/2001. Trileptal had previously been approved as adjunctive treatment for partial seizures in adults and pediatric patients and as monotherapy for adults with partial seizures on 1/14/00. In the approval letter for that application, we informed the sponsor that the Agency might be willing to conclude that Trileptal would be effective as monotherapy in pediatric patients based on a comparison of the pharmacokinetic/pharmacodynamic (PK/PD) relationship in the adjunctive setting in both adults and pediatric patients.

Specifically, we had suggested that if the PK/PD relationships were essentially the same in adults and pediatric patients in the adjunctive setting, we might be willing to conclude that the plasma levels known to be effective in adults in the monotherapy setting would be effective in pediatric patients as monotherapy. The sponsor was given the task of establishing the various elements of this approach.

The sponsor performed extensive analyses intended to address these issues, and submitted these analyses in a submission dated 2/9/01. As a result of that submission, and the Agency's reviews of it, an Approvable letter was issued on 12/12/01. In that letter, we asked the sponsor to address several outstanding questions:

- 1) We asked the sponsor to justify the identification of a concentration-response relationship on the basis of data generated in a study in which patients were not randomized to dose (in the pediatric adjunctive study, patients were titrated to a dose; in the adult adjunctive study, patients were randomized to fixed doses).
- 2) We asked the sponsor to further explore the equivalence of the PK-PD relationships determined for adults and pediatric patients in the adjunctive setting (this latter would only be important if the first point could be adequately addressed).

- 3) We asked the sponsor to further explore the effective concentration range in adults in the monotherapy setting, and develop pediatric monotherapy dosing recommendations.

The sponsor responded to this letter in a submission dated 2/6/03. This submission has been reviewed by Dr. Norman Hershkowitz, medical officer (review dated 8/7/03), Drs. John Duan and Joga Gobburu, Office of Clinical Pharmacology and Biopharmaceutics (review dated 7/30/03), Drs. Stella Machado and Meiyu Shen, Office of Biostatistics (review dated 7/1/03), and Dr. John Feeney, Neurology Drugs Team Leader (memo dated 8/7/03). The review team recommends that the application be approved.

I will briefly describe the sponsor's and reviewers' conclusions, and offer the rationale for the Division's action.

#### **Justification for Determining a Concentration-Response Relationship from a Study in Which Patients Were Titrated to Dose**

As noted above, we had serious concerns that because pediatric patients had been titrated to their final dose, it would be impossible to establish a concentration response relationship (see, for example, my memo of 12/12/01 for a discussion of the reasons why this is so). It also bears repeating that we had also expressed some concern that establishing a concentration-response relationship from a study in which patients were randomized to fixed doses (as was done in the adult adjunctive study) was also potentially problematic, but we had decided that this was acceptable.

The sponsor has addressed this concern in a number of ways, discussed by Dr. Hershkowitz.

First, the sponsor has attempted to establish that there is no effect of the pharmacodynamics on the pharmacokinetics of the drug (such an effect would hopelessly confound the attempt to establish a causal relationship of the drug on the dynamics; that is, to establish a concentration-response relationship). In this regard, the sponsor has demonstrated that there is dose linearity over a wide range of doses (300-2400 mg/day) in a variety of clinical indications. Further, they demonstrated that there was no relationship between baseline seizure frequency and clearance in adults and pediatric patients in the adjunctive setting. Further, Visit (that is, an assessment over time) was not a significant covariate in the PK analysis.

In addition, the sponsor performed multiple analyses that attempted to determine if there were additional confounders that could independently be affecting both concentration and effect, thereby possibly giving rise to a spurious concentration-response relationship.

In this regard, they examined the correlation in the variation in the dose-concentration relationship and the concentration-response relationship. The figures reproduced as Figures 1 and 2 in Dr. Hershkowitz' review (page 18 and 19) plot the dose/concentration residuals vs the concentration/efficacy residuals for the pediatric and adult studies, respectively; there is no correlation seen.

Additional analyses examining specific potential confounders also revealed no evidence that any confounder was correlated with both PK and PD in adults or pediatric patients. Finally, the sponsor examined the relationship between seizure control and adverse events at given concentrations. As Dr. Feeney points out, if seizure control and adverse events were correlated, and concentration was determined by adverse event (in the pediatric flexible dosing study), a spurious concentration-response could be detected. As Dr. Feeney notes, however, there were no meaningful correlations found.

Finally, the sponsor attempted to address the issue of the appropriateness of deriving a concentration-response relationship from this flexible dose study by examining the reasons for dosing increments in the pediatric study. If the sponsor could demonstrate that the dosing increments in the study were not made on the basis of seizure response, this might help to support the view that a valid concentration-response could be derived.

As Dr. Hershkowitz has described, the study was designed so that patients reached a target dose. By his calculation, 22 of 106 (21%) patients on drug in the pediatric study had a dose increase after the end of the titration period (Visit 3). In the absence of additional data from the sponsor, he presumes that such increases could have been employed to increase seizure control, and potentially confound the identification of a true concentration-response relationship (although the sponsor apparently asserts that these patients had the dose increased in an attempt to reach the target dose). Conversely, therefore, about 80% of patients did not seem to have the dose altered related to seizure control.

### **Equivalence of PK-PD Relationship in Adults and Pediatric Patients**

Previous analyses had determined that the PK-PD relationships constructed in adults and pediatric patients did not differ significantly, but the Agency had concluded that this was not the same as declaring that the relationships were "the same", or equivalent. As noted above, we had asked the sponsor to address this question of equivalence.

Of course, as various reviewers and the sponsor have all pointed out, the determination of equivalence is ordinarily planned for prospectively, and, in any case, is not typically examined in a setting of the sort we have here (that is, typically non-inferiority is examined between two active treatments, and a so-called non-inferiority "margin" is prospectively designated. In our case, we are

attempting to establish the "equivalence" of PK-PD relationships in two different populations, and it is being done entirely retrospectively). Nonetheless, Drs. Machado and Shen have attempted to address the question.

Drs. Machado and Shen adopted the view that in order to establish equivalence of the PK-PD relationships, the relationships should not only have the same shape, but, "...also that the predicted responses to a given concentration achieved by the two relationships are similar, over the range of concentrations likely to be experienced.". As they point out, the sponsor did not adequately pursue this point (they attempted to establish equivalence by comparing only the estimated slopes of the PK-PD relationships in adults and pediatric patients).

Based on the approach taken by Drs. Machado and Shen, they constructed Table 5 (page 39), which shows predicted Percent Change From Baseline (PCB) in seizure frequency for a series of given plasma concentrations. In general, over a wide range of plasma concentrations (about 17-112 mcml/l), the PCB in pediatric patients ranges from about 82-88% of that in adults, for a given plasma level. They further calculate the 95% confidence intervals for this ratio for a given plasma level, and the lower bound ranges from about .51 to .59.

They further evaluate the plasma levels that would need to be achieved in pediatric patients to result in an equivalent PCB to adults (that is, a ratio of about 1 in the PCB's). These values in pediatric patients are about 1.3-1.5 times greater than the levels in adults.

#### **Characterization of an Effective Plasma Range in Adults in the Monotherapy Setting**

The sponsor had previously proposed that the range of plasma levels achieved at the doses found to be effective in adults as monotherapy (1200 mg/day and 2400 mg/day) represented the effective plasma level range. We had concluded that this was clearly not so; for example, it was not obvious that the lowest plasma level achieved at the 1200 mg/day dose was an effective plasma level. Accordingly, we had asked the sponsor to further evaluate this question.

The sponsor proposes that the median plasma levels achieved at the doses found to be effective in adults as monotherapy should be the target plasma concentrations in pediatric patients; these values are 59 and 112 mcml/L at doses of 1200 and 2400 mg/day, respectively. At these levels, the PCB is -67% and -92%, respectively (the placebo response is about +4.2%), using a model constructed from the adult monotherapy data (see pages 17-19 of Drs. Duan and Gobburu's review for a detailed discussion of this point).

## **Choosing a Dose in Pediatric Patients That Will Result in Effective Plasma Ranges**

Given the sponsor's proposed plasma levels to be achieved in pediatric patients (as noted above, 59-112 mcml/L), they proposed a dosing regimen to achieve these levels.

Specifically, based on data from 30 pediatric patients treated with Trileptal as monotherapy, the sponsor has proposed a specific dosing regimen dependent upon the patient's weight. Drs. Duan and Gobburu have calculated (based on modeling of the adjunctive and pediatric monotherapy data) doses for monotherapy in pediatrics and have concluded (as has Dr. Hershkowitz) that the specific recommendations of the sponsor are adequate (see, for example, Table 18, page 37 of Dr. Hershkowitz' review).

### **COMMENTS**

The sponsor has addressed each of the points we had included in our Approvable letter of 12/12/01. I have the following comments on each of their responses.

- 1) The propriety of developing a concentration-response relationship based on data from a flexible dose study

The sponsor has presented numerous lines of reasoning and evidence to support the view that developing such a model is appropriate in this setting. Specifically, they have presented analyses that are designed to support the conclusion that the PD has not driven the PK and that there are no obvious confounders that could have driven a spurious relationship between concentration and response; I find these analyses reassuring. While I agree with both Drs. Hershkowitz and Feeney that these analyses cannot be considered absolutely definitive, the sponsor seems to have made all reasonable efforts to establish this point, and I think they have succeeded.

Also, critically, the sponsor has, in my view, adequately documented that for the vast majority of patients, dosage adjustments were made for adverse events, and that the final doses achieved in these patients were not dependent upon response. This is another important piece of data that supports the construction of a concentration-response relationship.

There is one other point worth addressing.

A number of the reviewers have commented on the small  $R^2$  values for the model used to describe the PK-PD relationships (0.17 for adults, 0.09 for pediatric patients). This reflects the inherent variability of the data, and in discussions with Dr. Gobburu, he suggests that correlations of this degree are the norm in this sort

of modeling. The p-values tell us that there is a non-zero slope for the relationship of concentration to response, which establishes a relationship. The poor correlation is expected for data like this, and is not to be interpreted as invalidating the model in any way (the model constructed is a typical model for this sort of data).

In sum, then, while these analyses cannot be absolutely comprehensive and complete, they are adequate to establish that it is appropriate to construct a concentration-response relationship.

## 2) Equivalence of the PK-PD relationships in the adjunctive setting in adults and pediatric patients

Drs. Machado and Shen have examined this question, as described above. I agree that their approach to evaluating equivalence is superior to that of the sponsor; that is, Drs. Machado and Shen evaluated the degree of seizure reduction for a given plasma concentration, and did not limit their analysis to an evaluation of the ratio of the slopes, as did the sponsor (it is also worth noting that Drs. Machado and Shen concluded that the approach to deriving the model for the PK-PD relationship employed by the sponsor was basically sound).

Clearly, the Agency's analysis did not establish absolute identity in the relationship of concentration to response between adults and children in the adjunctive setting. As noted above, for a given plasma concentration, the estimate of the response in pediatric patients was about 80-85% of that seen in the adults. The lower limit of the confidence interval of this estimate was about 55%, with the upper limit on average about 110%.

There is no standard, of which I am aware, to apply to this problem to establish equivalence. I would conclude that the estimate of the ratio of response shows, within acceptable limits, relative comparability, but the lower end of the confidence limit suggests that we cannot have complete confidence that this is a stable estimate, although I would suggest that the width of the confidence interval undoubtedly reflects the underlying variability in the data.

While absolute identity was not demonstrated, and the lower end of the confidence interval suggests that the true difference may be substantial, this latter is most likely due to the variability in the data, and the estimate of the ratio of the mean responses seems reasonably close to 1 to strongly suggest that there is reasonable comparability between the two PK-PD relationships (they are, as noted in earlier reviews, not statistically significantly different; I refer the reader to Dr. Vanitha Sekar's OCPB review of 12/7/01, page 7, Figures 6a and 6b for a visual representation of the similarity in the concentration-response relationship between adults and pediatric patients).

Of considerable interest in the evaluation of the similarity in PK-PD relationships between the two populations, is the observation, made by Dr. Gobburu and others, that the doses recommended in labeling as effective in the adjunctive setting in adults and pediatric patients are quite comparable. While this does not establish the identity of the PK-PD relationships (it is, of course, possible that a given dose, or plasma level, in one population results in a different degree of seizure reduction; indeed, the modeling seems to suggest that the degree of seizure reduction at a given plasma level may not be identical in the two populations) nonetheless the similarity of effective doses is reassuring.

For these reasons, then, I conclude that reasonable comparability in the PK-PD relationships between adults and pediatric patients in the adjunctive setting has been demonstrated.

3) Identification of the effective concentration range in adults receiving monotherapy treatment.

The sponsor has suggested that the median concentrations associated with the doses found to be effective in adults provide a reasonable range of effective plasma levels in adults, and therefore in pediatric patients. All of the reviewers find this acceptable, as do I.

4) Identification of doses in pediatric patients that will result in effective plasma levels.

Agency reviewers and the sponsor have calculated doses in pediatric patients that will result (although not, of course, in all patients), in the plasma levels predetermined to be the appropriate levels (identified in point 3 above); the results of our analyses agreed with those of the sponsor.

While, as noted, these doses will not result in the target plasma levels in all patients, it is fair to say that in a typical controlled trial, not all patients who receive an "effective" dose achieve appropriate plasma levels (whatever those are), or achieve seizure control (however that is determined). Therefore, the fact that the calculated doses will not result in "appropriate" plasma levels in all patients is not particularly worrisome.

It could be argued that, based on the estimate of the ratio of pediatric to adult response to any given plasma level in the adjunctive setting (about 85%), the dose in monotherapy should be adjusted upwards in pediatric patients.

Given the vagaries of the entire modeling enterprise, it is difficult to conclude that the specific result obtained in the adjunctive setting should guide specific monotherapy dosing recommendations. The analyses of the adjunctive setting data were designed to establish "equivalence" of the PK-PD relationships between adults and pediatric patients. Once this is established (which, as I

noted above, I believe has been shown to a reasonable degree), this permits us to conclude that the plasma levels associated with effectiveness as monotherapy in adults should be associated with effectiveness in the monotherapy setting in pediatric patients. Once this is accepted, the dosing recommendations in pediatric monotherapy can, and should, be calculated on the basis of the kinetics of the drug in pediatric patients in the monotherapy setting; this is what has been done.

For these reasons, then, I believe that appropriate pediatric monotherapy dosing recommendations have been calculated.

In addition to the factors noted above, it is important to make a few additional points.

As Drs. Feeney and Hershkowitz have noted, the meta-analysis of the monotherapy data in pediatric patients strongly supports the effectiveness of the drug in this setting. While this analysis is certainly not definitive (for reasons the reviewers, including myself, have expressed in earlier memos), the results are clearly consistent with the conclusions reached here. Further, the doses used in the studies combined in the meta-analyses closely approximate the doses calculated here as being effective in pediatric patients. Finally, as previously noted, the similarity of the effective doses in adults and pediatric patients in the adjunctive setting provide considerable comfort that the doses chosen as being effective in pediatric patients as monotherapy are reasonable.

It is important to note that approval of the use of Trileptal as monotherapy in pediatric patients would represent the first time, in my experience, that we would have approved a significant indication on the basis of modeling and data from related settings, and not on the basis of direct empirical evidence from an adequate and well-controlled clinical trial.

Specifically, we have to date required sponsors to perform controlled trials in pediatric patients (monotherapy and adjunctive to support those claims) even if the drug has been shown to be effective in both settings in adults. Further, unlike in this case, we have to date required controlled trials in pediatric patients in the monotherapy setting (if the sponsor wished to obtain that claim), even if the drug was approved for adults (mono-and adjunctive therapy) and for pediatric adjunctive use. Indeed, there are several drugs that have obtained pediatric monotherapy claims on the basis of such studies, and I believe that there are sponsors at the moment studying their drugs as pediatric monotherapy.

However, with this application, we have re-considered this approach. Specifically, we have, prior to this final action, provisionally concluded that evidence of effectiveness in adults, mono-and adjunctive therapy, and in pediatric adjunctive therapy, reasonably supports the view that the drug will be effective as pediatric monotherapy. I still believe that this is a reasonable

conclusion. While it represents a fundamental shift in our approach, and while it is theoretically possible that a drug could be effective in the former three settings and not in the latter, I believe that it is reasonable to conclude that such an outcome would be extraordinarily unlikely. There is certainly overwhelming support in the epilepsy community for this conclusion, and it is well known that it is becoming increasingly difficult for sponsors to perform adequately designed studies in the pediatric monotherapy setting, especially of marketed drugs. For all of these reasons, then, I have concluded that this approach is acceptable in this case.

The difficulty, of course, in such a conclusion, is to decide what dose will be effective in the new, unstudied, setting. As has been described, we have decided that the approach taken here is appropriate. Specifically, we have chosen the dose based on the plasma levels associated with effectiveness in adults in the monotherapy setting. This choice is predicated on a showing that similar plasma levels in adults and pediatric patients in the adjunctive setting result in similar degrees of seizure control. This approach was discussed at a regulatory briefing on 7/18/03, attended by the Director of CDER and the Associate Director of CDER for Medical Policy, as well as others, and was endorsed by the group.

I have discussed above the specific details of the analyses that purport to establish each step in the pathway that leads to the conclusion that the drug is effective as monotherapy in pediatric patients, and that appropriate dosing recommendations can be offered. I believe that the criteria have been fulfilled.

One could argue that endorsing such an approach could lead to the abandonment of adequate controlled trials in pediatric patients.

While I believe that this action might decrease the number of trials performed in certain settings, it is important to note that the approval of this application would be dependent upon an absolute requirement that the drug be shown to be effective in pediatrics (at least in the adjunctive setting) and in adults as both adjunctive and monotherapy. I believe that such an approval does not portend a movement towards the cessation of all pediatric studies; it does, however, set a precedent in some settings for not requiring controlled trials in the monotherapy setting in pediatric patients, if all of the other data are available. Most would argue that this is the appropriate direction in which to move.

It is possible, to be sure, that the approach we have taken may result in a wrong conclusion. That is, it is at least theoretically possible that a drug that works in three of the possible settings does not work in the fourth (pediatric monotherapy), and/or that the specific methodology used to determine the pediatric monotherapy dose is flawed, and/or that we have significantly misinterpreted the data before us. However, I believe that, in the face of difficulty in completing adequate controlled trials in this setting, the logic of the approach taken, the

reassuring results of the meta-analysis and the doses used in those studies, and our interpretation of the data in hand, the likelihood that the current judgment is significantly mistaken is small. Indeed, in many controlled studies, especially ones utilizing flexible dosing regimens, we ordinarily obtain poor, or even misleading, dosing data, and therefore cannot provide ideal, or easily interpretable, dosing recommendations (although it must be admitted that in such studies, we can confidently conclude that the drug is effective under the conditions that obtain in the study).

Nonetheless, I believe that the data before us support the approval of the application. Therefore, I will issue the attached Approval letter with appended labeling.

Russell Katz, M.D.

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## **DNDP REVIEW OF NDA SUPPLEMENT (response to approvable)**

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**Brand Name:** Trileptal

**Generic Name:** Oxcarbazepine (Trileptal <sup>TM</sup>)

**Sponsor:** Novartis

**Indication:** Partial Seizures

**NDA Number:** 21-014 (S-003)

**Original Receipt Date:** February 7, 2003

**Review Author:** N. Hershkowitz, MD,PhD

**Review Completed:** July 21, 2003

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Approved by  
On original

## 1. Executive Summary

This is a review to the Sponsor's response to an approvable letter for a labeling supplement that described a theoretical approach, referred to as the PK/PD bridging analysis, to justify labeling recommendation for monotherapy use of the anticonvulsant Trileptal in the pediatric population in the absence of direct double-blind placebo-control empirical evidence. This approach uses data available from double-blind pivotal trials that have already been reviewed and deemed adequate for approving monotherapy treatment in an adult population as well as adjunctive treatment in both pediatric and adult populations. The present submission addresses the following issues:

- 1) Justification of a concentration/response analysis derived from studies where patients were randomized by dosage (flexible and fixed).
- 2) Determination of equivalence between concentration response relationships between pediatric and adult adjunctive studies.
- 3) If points 1 and 2 are adequately addressed, determine a range of concentrations associated with adequate monotherapy seizure control in adults.
- 4) Determine theoretical recommended pediatric doses from the concentrations derived in point 3.

To help justify the use of dosage to construct response curves the Sponsor demonstrates that pharmacokinetic relations are generally independent of disease severity. The most helpful analysis performed by the Sponsor is the demonstration of the lack of effect of baseline seizure activity on clearance. The Sponsor also demonstrates that visit during adjunctive trials is not a significant covariate in drug clearance.

An issue raised by this division regarding the propriety of performing a concentration response analysis from data where patients were randomized by dosage is the possibility of an unknown factor effecting both pharmacodynamic and pharmacokinetic relationships. While the previous analysis helps to examine this issue the Sponsor performs a more sophisticated analysis. In this analysis the Sponsor shows a lack of correlation between residual errors of models describing pharmacodynamic and pharmacokinetic variables in adjunctive trials. While this is helpful it is not definitive and is dependent on the degree that other factors contribute to the residual error. The correlation would be masked by other covariates that strongly, but unequally effect the residuals of pharmacokinetic and pharmacodynamic relationships. In conclusion, although the presence of a correlation may suggest confounding, the lack of correlation does not necessarily rule such an effect. This analysis, however, is helpful.

The Sponsor also carries out what is referred to as a "sensitivity analysis" that simply demonstrates the lack of significant correlation of known covariates to

pharmacodynamic and pharmacokinetic relationships. This is also helpful but dependent on covariates that can be identified.

Flexible dosing, used in the pediatric adjunctive trial, required specific justification. If dosage is adjusted to efficacy, the use of such a paradigm can potentially distort the final concentration response relationships. The Sponsor argues that dosage changes for the vast majority of patients were for reasons of adverse events. While this was well documented, 22 % of patients had dosage increase at some point that may be suspect for efficacy adjustment. This percent may be sufficiently small to justify the Sponsor's argument.

This reviewer believes that while each individual analysis does not alone justify the construction of concentration response curves, the consistent findings of all of the analyses collectively justify this approach.

The Sponsor takes a modeling approach in an effort to examine the pharmacodynamic equivalence between pediatric and adult patients who participated in adequately controlled pivotal studies. The Sponsor determines that two different models best describes the two different populations; i.e. pediatric and adult. The basis of the sponsor analysis is principally faulted by the fact the two models are rather different. Moreover, it is pointed out that the models described exhibit a low correlation coefficient ( $R^2$  value was between 0.09 and 0.17). As pointed out by OCPB, while this correlation is low the chosen model appears reasonable. The Sponsors analysis is incomplete in that in most cases the analysis consists of an examination of non-inferiority and not equivalence.

With these limitations in mind, OB performed an analysis based upon a single model for pediatric and adult groups. They demonstrated that while the point estimate for pediatric and adult pharmacodynamic relationships were similar, the confidence interval ranges were somewhat broad. This reviewer feels that OB evaluation is both more appropriate and understandable. Thus, examination reveals that pediatric responses were approximately 85% of the adult responses for all concentration except placebo. The 95% confidence interval for these points was 50% to 122% (percent of pediatric to adult response). These ranges are somewhat broad. As there is no precedence for this type of analysis it is difficult to determine what goal posts are adequate. A common goal post set for equivalence testing by this agency in PK equivalence studies for the comparison of generics to brand name products is 80 to 125 percent. While these values are not contained within this range it may be argued that, with other supporting information (e.g. meta-analyses), the findings are sufficient to assume equivalence.

The Sponsor recommends that two concentrations be used for the determination of the final pediatric dosage recommendations. These are 59.1  $\mu\text{mol/L}$  and 112  $\mu\text{mol/L}$ . These values represent the median concentrations associated with adult monotherapeutic dosages of 1200 and 2400 mg/day. The selection is reasonable, as the dosages of 1200 and 2400 mg/day have been approved for initiation or conversion to monotherapy, respectively. These dosages represent an adequate range of seizure control in adult monotherapy trials (67% and 92%). Using Pharmacokinetic data the Sponsor derives

recommended doses for pediatric population that is based upon weight. The final recommended doses presented by the Sponsor appear adequate to this reviewer.

Safety data on recommended doses for both monotherapy and adjunctive therapy in the pediatric population accompanied this application. All these data were reviewed by this division in the past. These data do not indicate any additional safety risks when Trileptal is administered as monotherapy versus add-on treatment.

In conclusion, the Sponsor has constructed a cogent rationale for the use of Trileptal as monotherapy. While each argument may not stand alone, they collectively, with previously submitted meta-analysis, make a strong argument for approval. The dosage recommendations appear adequate. They were based upon sound pharmacokinetic and pharmacodynamic principles. This reviewer recommends approval.

## 2. Background and History

Trileptal (oxcarbazepine) is an anticonvulsant that has been approved for monotherapy or adjunctive therapy use in the treatment of partial seizures in adults and as adjunctive therapy in the treatment of partial seizures in children ages 4-16. The approval was based upon empirical evidence presented in the initial NDA.

This division has typically required that indications for pediatric anticonvulsant use be directly supported by empirical evidence from placebo-controlled double-blinded pediatric studies. Ethical issues surrounding the use of placebo controlled trials in pediatric epilepsy have been widely debated. The present submission is the culmination of several years of collaboration that this division has had with Novartis that attempts to provide a theoretical framework for an alternative scheme for the approval of monotherapy use in a pediatric population without direct empirical evidence.

The following table provides a summary of the important regulatory decisions and dates regarding this submission. These will be discussed in greater depth below.

Table 1 Summary of the Regulatory History if the Present Submission

Submission/Meeting	Date	Action
Original NDA submission (21-014).	4/25/98	Approvable for miscellaneous deficiencies.

Sponsor's complete response to the approvable letter includes a request for pediatric monotherapy labeling.	11/15/99	Application approved for adult and pediatric adjunctive use and adult monotherapy. Pediatric monotherapy requested based upon a 3-point argument presented in text. Labeling for pediatric monotherapy was rejected. PK/PD bridging analysis proposed by the division (letter dated 1/14/00).
Meeting with Sponsor	4/24/00	Discussed general issue regarding limitations of PK/PD analysis.
Supplement submitted with bridging analysis (S-003) for monotherapy use in children.	2/9/01	Approvable because of inadequacies of bridging analysis (letter dated 12/12/01). The submission also included a variety of meta-analyses of pediatric monotherapy data.
Meeting with Sponsor.	4/4/02	Sponsor presents a plan for future response to the approvable letter to the supplement (S-003).
Meeting with Sponsor.	11/6/02	To discuss preliminary analysis of equivalence by Sponsor.
Complete response to approvable letter for supplement (S-003).	2/6/03	Under review.

The original NDA, submitted on September 25, 1998, contained 6 adequate pivotal placebo controlled trials. Four examined monotherapy in a predominately adult population (004, 025, 026 and 028) whereas the remaining two studies examined adjunctive therapy in adults and in children (OT/PE1 and 011, respectively). Although no pediatric pivotal monotherapy trials were included in the application, because of age cutoffs, a minimal number (n=47) of pediatric patients were included in the monotherapy studies. Pivotal trials are summarized in the two tables below:

**Table 2 Summary of pivotal monotherapy trials**

Therapy	Control	Protocol	# of centers	Design	Age (years)	Randomized Treatment	Total # Randomized	Duration of Double-blind treatment
Monotherapy	Placebo	004	10	Double-blind, parallel, presurgical, inpatient	11-65	OXC 2400 mg/day Placebo	51 51	10 days
Monotherapy	Placebo	025	10	Double-blind, parallel, recent-onset patients	≥ 10	OXC 1200 mg/day Placebo	32 35	90 days
Monotherapy	Low-dose	026	12	Double-blind, parallel, substitution of CBZ by OXC	≥ 12	OXC 2400 mg/day OXC 300 mg/day	51 45	126 days <sup>1</sup>
Monotherapy	Low-dose	028	9	Double-blind, parallel, substitution of 1-2 AEDs by OXC	≥ 12	OXC 2400 mg/day OXC 300 mg/day	41 46	126 days

<sup>1</sup> Patients in Protocol 026 also received treatment during a 28-day Open-label Conversion Phase and a 56-day Baseline Phase.

*Table 3 Summary of pivotal adjunctive therapy trials*

Therapy	Control	Protocol	# of centers	Design	Age (years)	Randomized Treatment	Total # Randomized	Duration of double-blind treatment <sup>2</sup>
Adjunctive	Placebo	011	47	Double-blind, parallel patients on 1-2 AEDs	3-17	OXC (30-46 mg/kg/day) Placebo	138 129	112 days
Adjunctive	Placebo	OT/PE1	60	Double-blind, parallel, patients on 1-3 AEDs	15-65	OXC 2400 mg/day <sup>1</sup> OXC 1200 mg/day OXC 600 mg/day Placebo	174 177 168 173	182 days

<sup>1</sup> This treatment group includes 47 patients who were dosed at 1800 mg/day per protocol amendment.

<sup>2</sup> The length of double-blind treatment excludes any tapering periods that may have occurred.

In their response to the approvable letter for the original NDA the Sponsor requested pediatric monotherapy labeling (November 15, 1999). The request was based upon a 3-point argument: 1) The recommendation by the ILAE that states “because the efficacy of AEDs seems to be the same in childhood...partial epilepsy...there is no obvious reason to repeat controlled efficacy studies of childhood partial epilepsy previously performed in adults,” 2) The Sponsor’s meta-analysis of children who participated in the original monotherapy adult studies that demonstrated some degree of efficacy; 3) The claim that that PK differences were not sufficiently large to require dosage adjustments based upon age.

The FDA notified the Sponsor, in a letter dated January, 14, 2000, that Trileptal has been approved for adjunctive treatment in adults and children and monotherapy in adults for the treatment of epilepsy of partial onset. Its use as monotherapy in the pediatric population was specifically not approved. In our approval letter this division noted that while meta-analysis came close to addressing the question of pediatric monotherapy an insufficient number of patients (17 drug and 12 placebo) were included to provide a compelling argument to justify labeling dose recommendations.<sup>1</sup> This division also did not agree with the Sponsor’s claim that PK differences were not large enough to require a specific consideration of potential dosing differences between ages. Studies had previously demonstrated a 30-40% increase in clearance in children less than 8 years old.

In that letter this division suggested an alternative approach that is described as follows. “This would consist first, of comparing the plasma levels associated with a dose giving seizure control in the adjunctive setting in adults and pediatric patients. If these levels were similar, it would be reasonable to

<sup>1</sup> This was particularly true for the youngest patients. Thus, there were a total of 3 placebo and 3 drug treated patients between ages 6 and 11 years old.

conclude that plasma levels associated with seizure control in adults during Trileptal monotherapy would be similar to those that would provide seizure control in pediatric patients during Trileptal monotherapy. Then, a dosing regimen in which these exposure levels could be reliably achieved when Trileptal is given to pediatric patients as true monotherapy could be determined.” This will be referred to as a PK/PD bridging analysis.

A meeting with the Sponsor was held on April 24, 2000. The Sponsor was told that approval without studies would be precedent setting. The division was concerned that there was limited safety data that related to serum concentration and the existing trials contained a limited number of patients below the age of 8.

The Sponsor subsequently submitted an NDA supplement (S-003) on February 9, 2001 for which an approvable status was granted. The approvable letter (December 12, 2001) discussed some of the pitfalls in the Sponsor's analysis. These are listed in the bulleted items below.

- The principle approach taken by the Sponsor was to carry out an examination of pharmacodynamic similarity between adjunctive pediatric and adult trials and show that the concentration ranges for which statistically significant seizure control was demonstrated overlapped between these two populations. The division concluded that this simple analysis was inadequate to demonstrate pharmacodynamic similarity. As a result the division performed its own analysis. Plots of  $C_{min}$  Versus 28-day seizure frequency for adult and pediatric patients receiving adjunctive treatment were constructed and compared. There was no significant difference between the two populations. The Sponsor was requested to perform a similar analysis.
- The Sponsor was asked to justify the above analysis in view of the fact that data had not been randomized to concentration groups as a part of protocol design. The Sponsor was told in the approvable letter that: “In trials in which patients are randomized to fixed doses (as was done in the adult study), one could argue that examining the concentration– response relationship is justifiable, given that there is a reasonable correlation of dose with plasma level. However, in the pediatric adjunctive study, patients were not randomized to fixed doses; rather, they were randomized to a flexible dose range. In such a study, the ultimate dose reached is determined by many (unknown) factors, and it is well accepted that no useful dose-response data can be generated in such a study. This makes any attempt to establish a concentration-response relationship in this study problematic (even though we have performed one). Before we can accept the results of such an analysis, you will need to justify this approach, both for the fixed dose adult study, but also, more importantly, for the flexible dose pediatric study.”
- The point was made that a lack of a statistically significant difference is not the same as concluding that the populations showed equivalence. The Sponsor was asked to provide a more definitive analysis of the equivalence of the PK/PD relationship for these two populations.
- In their submission the Sponsor proposed effective dose ranges that applied to all pediatric patients. Examination of these ranges, based upon the

Sponsor's model, indicated that a large fraction of patients, particularly those who are younger (low weight), would not achieve sufficient theoretical seizure control at the proposed low dose. Thus, the Sponsor was told that "it is not immediately obvious that this is the appropriate manner in which to construct a therapeutic range... it is not obvious that the lowest plasma levels achieved at the lowest effective dose are, in fact, effective." This was likely the result of the increased clearance observed in the younger patient population. The Sponsor was asked to more clearly justify the recommended doses.

- The Sponsor submitted two principal new meta-analyses. The first new analysis included the original patients along with additional patients from a pediatric double-blind, placebo-control pediatric study (006) that was discontinued because of recruitment problems. This study added additional 22 patients (9 drug and 13 placebo). The second meta-analysis included patients from active control trials. This division discussed particular issues in this meta-analysis that would detract from it including the fact that it "combined data from populations that were apparently different." For example, placebo and drug treatment groups differed in regard to baseline seizure frequency and age. The Sponsor was informed that "while the results of these analyses are consistent with a conclusion that Trileptal is effective as monotherapy in pediatric patients, we do not consider them definitive."

The Sponsor met with this division on April 4, 2002 for additional guidance on responding to the approvable letter for monotherapeutic labeling based upon the pharmacodynamic/pharmacokinetic approach. At that meeting the Sponsor presented their approach to the information requested in the 12/12/01 approvable letter. The present submission predominately uses the approach outlined at that meeting. At that meeting the Sponsor was told that although the approach presented for the PK/PD bridging analysis appeared "reasonable" the analysis will have to undergo review.

The Sponsor supplied this division with additional information on their equivalence analysis in a meeting held on November 6, 2002. The division noted at that meeting that while the approach appeared acceptable the final decision would be a matter for review. The division expressed some concern that the pharmacodynamic models developed for adjunctive adult and pediatric use appeared to have a different dependency on baseline seizure frequency.

In summary, the analysis presented by the Sponsor can be divided into the following distinct steps:

- 5) Justification of a concentration/response analysis derived from studies where patients were randomized by dosage (flexible and fixed).
- 6) Determination of equivalence between concentration response relationships between pediatric and adult adjunctive studies.
- 7) If points 1 and 2 are adequately addressed, determine a range of concentrations associated with adequate monotherapy seizure control in adults.
- 8) Determine theoretical recommended pediatric doses from the concentrations derived in point 3.

### 3. Pharmacokinetic/Pharmacodynamic Bridging Analysis

#### 3.1 Justification of PK-PD analysis

As noted above, this division expressed concern over the propriety of the comparison of concentration-response curves derived from studies where patients were randomized to dosage groups. This was of particular concern in the pediatric studies that used a flexible dose design. In a meeting with the Sponsor (4/04/02) this division recommended that the sponsor should attempt to address the issue of the potential for the “pharmacodynamics (response) to influence the pharmacokinetics” in a study designed as a flexible dose trial. The division noted additional justification based on mechanism of action of the drug (for e.g., no correlation between an adverse effect and seizure control) and knowledge of drug characteristics (e.g., is pharmacokinetics affected by disease state or does the pharmacokinetics change over time with improvement in disease in the Phase 3 trials) may be useful.”

As noted in previous reviews oxcarbazepine is rapidly metabolized into the active 10-monophydroxy derivative (MHD) metabolite. This occurs to such an extent that oxcarbazepine may be considered a pro-drug of MHD and all future pharmacokinetic/pharmacodynamic analysis will be described in terms of MHD concentrations.

A Preliminary discussion of some of these issues follows. However, as a part of the Sponsors argument is based upon the model used for the bridging analysis a discussion of the model will precede a more complex discussion of confounding variables.

#### 3.1.1 Evidence for the lack of influence of pharmacodynamic factors on pharmacokinetics factors

- The Sponsor argues that steady state dose linearity has been demonstrated over a wide range of doses (300 mg/day to 2,400 mg/day) for many patient types (epilepsy patients on adjunctive or monotherapy treatment, patients with trigeminal neuralgia pediatric patients and healthy individuals). While this argument is helpful this reviewer will note that there is no direct comparison of dose/concentration curves (i.e. comparison of slopes and intercepts) nor is there a statistical evaluation of linearity; i.e. examples of fitted curves are presented but no r values given; see Appendix 3 of submission).
- The Sponsor examined the potential that the Disease State may effect drug clearance. This was performed for study 011 (reference cited- p20) and OT/PE1 (appendix 4) by demonstrating that baseline seizure frequency was

not a significant covariate of clearance in a population pharmacokinetic model ( $p=0.6$  and  $p=0.7$ , respectively). This reviewer feels that this analysis is helpful.

- Another analysis performed by the Sponsor to support the notion of an absence of pharmacodynamic influence on pharmacokinetics is a determination of visit as a potential covariate in the pharmacokinetic analysis of 011 and OT/PE1. Visit was not found to be a significant covariate for both 011 and OT/PE1 ( $p=0.008$  and  $p>0.2$ ). This analysis was submitted in response to this division's request and is based upon the presumption that seizure control may be different at different times in the course of therapy. This reviewer feels that if indeed the visit were a significant covariate the bridging analysis would be put into question. While such an analysis is helpful it only answers the question if PK is not affected by the expression of the Disease State. There may be underlying processes that effect seizure occurrence and PK in a parallel fashion. Notwithstanding this, the analysis is helpful.

#### *3.1.1.1 Reviewer's Comment*

The Sponsor has carried out the requested analysis by this division. While there is no careful dose response comparison performed for the first bulleted item, the analysis generally suggests that PK is not influenced by disease state. The most helpful analysis is the lack of effect of baseline seizure activity on clearance.

#### *3.1.2 On the Issue of dose adjustment according to A Flexible Dosing Schedule*

The argument was raised by the division that deriving a concentration/response relationship from a flexible dose protocol design, as used in study 011, might be particularly troublesome because of the lack of randomness in dose selection. Thus, patients with resistant epilepsy may have their dose adjusted upward to control seizures. Such a design can obfuscate the concentration dependency; e.g. it may result in a final concentration/response curve that is relatively flat. The Sponsor argues that most dosage adjustments in this protocol involved either an inability to achieve the targeted dosage or a reduction in this dose because of adverse events. The Sponsor supports this conclusion by arguing that "almost all dose changes were due to tolerability reasons." This conclusion is based upon the following argument. The study consisted of a 14-day titration period during which patients were titrated to an optimum daily dose (defined as the lowest dose that provided seizure control with acceptable tolerability) with the intention of achieving a given targeted dose. The targeted dose was based upon the patient's weight. The protocol stipulated that dosing was not to be altered during the Maintenance Phase but exceptions were permitted, with approval by the Sponsor's monitor, if problems with tolerability or seizure control were observed. The titration phase ended at visit 3.

The following table presents information on whether patients achieved the targeted dose and whether the dose was adjusted following visit 3, during the maintenance phase.

*Table 4 Number of patients with and without deviations from target dose and dose adjustments after titration*

Dose at Visit 3 (end of titration)	Doses after Visit 3	Oxcarbazepine (N=109)	Placebo (N=128)
Reached target	No change	50 (74%)	96 (82%)
	Decreased	10 (15%)	12 (10%)
	Increased	1 (2%)	3 (3%)
	Decreased and increased	7 (10)	6 (5%)
	Total	68	117
Less than target	No change	17 (43%)	1 (14%)
	Decreased	10 (25%)	2 (29%)
	Increased	7 (18%)	4 (57%)
	Decreased and increased	6 (15%)	0 (0%)
	Total	40	7
Exceeded target	No change	0 (0%)	2 (50%)
	Decreased	1 (100%)	1 (25%)
	Increased	0 (0%)	1 (25%)
	Decreased and increased	0 (0%)	0 (0%)
	Total	1	4

The Sponsor points out that while some of the patients achieved the targeted dose at the end of the titration phase (visit 3) others did not. Only one exceeded it. Of the 40 patients who did not reach the targeted dose 34 did so for stated reasons of adverse events. No stated reasons were given in 5 of these patients but these patients were noted to have adverse events and one is noted to have a "slower titration." All dose decreases after visit 3 were associated with adverse events. The dose increases following visit 3, according to the sponsor, consisted of "attempts to reach the targeted dose." The two patients who exceeded the targeted dose (one at the end of titration and one during maintenance) did so according to the Sponsor because of adjustments for body weight. Increases following titration for those who did not achieve targeted dose were, according to the Sponsor, attempts to reach the targeted dose. The reasons for dose change are documented in Appendix 10 provided by the Sponsor. This principally documents reasons associated with reductions after visit 3. No original documentation is provided regarding patients who did not achieve targeted dose at the end of titration or reasons for subsequent increase.

Without more documentation this reviewer feels that any increase in dose (either an increase or a decrease followed by an increase) is suspect for dosage

alterations with the intention of increase in seizure control. The single case of the patient whose dose is higher than titration may be included in this category. Therefore 22 of the 106 patients on drug (21%) from 011 are suspect. This however leaves 79% of the patients where there is sufficient evidence that titration was performed for efficacy.

### 3.1.2.1 Reviewer's Comment

The vast majority of patients had no change in dosage or well document adjustments for reasons of adverse events. Twenty-one percent of patients had dosage increase at some point that may be suspect for efficacy adjustments. This may be sufficiently small so as not to invalidate a pharmacodynamic comparison of this data.

### 3.1.3 Modeling of Concentration response Relation

The Sponsor has taken a modeling approach for the pharmacodynamic comparisons of pediatric and adult concentration response curves. This model must first be presented before further discussions of confounding variables.

In order to compare concentration/responses relations the Sponsor derived a model for patients from the pediatric and adult adjunctive patients. Although studies O/PE1 and 011 were predominately composed of adult and pediatric patients, respectively, a small number of pediatric patients and adult patients were studied in OT/PE1 and 011, respectively (see tables 1 and 2). Therefore, the adult model was derived using data of 464 adults in study OT/PE1 and 16 adults in study 011. The pediatric model used 221 pediatric patients in study 011 and 9 pediatric patients in OT/PE1.

The derived model for OT/PE1 is as follows:

$$\text{Log (percent change + 110)} = \beta_0 + \beta_1 * C_{\min} + \beta_2 * C_{\min} * [\text{log}(\text{baseline seizure frequency}) - 2.5] + \varepsilon$$

(equation 1)

This model was selected from 8 potential candidates. They were calculated through  $R^2$  regression analysis and subsequently confirmed through residual analysis.  $C_{\min}$ , in this case, represents average observed trough values for each patient. Percent change represents the 28-day seizure frequency during the double-blind phase. A constant of 110 is added to the percent change to maintain a positive sign within the log function.  $\beta$  Values represent constants with  $\beta_0$  the response at 0 concentration ("the placebo effect") and  $\beta_1$  the mean concentration/response slope. As the best-fit model was one where response was dependent on baseline frequency the constant  $\beta_2$  describes the proportionality of this relation.  $\varepsilon$  is the residual error that describes the difference of an individual observation from that calculated through the model. In deriving this model 9 patients, representing a total of 3% of patients on drug, were

identified as “outliers.” These patients appeared to be non-compliant as their concentrations appeared far less than that of patients taking a similar dose. These patients were excluded from the determination of the model; later analysis is performed both including and excluding these patients.

The model derived for study 011 is as follows:

$$\text{Log}(\text{percent change} + 110) = \beta_0 + \beta_1 * C_{\min} + \varepsilon \quad (\text{equation 2})$$

Because trough values were not obtained during the study the  $C_{\min}$  value was determined by population pharmacokinetics as the serum concentration 12-hours after dose at steady state. Other values have the same meaning as the equation above. In this case baseline frequency was not determined to be an important factor in the concentration/response relation. That function is therefore missing from the equation.

The relation between dose and concentration for both 011 and OT/PE1 were modeled to the following equation:

$$\text{Log}(C_{\min}) = \beta_0 + \beta_1 * \text{Interact} + \beta_2 * \log(\text{dose in mg/m}^2/\text{day}) + \varepsilon \quad (\text{equation 3})$$

This equation allows for the calculation of concentration based upon dose per body surface area per day. The interact function ( $\beta_1$ ) represents change in concentration brought about by drugs that will influence clearance (carbamazepine, phenytoin and phenobarbital).  $\beta_2$  represent the proportionality between dose and concentration.  $\varepsilon$  has the same meaning as above.

The above analysis consists of correlating the average seizure response to the average serum MHD concentration over the full double-blind phase. This is referred to as a univariate analysis. The Sponsor also carried out a repeated-measure analysis such that the modeling is based upon individual visits. This analysis was found similar to the univariate approach. Thus the parameters  $\beta_0$ ,  $\beta_1$  and  $\beta_2$  had similar values. Baseline frequency was found to be an important factor in the adult but not in pediatric populations. Off note, pediatric, but not adult, patients receiving placebo exhibited some improvement over time.

### 3.1.3.1 OCPB's analysis of the model

As noted above this division has raised the issue that the fact that the two models differ raises the issue as to whether such populations can be considered pharmacodynamically equivalent (see meeting minutes for teleconference on November 6, 2002). PK attempted to examine how much this actually alters the concentration response. Thus they note that the difference between these two relationships can be found in the baseline frequency interaction term in adults,  $\beta_2 * C_{\min} * [\log(\text{baseline seizure frequency}) - 2.5]$ . The terms associated with  $\beta_1$  and

$\beta_2$  can be rewritten as  $C_{min} * (\beta_1 * + \beta_2 * [\log(\text{baseline seizure frequency}) - 2.5])$ . From this it is apparent that the slope for the full concentration/response relation is represented by  $(\beta_1 * + \beta_2 * [\log(\text{baseline seizure frequency}) - 2.5])$  and the baseline seizure frequency dependent part of the slope is represented by  $\beta_2 * [\log(\text{baseline seizure frequency}) - 2.5]$ . Dr. Duan calculated the percent of contribution of the frequency dependent term to the full slope of the relationship. This is contained in the table below. The percent contribution of baseline seizure frequency component increases with frequency.

**Table 5 The contribution of the  $\beta_2$  term to the slope of adult concentration response curve**

Seizure Frequency	% Weight
5.9	- 27
29	0
21	13
1800	60

The distribution of baseline seizure frequency is presented below.

**Table 6 Baseline seizure frequency distribution for adults in OT/PE1**

Variable	Min	Q1	Median	Mean	Q3	Max
Seizure freq.	2.0	5.9	8.9	29	21	1800

From these tables Dr. Duan points out that it can be concluded that lower and upper quartiles of the population studied can include a percent influence of the full slope from the baseline frequency interaction term of -27% to 13%. This is a rather large difference and because of this Dr Duan concludes that such an analysis is difficult to interpret.

### 3.1.3.2 OB's Comment

It is noteworthy that the correlation coefficient derived for the both models is rather low. This puts some of the utility of this analysis in question. There is further discussion on this issue in the section on equivalence.

### 3.1.3.3 Reviewer's Comment

The basis of the sponsor analysis is principally faulted by the fact the two models are rather different. This may put into question the pharmacodynamic

equivalence of these two populations or alternatively the selected models. OB and QCPB raise the issue of the propriety of the model in use and because of this OB performs an alternative analysis for equivalence (see below). The final determination of equivalence may have to be jointly based upon both the Sponsors and this division's analysis. Before equivalence is discussed, however, a discussion of confounding variables will be made that is based upon the present model.

### *3.1.4 Examination for confounding variables*

The Sponsor attempted to rule out factors that may independently influence both the dose/concentration and concentration/response relationship. Such factors may cause a spurious relationship between concentration and response in the case where only dose is correlated to response. These factors are referred to as confounding variables. The following discussion describes a number of approaches used by the Sponsor to investigate for the presence of potential confounding variables.

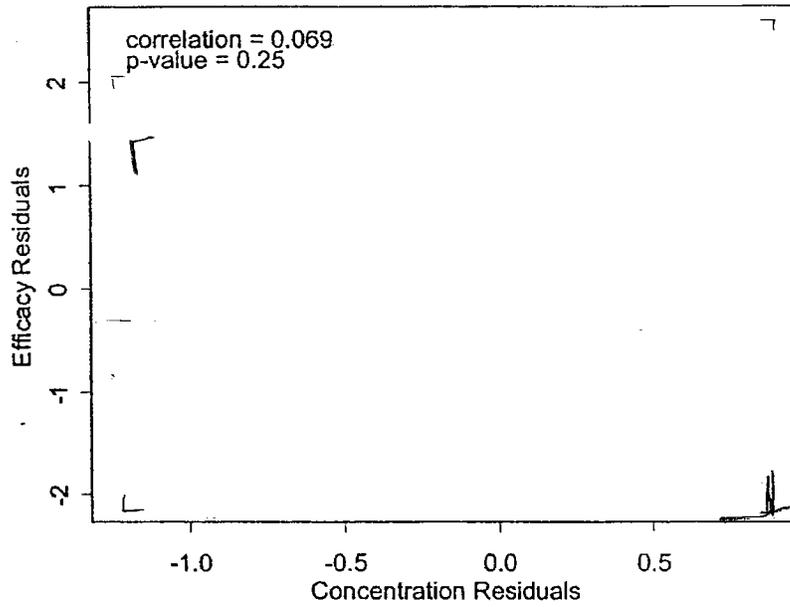
#### *3.1.4.1 Examination for mutual variation of in dose/concentration and concentration/response relationships*

The Sponsor examined the correlation in individual patient variation between the dose/concentration and concentration/response relationships. The individual variation was measured in terms of the residual error,  $\epsilon$ . Two techniques were used; the univariate approach and the repeated measure approach.

The univariate approach simply uses two data points for each patient as represented by the residual of the mean change in frequency over the double-blind period and the residual for mean "trough" serum concentration. The Sponsor has correlated residuals by plotting the concentration/response  $\epsilon$  (Efficacy) against the dose/concentration  $\epsilon$  (Concentration). These plots are presented below for both studies:

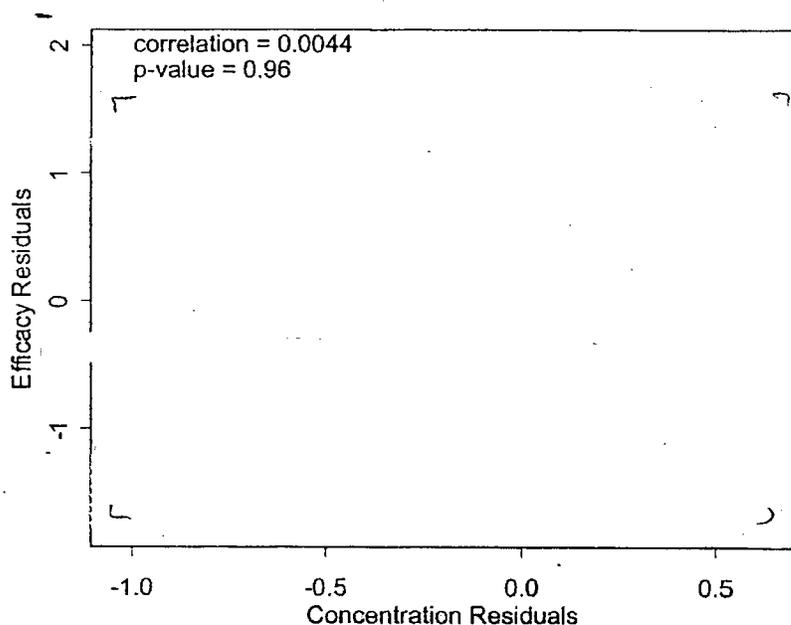
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**Figure 1 Correlation analysis of residuals for study OT/PE1**



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**Figure 2 Correlation analysis of residuals for study 011**



As apparent from the figure there was no significant correlation between these sets of residuals for either study.

The repeated-measure analysis was similar to the univariate analysis except data was analyzed by visit; i.e. each *visit* was associated with a single data point. Correlation coefficients using this analysis were low (0.037 to 0.096) and none of the correlation were found significant (p of 0.34 to 0.7).

#### 3.1.4.1.1 Reviewer's Comment

This reviewer believes that this does not fully rule out a confounding effect. The correlation would be masked by other covariates that strongly, but unequally effect the residuals of pharmacokinetic and pharmacodynamic relationships. In conclusion, although the presence of a correlation may suggest confounding, the lack of correlation does not necessarily rule such an effect.

#### 3.1.4.2 Sensitivity Analysis

Sensitivity analysis is based upon approaches developed by Cornfield et. al. and latter revised by Rosenbaum and Rubin.<sup>2</sup> The latter approach was adapted by the Sponsor. Thus the Sponsor first identified an empirical model for the relationship between concentration and response and dose and

<sup>2</sup> Rosenbaum and Rubin J R Statist Soc B 45(2): 212-218, 1983.

concentration. These are represented in the models described by equations 1, 2 and 3. Next other baseline covariates are identified and their Pearson's correlation with both the dose/concentration or concentration/response relationships are calculated. For concentration ( $C_{min}$ ) only patients on drug are considered, as all patients on placebo would have 0 concentration. For response (seizure frequency) placebo and drug were separately considered "to establish appropriate correspondences with  $C_{min}$ ." The following tables contain the data for the selected covariates in both studies.

**Table 7 Covariates and their correlations with PK and efficacy in Study OT/PE1**

Covariate	Correlation with:		
	$C_{min}$	log(percent change in seizure frequency + 110)	
	Trileptal	placebo	Trileptal
Age	-0.06	0.07	-0.03
Height	-0.00	-0.08	0.05
Weight	-0.10	-0.07	0.10
Body Surface Area	-0.09	-0.08	0.10
Creatinine Clearance	-0.02	-0.09	0.06
Gender (1=Female, 0=Male)	0.02	0.00	-0.08
Interacting AEDs (1=yes, 0=no) <sup>a</sup>	-0.11	0.15	0.06
Number of AEDs	-0.05	0.01	0.02
> 2 AEDs (1=yes, 0=no)	-0.07	0.04	-0.03

a) Taking AEDs that interact with MHD pharmacokinetics

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**Table 8 Covariates and their correlations with PK and efficacy in Study 011**

Covariate	Correlation with:		
	$C_{min}$	log(percent change in seizure frequency + 110)	
	Trileptal	placebo	Trileptal
Age	0.08	0.16	-0.01
Height	0.08	0.25	0.01
Weight	0.11	0.13	-0.11
Body Surface Area	0.11	0.16	-0.08
Creatinine Clearance	-0.10	0.18	-0.22
Gender (1=Female, 0=Male)	0.10	0.05	-0.17
Interacting AEDs (1=yes, 0=no) <sup>a</sup>	-0.34	0.08	-0.04
Number of AEDs	-0.33	0.05	0.03
> 1 AED (1=yes, 0=no)	-0.27	0.09	-0.01
> 2 AEDs (1=yes, 0=no)	-0.27	0.00	0.01

a) Taking AEDs that interact with MHD pharmacokinetics

From these tables it can be observed that correlations of covariates in study OT/PE1 are very small (up to 0.15). Although larger in 011 (up to 0.34), they are still on the low side. More important, except for weight, none of the highest correlating covariates exhibited high correlation in both PK and PD measures. For example while correlation for “interacting AEDs” was relatively large in 011 for PK measure (-0.34) it was low for PD measure (-0.03). The mutual high correlation is necessary in order to consider a covariate as a confounding variable; i.e. it should have a potential similar effect on both pharmacokinetic and pharmacodynamic relationships.

The Sponsor performed a calculation to determine what degree of alteration would occur if a covariate were similarly correlated in both pharmacokinetic and pharmacodynamic measures. This was measured by the percent change in the constants  $\beta_0$ ,  $\beta_1$  and  $\beta_2$  from equation 1 and 2. For OT/PE1 a simultaneous correlation for a covariate of 0.15, which was greater than the largest observed change in a single covariate (weight), will produce a change of approximately 1%, 7% and 13% in  $\beta_0$ ,  $\beta_1$  and  $\beta_2$ . Similarly a mutual correlation of a covariate of 0.3 in study 011 will produce a change of <1% and 8% in  $\beta_0$ , and  $\beta_1$ , respectively. The Sponsor concludes that in order for a covariate to influence the PD relationship it would have to have a high correlation in both PD and PK parameters. In conclusion, the correlation observed for the listed covariates would only minimally contribute to concentration/response relationship.

### 3.1.4.2.1 Reviewers Comment

The main issue raised by this reviewer regarding such an analysis is that it limits one to the study of only known covariates. Moreover, as this division previously noted that disease severity would be a potential confounding issue it would be useful to examine baseline seizure frequency as a potential covariate in this analysis. This reviewer is uncertain as to how this would be factored into this relationship as it is already a factor in the model for OT/PE1.

#### *3.1.4.3 Other Analyses for Confounding Factors*

The Sponsor performs two additional analyses for confounding variables, instrumental analysis and analysis by partial correlations. Only the latter will be discussed as it directly explores an issue raised by this division. This division had previously noted, "...the sponsor should attempt to address the issue of the potential for pharmacodynamics (response) to influence pharmacokinetics in a study designed as a flexible dose trial. Additional justification based on mechanism of action of the drug (for e.g., no correlation between adverse effect and seizure control)...will be useful." Thus, as previously noted, any factor that influences both PK and PD relationships may be considered a confounding factor. Adverse events may be such a factor in that it may influence both the final concentration and efficacy.

To examine for this confounding factor the Sponsor performs a partial correlation between efficacy and safety, adjusting for concentrations. The Sponsor demonstrates through this analysis that while various adverse events and seizure control are statistically significantly correlated that when adjusted for concentration these factors are no longer significantly correlated.

##### *3.1.4.3.1 Reviewers Comment on Analysis by Partial Correlations*

Another way of viewing this issue is that the Sponsor demonstrated that concentration adverse event and concentration efficacy relationships are not necessarily fixed equal among all patents. That is different patients may be differently sensitive to seizure control or adverse events. This is consistent with this reviewer's clinical experience.

#### *3.1.5 Other Model Dependent Analysis that justify bridging studies*

##### *3.1.5.1 Dependence of PK/Efficacy on dose adjustments in 011*

To demonstrate that flexible dosing had little significant effect on the final concentration response relation the Sponsor attempts to demonstrate that modeling using the original concentration response relation as presented in equation 2 ( $\text{Log}(\text{percent change} + 110) = \beta_0 + \beta_1 * C_{\text{min}} + \epsilon$ ) exhibits a better fit then when the model is derived from one of the following subsets of patients who experienced dose alterations (see table 4, above): 1) patients achieved dose less then targeted dose at visit 3; 2) patients who achieved dose less then targeted dose or there was a change after visit 3. This analysis demonstrated that the model derived from these populations was not significantly different from the original model.

### 3.1.5.1.1 Reviewer's Comment

This reviewer believes this is helpful but the problem with this analysis is the same problem that exists with any determination of equivalence using a simple statistical testing of the null hypothesis. That is, there is no understanding as to what constitutes the magnitude of the smallest determinable difference (the delta). The Sponsor does not discuss this.

### 3.1.6 Baseline Seizure Frequency

In this analysis the Sponsor examines how frequency effects modeling equations derived above (equation 1 and 2). Statistical parameters for baseline seizure frequency are presented the table below.

**Table 9 Distributions of baseline seizure frequency for adults (n=480) and pediatric patients (n=230) in studies OT/PE1 and 011**

Variable	Group	Min	Q1	Median	Mean	Q3	Max
Frequency	Adults	2.0	5.9	8.9	29	21	1800
	Pediatric patients	2.0	7.0	13	45	39	1500
Log Frequency	Adults	0.68	1.8	2.2	2.5	3.0	7.5
	Pediatric patients	0.69	1.9	2.6	2.9	3.7	7.3

The Sponsor notes that both adult and pediatric data exhibits right skewness although the pediatric data appeared to exhibit a greater degree of

skew. The distributions however were not found to be statistically different (p=0.45 by Kolmogorov test). The log scale was therefore used in modeling (see equation 1). Both populations were evaluated using the equation 1 and 2 including and excluding outliers. The result of this analysis is contained in the table below.

*Table 10 Parameter estimates for PK/Efficacy models*

Group	$\hat{\beta}_0 \pm \text{s.e.}$	$\hat{\beta}_1 \pm \text{s.e.}$ (p-value)	$\hat{\beta}_2 \pm \text{s.e.}$ (p-value)
Adults (full model, without outliers, n=472)	4.56 ± 0.04	-0.0103 ± 0.0011 (0.0000)	0.0031 ± 0.0008 (0.0002)
Pediatric patients (full model, without outliers, n=228)	4.54 ± 0.06	-0.0068 ± 0.0016 (0.0000)	-0.0008 ± 0.0009 (0.4)
Pediatric patients (reduced model, without outliers, n=228)	4.54 ± 0.06	-0.0071 ± 0.0015 (0.0000)	
Adults (full model, all data, n=480)	4.54 ± 0.04	-0.0099 ± 0.0011 (0.0000)	0.0031 ± 0.0008 (0.0002)
Pediatric patients (full model, all data, n=230)	4.55 ± 0.06	-0.0069 ± 0.0016 (0.0000)	-0.0008 ± 0.0009 (0.4)
Pediatric patients (reduced model, all data, n=230)	4.55 ± 0.06	-0.0072 ± 0.0015 (0.0000)	

Full model:  $\log(\text{percent change}+110) = \beta_0 + \beta_1 \cdot C_{\min} + \beta_2 \cdot C_{\min} [\log(\text{baseline seizure frequency})-2.5] + \varepsilon$   
 Reduced model:  $\log(\text{percent change}+110) = \beta_0 + \beta_1 \cdot C_{\min} + \varepsilon$

What is apparent from this data is that unlike modeled adult patients pediatric patients are only minimally dependent on baseline seizure frequency and may be considered not dependent at all. In summary, baseline frequency appears to be an important factor in the derived model for the adult but not pediatric population.

### 3.1.6.1 Reviewer's Comment

Presumably this justifies the reason to use two separate models for pediatric and adult pharmacodynamic relationships. Problems with the use of separate have already been discussed above. These issues will be expanded upon in the discussions on equivalence testing.

### 3.1.7 Placebo Response

In talks with the Sponsor this division expressed some concern that the slope in the derived models was a step function between placebo and drug treatment condition. The Sponsor responds to this by calculating the  $\beta$  constants from the model without placebo patients included. These data are included in the table below.

**Table 11 Parameter estimates for PK/Efficacy models, excluding placebo**

Group	$\hat{\beta}_0 \pm \text{s.e.}$	$\hat{\beta}_1 \pm \text{s.e.}$ (p-value)	$\hat{\beta}_2 \pm \text{s.e.}$ (p-value)
Adults (full model, without placebo, without outliers, n=295)	4.46 ± 0.08	-0.0084 ± 0.0017 (0.0000)	0.0032 ± 0.0009 (0.0004)
Pediatric patients (reduced model, without placebo, without outliers, n=104)	4.48 ± 0.21	-0.0062 ± 0.0035 (0.08)	
Adults (full model, without placebo, n=303)	4.41 ± 0.08	-0.0075 ± 0.0017 (0.0000)	0.0033 ± 0.0009 (0.0003)
Pediatric patients (reduced model, without placebo, n=106)	4.57 ± 0.21	-0.0075 ± 0.0034 (0.03)	

Full model:  $\log(\text{percent change}+110) = \beta_0 + \beta_1 * C_{\min} + \beta_2 * C_{\min} * [\log(\text{baseline seizure frequency})-2.5] + \epsilon$   
 Reduced model:  $\log(\text{percent change}+110) = \beta_0 + \beta_1 * C_{\min} + \epsilon$

The Sponsor notes that comparison of the  $\beta_0$  term excluding placebo (Table 11) with that including placebo (Table 10) indicates little difference and therefore the concentration response curve does not constitute a simple step function. As further support of this is the significantly negative slope ( $\beta_1$ ) in all cases except pediatric patients without outliers where the significance is "marginal" (0.08).

**3.1.7.1 Reviewer's Comment**

This appears to be a relatively sound argument.

**3.2 PKIPD Equivalence Between Adult and Pediatric adjunctive Patients in Pivotal Studies.**

In the previous NDA supplement the Sponsor reported that pharmacodynamic identity between pediatric and adult patients can be concluded from pivotal adjunctive trials. This was based upon the simple demonstration that plasma concentrations resulting from dosages producing effective seizure control overlapped between both studies. This division considered this inadequate in that it did not constitute a true pharmacodynamic

comparison; i.e. a comparison between concentration/response curves. This division carried out its own analysis such that concentration/response curves from the pediatric and adult studies were constructed using least squares and statistically compared. No statistical significance was observed between these two populations. The division, however, felt that a higher standard of proof of identity was required. The division requested that the Sponsor approach this in the fashion of non-inferiority testing. More specifically the Sponsor was requested, as per FDA meeting minutes 4/4/02, to: "approach this issue in a fashion developed for the testing of non-inferiority. It would be helpful if the sponsor would make a statistical determination as to what is meant by equivalence. That is, establish statistical criteria for equivalence and determine what is the largest difference (or margin) between samples that will lead to a conclusion of equivalence."

While the Sponsor performs a non-inferiority analysis they take a somewhat different approach. The Sponsor points out that the demonstration of non-inferiority in the present case differs in three ways to the non-inferiority testing that is routinely carried out:

- The acceptable non-inferiority fraction<sup>3</sup> (f) is usually specified in advance. A sample size is then selected based upon this information. In the present analysis f will be determined and the sample size is already fixed.
- The goal is usually to show that a new agent is similar to an active control. In the present analysis the goal is to show that single agent acts similarly in two populations. There are generally no placebo controls in non-inferiority studies. These are available in this study.
- The usual analysis involves comparisons between a single dose. The present analysis will examine comparison of concentration response relationships.

### 3.2.1 Methodology

The Sponsor notes that non-inferiority is based upon the statistical demonstration that the difference between a "test" agent and placebo is greater than a minimal fraction of the difference between an active control and placebo. This minimal fraction is referred to as the non-inferiority fraction. The above statement can be described mathematically by the following non-equality statement:

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<sup>3</sup> The non inferiority fraction is the smallest fraction of the difference between a comparison treatment response and control population response such that a test treatment response will be concluded to be "non-inferior" to comparison treatment response if the difference between a test population response and control population response is equivalent or greater than this value. This can be expressed mathematically as follows:

$$|\mu_T - \mu_0| > f |\mu_A - \mu_0|$$

Where f is the non-inferior fraction,  $\mu_T$  is the value of the response of the test population,  $\mu_A$  is the value of the response comparison treatment population and  $\mu_0$  is the value of the response of the placebo population

$$|\mu_T - \mu_0| > f |\mu_A - \mu_0| \quad (\text{equation 4})$$

f is the non-inferiority fraction,  $\mu_T$  is the value of the response of the test population,  $\mu_A$  is the value of the response comparison treatment population and  $\mu_0$  is the value of the response of the placebo population.

The Sponsor has adapted the non-inferiority analysis in the evaluation of the derived model described above: i.e.

Equation 1

$$\text{Log (percent change + 110)} = \beta_0 + \beta_1 * C_{\min} + \beta_2 * C_{\min} * [\log(\text{baseline seizure frequency}) - 2.5] + \epsilon$$

Equation 2

$$\text{Log (percent change + 110)} = \beta_0 + \beta_1 * C_{\min} + \epsilon$$

In this derivation the Sponsor has arbitrarily assigned the role of the test population to the pediatric patients and the control patients to the adult patients. Because the effect of the drug is dependent baseline seizure frequency in adults, the model analysis is carried out separately for patients with different baseline seizure frequencies. The Sponsor therefore defines the following variables:

$\mu_{A,x,b}$  = mean Log (percent change + 110) at  $C_{\min} = x$  for adults with log baseline seizure frequency of b

$\mu_{T,x}$  = mean Log (percent change + 110) at  $C_{\min} = x$  for pediatric patients

Equation 1 and 2 can then be expressed as:

$$\mu_{A,x,b} = \beta_{0,A} + \beta_{1,A}X + \beta_{2,A}X[b-2.5] \quad (\text{equation 5})$$

$$\mu_{T,x} = \beta_{0,T} + \beta_{1,T}X \quad (\text{equation 6})$$

The Sponsor then evaluates the model for non-inferiority for pediatric patients versus adult patients with a mean log baseline frequency of 2.5 (actual mean frequency of 12). Because the frequency dependent function ( $\beta_{2,A}X[b-2.5]$ ) reduces to zero the equation for adults simplifies to:

$$\mu_{A,x,b} = \beta_{0,A} + \beta_{1,A}X \quad (\text{equation 7})$$

The placebo response determined by equations 5 and 6 for adults with log baseline frequency of 2.5 and pediatric patients reveal the placebo response to be described by the following:

$$\mu_{A,0,2.5} = \beta_{0,A} \quad (\text{equation 8})$$

$$\mu_{T,0} = \beta_{0,T} \quad (\text{equation 9})$$

The null hypothesis derived from equation 4 may state as:

$$|\mu_T - \mu_0| \leq f |\mu_A - \mu_0|$$

When values from equations 6 through 9 are substituted for expressions in the null hypothesis one obtains:

$$H_{null}: |\beta_{0,T} + \beta_{1,T} \times \beta_{0,T}| \leq f |\beta_{0,A} + \beta_{1,A} \times \beta_{0,A}| \quad (\text{equation 10})$$

This equation simplifies because: 1)  $\beta_0$  from placebo and Test/Active subtract out, 2) the x term (concentration) cancels out as it is on both sides of the inequality expression. What is left is a statement about slope of the concentration/response model:

$$H_{null}: \beta_{1,T} \geq f \beta_{1,A} \quad (\text{equation 11})$$

The alternative hypothesis in this case is as follows:

$$H_{alt}: \beta_{1,T} < f \beta_{1,A}$$

It appears to this reviewer that by rejecting the null hypothesis one can conclude that  $\beta_{1,T}$  is less than  $\beta_{1,A}$ . This sets the lower limit for  $\beta_{1,T}$  but not the upper limit. If it is larger one will conclude equivalence.

The inequality statement can now be re-written in the form of a question about ratio of slopes and the non-inferiority fraction as follows:

$$H_{null}: \beta_{1,T}/\beta_{1,A} \leq f \quad \text{Vs.} \quad H_{alt}: \beta_{1,T}/\beta_{1,A} > f$$

Note the direction of the inequality changes because of the change in sign of the ratio (two divided negatives become positive).

As f was not pre-specified the Sponsor now attacks the problem to determine the largest f that would lead to a rejection of the  $H_{null}$  when testing at  $\alpha = 0.05$ ; i.e. the smallest f for which  $H_{null}$  is not rejected, which is the lower bound of the 95% confidence interval for  $\beta_{1,T}/\beta_{1,A}$ . The uses two quadratic formulas (see Sponsors formulas 2.1.14 and 2.1.15) to determine the confidence interval for  $\beta_{1,T}/\beta_{1,A}$  for the case presented above, where adult baseline seizure frequency is 12. This formula, however, calculates both the upper and lower ranges; i.e. it is a test of equivalence and not one of non-inferiority. The Sponsor then proceeds with the performance of non inferiority evaluation of adult frequency seizure baselines. These analyses are included next.

### 3.2.2 Analysis of non-inferiority

The table below presented by the Sponsor demonstrates the non-inferiority analysis for patients where the adult baseline seizure frequency is 12.

**Table 12 Comparison of PK/Efficacy relationship demonstrating non-inferiority of pediatric patients relative to adults with baseline seizure frequency of 12 seizures/month**

Data Set	$\hat{\beta}_{1,A}$	$\hat{\beta}_{1,T}$	$\hat{\beta}_{1,T}/\hat{\beta}_{1,A}$	f <sup>a</sup>
Without outliers	-0.0103	-0.0071	0.68	0.38
With outliers	-0.0099	-0.0072	0.72	0.41

a) f, the noninferiority margin, was determined by comparing pediatric patients to adults who had a baseline seizure frequency of 12.

The point estimate, based upon the model, for the ratio of slopes ( $\beta_{1,T}/\beta_{1,A}$ ), without outliers, was 0.68. The non-inferiority margin (f) was 0.38. The 95% confidence interval was value 0.38 to 1.05. This latter range, obtained for patients experiencing 12 seizures/month, is a true confidence interval for equivalence testing. Unfortunately it appears to be the only equivalence confidence interval presented by the Sponsor. All remaining analyses include testing for non-inferiority, not equivalence. As will be seen the agency (OB) performs its own calculations to derive a variety of such confidence intervals.

The remainder of the Sponsor's presentation addresses the lower limit of this range; i.e. non-inferiority and not equivalence. To better illustrate the analysis the Sponsor presents a table that compares the theoretical pediatric non-inferiority limit in patients with different baseline seizure frequency at a single reference  $C_{min}$  of 40.8. The data is presented in the table below.

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**Table 13 Comparison of expected changes from baseline for pediatric patients and adults, different adult baseline seizure frequencies at  $C_{min} = 40.8 \mu\text{mol/L}$**

Adult baseline seizure frequency (seizures per month)			Predicted percent change		Predicted seizure frequency <sup>d</sup> starting from adult baseline value		Predicted seizure frequency <sup>d</sup> starting from ped. geometric mean (18 per month)
Source <sup>a</sup>	Value	f <sup>b</sup>	Adults	Pediatric "noninferiority" <sup>c</sup>	Adults	Pediatric "noninferiority"	Pediatric "noninferiority"
Q25 Adult	5.9	0.32	-52.5%	-30.6%	2.8	4.1	12.5
Q50 Adult	8.9	0.35	-49.4%	-30.6%	4.5	6.2	12.5
GM Adult	12	0.38	-47.1%	-30.6%	6.3	8.3	12.5
GM Ped.	18	0.43	-43.8%	-30.4%	10.1	12.5	12.5
Q75 Adult	21	0.45	-42.5%	-30.3%	12.1	14.6	12.5

Note: 40.8  $\mu\text{mol/L}$  is the median  $C_{min}$  for adults at 1200 mg/day on adjunctive therapy, as reported in the sNDA

a) Q25 = first quartile, Q50 = median, Q75 = third quartile, GM = geometric mean

b) Noninferiority margin, determined as described in Section 2.3.3, comparing to adults with a baseline seizure frequency given in the adjacent column

c) "Pediatric 'noninferiority'" corresponds to predictions made by assuming that the slope of the PK/Efficacy relationship for pediatric patients is f times that of the adults

d) New seizure frequency predicted under maintenance treatment producing  $C_{min} = 40.8 \mu\text{mol/L}$

To understand this table it is best to first examine data based upon a single adult frequency of 12. These data are presented in the third row of the table. Using the pharmacodynamic model (equation 1) one can calculate the expected change in seizure frequency in adults; i.e. -47.1% or a reduction 12 seizures/month to 6.3 seizures /month. As noted previously the non-inferiority margin at this adult seizure frequency is calculated as 0.38. To calculate what this means in terms of expected actual lower values of changes in the pediatric population that would be considered as non-inferior the sponsor uses equation 6; i.e.  $\mu_{T,x} = \beta_{0,T} + \beta_{1,T}X$ . Except, the Sponsor substitutes the value of  $f\beta_{1,A}$  for the value of  $\beta_{1,T}$  to obtain the lower limit for non-inferiority. This is based upon the null hypothesis statement:  $\beta_{1,T} \geq f\beta_{1,A}$ . Using this, the Sponsor solves for response and then calculates the actual percent change in frequency based upon equation 2: i.e.  $\mu_{T,x} = \text{Log}(\text{percent change} + 110)$ . From this the lower range for the non-inferiority for pediatric seizures predicts a -30.6% change. This means pediatric patients with a seizure frequency of 12 will have their seizures reduced to 8.3. It is noteworthy that the calculated non-inferiority value changes minimally although the adult response changes significantly with changes in the baseline seizure frequency. Examination of the table demonstrates that the f, the non-inferiority margin, varies from 0.32 to 0.45, at different frequencies. The Sponsor believes that this supports the Sponsors contention of the equivalence of the PK/PD relationships between pediatric and adult populations.

The Sponsor performs a simulation experiment to further demonstrate the similarity between pediatric and adult PK/Efficacy relationships. The patients divided study OT/PE1 into random halves, stratified by dose, 1,000 times. The model described in equation 1 was fitted to each half. The difference between the percent change in baseline between each random half was compared to its complement half at each selected  $C_{min}$  values (0.0, 17.0, 40.8, 68.0, and 73.8). What was demonstrated were the differences observed between pediatric and adult patients shown in the above Table 13 were contained within the 25th to 90th percentile for the simulated difference from the same population (OT/PE1). The Sponsor argues that this demonstrates that the pediatric population was similar to the adult population.

### *3.2.3 Using non-inferiority to justify differences in pediatric and adult models.*

As noted above, in a teleconference with the Sponsor on November 6, 2002 some concern was expressed to the Sponsor that in the derivation of the pharmacodynamic model the baseline seizure frequency was identified as an important variable in adults but not in children. This indicated to the division that the pharmacodynamic behavior of these two populations might be different. The Sponsor was asked to discuss this issue in the present submission. With reference to the above figure, the Sponsor argues that although the non-inferiority fraction varies in adults from 32% to 45 % for different frequencies the “predicted reduction of seizure frequency for pediatric patients in terms of percent change was insensitive to the choice of adult baseline seizure frequency.” In other words predicted seizure frequency change obtained through inferiority analysis were generally comparable

### *3.2.4 OB's analysis of equivalence.*

OB reanalyzed data presented by the Sponsor, in a way that was felt to be more appropriate, to further investigate the equivalence of the two populations. The reviewer on OB felt that that the similarity of these two curves should be based upon similarity of not only slopes but also intercepts (placebo). The analysis should also start with the assumption that the models are similar. Consequently, for their analysis the adult model was simplified so as to not factor in the baseline frequency dependency ( $\beta_2$  was 0 for both studies). OB performed 2,000 simulations for the two independent trials (one for the 480 adult patients and the other for the 230 pediatric patients). This allowed the comparisons of like

models. Equivalence testing was performed from these simulations. Responses were then obtained for a variety of concentrations as were the median f values and its 95% confidence intervals are presented in the table below.

**Table 14 Equivalence testing as performed by OB**

Cmin	Median % change in frequency determined by Sponsor		Median % change in frequency determined by OB		Median value determined by OB ratio(median)	95% CI of Ped/adult ratio determined by the OB	
	Peds	Adults	Peds	Adults		2.50%	97.50%
0	-16.7	-14.1	-15.7	-15.4	1.037	-0.01	3.458
17	-27.2	-29.5	-26.6	-30.4	0.875	0.377	1.462
40.8	-40	-47	-39.6	-47.9	0.828	0.509	1.185
59.1			-48.1	-58.5	0.828	0.558	1.121
68	-52.2	-62.3	-51.8	-62.9	0.822	0.544	1.085
73.8	-54.5	-65.1	-54.5	-65.8	0.829	0.551	1.084
112			-68.0	-80.1	0.848	0.598	1.047

Examination of the first four column reveals that the response obtained by the OB's simplified model approach is similar to that obtained by the Sponsor for pediatric and adults populations at a variety of concentrations except the final f values is slightly shifted to the right (the median and confidence intervals of f tend to greater). The additional concentrations of 59.1 and 112 were included, as these are the concentrations associated with the final recommended dosages. No Sponsor values are included, as they did not perform the calculation at these concentrations. The median pediatric dose generally is 82% to 87% of the adult dose. This is rather close. The 95% confidence interval for this runs anywhere from 38% - 146% (at low concentrations) to 60% to 105% (at high concentrations).

OB performed a series of calculations that were made based on the above results which illustrated what concentration would be required in the pediatric population to produce a similar response as various given adult concentrations.

**Table 15 Calculated Cmin values for pediatric patients such that they achieve the same response for adults at different given concentrations**

Cmin peds	Cmin adults	%change peds	% change adults	Ratio	2.50%	97.50%
24	17	-30.5	-30.5	1.000	0.494	1.620
58	40.8	-47.7	-47.8	1.004	0.644	1.374
84	59.1	-58.6	-58.4	1.002	0.696	1.316

98	68	-63.2	-63.0	1.006	0.696	1.294
-107	73.8	-65.8	-65.8	1.000	0.713	1.262
161	112	-79.9	-80.0	1.002	0.744	1.200

### 3.2.5 Reviewer's Comment

Both OCPB and OB felt that the use of the Sponsors derived model was not a wholly adequate form of analysis. The principal issue is whether you can use a model that assumes a difference in the behavior of both populations to demonstrate that both populations are actually similar. OB questions the models that were in fact selected as they showed rather low correlation coefficients ( $R^2$  value was between 0.09 and 0.17). Statistical testing, however, revealed a statistically significant correlation. OCPB, however, points out that the model selected is reasonable and in discussions with them suggests that they believe the poor correlation coefficient is a result of variability in the data. In discussions with them they noted that poor correlations are not unexpected in PK/PD modeling. This reviewer points out that the Sponsor really only presents one equivalence analysis for patients experiencing a seizure frequency baseline of 12 seizures/month. All other analyses are really noninferiority type testing; i.e. they examine the lower limit of the equivalence confidence interval. The OB reviewer also notes that the Sponsor only performed a final analysis in the slope of the relationship, ignoring issues of the equivalence of the intercept. It should be noted that in the presentation of the methodology of non-inferiority testing this reviewer was convinced that the slope could be theoretically ignored (see equation 10 and 11).

With these limitations OB performed an analysis based upon a single model for pediatric and adult groups. They demonstrated that while the point estimate for pediatric and adult pharmacodynamic relationships were similar the confidence interval ranges were somewhat broad. This reviewer feels that OB evaluation is both more appropriate and understandable. Thus, examination of table 16 reveals that pediatric responses were approximately 85% of the adult responses for all concentration except placebo. The 95% confidence interval for these points was 50% to 122% (percent of pediatric to adult response). These ranges are somewhat broad. As there is no precedence for this type of analysis it is difficult to determine what goal posts are adequate. A common goal post set for equivalence testing by this agency in PK equivalence studies for the comparison of generics to brand name products is 80 to 125 percent. While these values are not contained within this range it may be argued that, with other supporting information, such meta-analyses, it may be sufficient to assume equivalence.

**3.2.6 Other analyses to examination differences between adult and pediatric patients.**

The Sponsor calculates the expected percent change from baseline for adults with a mean baseline seizure frequency of 12 and pediatric populations at a variety of pertinent  $C_{min}$ s based upon equations 1 and 2 respectively. This is presented in the table below. The difference between the model's mean is given, as is the 95% confidence interval for this difference. The Sponsor notes that "the fact that the 95% confidence intervals...for the differences between adults and pediatric patients contained zero indicates that the PK/Efficacy relationships for adults and pediatric patients were not statistically significantly different." This is a simple analysis of difference and not a test of equivalence. to determine a statistical difference between responses determined through the Of note the confidence interval of difference can be up to 22%. Moreover, data for other adult frequencies are not presented.

**Table 16 Comparison of adults and pediatric patients with respect to model-predicted percent change from baseline in seizure frequency**

$C_{min}^1$ ( $\mu\text{mol/L}$ )	Percent Change from Baseline		Difference: Pediatric Patients - Adults	
	Pediatric Patients	Adults <sup>2</sup>	Estimated Difference (% relative to adults)	95% Conf. Int. <sup>3</sup> for Difference
0.0	-16.7	-14.1	-2.5 (-17.9%)	(-15.0, 9.9)
17.0	-27.2	-29.5	2.3 (7.8%)	(-6.5, 11.1)
40.8	-40.0	-47.0	7.0 (14.8%)	(-2.5, 16.4)
68.0	-52.2	-62.3	10.1 (16.2%)	(-1.9, 22.1)
73.8	-54.5	-65.1	10.6 (16.2%)	(-1.5, 22.6)

1) 17.0, 40.8, 68.0, and 73.8  $\mu\text{mol/L}$  were the observed median concentrations corresponding to 600, 1200, 1800, and 2400 mg/day for adults during adjunctive therapy, as reported in the Supplemental NDA.

2) Adults with a baseline seizure frequency of 12 per month.

3) From bootstrapping. See Appendix 9 for details.

**3.3 Determination of effective concentrations**

Following the proof of the pharmacodynamic equivalence of pediatric and adult populations during adjunctive treatment the Sponsor was asked to perform an evaluation of effective treatment dosage in the pediatric population. This was to be determined by calculating the dosage that will produce similar

concentrations in children that had been observed to be associated with effective seizure control in adults who were receiving monotherapy. A similar analysis was performed the previous supplement, however, examination of the data indicated a number of patients, particularly those in the younger age groups, would not achieve sufficient concentrations for theoretical seizure control. This was likely because age/weight influence on clearance were not factored in to the final recommended doses. Because of this as noted above, the division asked that simulations be performed “to assess the distribution of predicted response using the proposed dosing regimen.” To accomplish this the Sponsor modeled pediatric and adult monotherapy data derived from the following double-blind, placebo-controlled studies: 004, 006, and 025.

The model derived from adult adjunctive treatment (i.e., Log (percent change + 110) =  $\beta_0 + \beta_1 * C_{min} + \beta_2 * C_{min} * [\log(\text{baseline seizure frequency}) - 2.5] + \epsilon$ , equation 1) was fit to adults and pediatric patients. These data are presented in the table below.

**Table 17 Parameter estimates for PK/Efficacy monotherapy**

Group	$\hat{\beta}_0 \pm \text{s.e.}$	$\hat{\beta}_1 \pm \text{s.e.}$ (p-value)	$\hat{\beta}_2 \pm \text{s.e.}$ (p-value)	Residual standard deviation
Adults (full model) n=132	4.73 ± 0.12	-0.0156 ± 0.0031 (0.0000)	-0.0007 ± 0.0018 (0.7)	1.11
Adults (reduced model) n=132	4.74 ± 0.12	-0.0165 ± 0.0021 (0.0000)		1.10
Pediatric population (full model) n=30	4.03 ± 0.36	-0.0116 ± 0.0068 (0.10)	0.0008 ± 0.0033 (0.8)	1.59
Pediatric population (reduced model) n=30	4.02 ± 0.35	-0.0115 ± 0.0066 (0.09)		1.56

Data from Studies 004, 006, and 025, the placebo-controlled monotherapy studies.  
 Full model:  $\log(\text{percent change} + 110) = \beta_0 + \beta_1 * C_{min} + \beta_2 * C_{min} * [\log(\text{baseline seizure frequency}) - 2.5] + \epsilon$   
 Reduced model:  $\log(\text{percent change} + 110) = \beta_0 + \beta_1 * C_{min} + \epsilon$

Off note, in no case was the  $\beta_2$  factor found to be significant, indicating no significant baseline seizure dependency. This factor was therefore not included in the final modeling. The  $\beta_1$  factor (concentration dependency) for the pediatric population was also found not to be significant. The Sponsor notes that this resulted from the small number of patients in this sample size (n=30).

The figure below presents a plot of adults on monotherapy from studies 004 and 025. The superimposed curve is the final fitted model (Log (percent change + 110) =  $\beta_0 + \beta_1 * C_{min}$ ).

Table 18 Estimated doses needed to achieve effective concentration ranges in pediatric patients of

Weight (kg)	MHD plasma levels during monotherapy: $C_{min}$ ( $\mu\text{mol/L}$ )			
	59.1 (median concentration at 1200 mg/day in adults)		112 (median concentration at 2400 mg/day in adults)	
	Dose (mg/day)	Dose/body wt. (mg/kg/day)	Dose (mg/day)	Dose/body wt. (mg/kg/day)
20	600	30.0	900	45.0
25	900	36.0	1200	48.0
30	900	30.0	1200	40.0
35	900	25.7	1500	42.9
40	900	22.5	1500	37.5
45	1200	26.7	1500	33.3
50	1200	24.0	1800	36.0
55	1200	21.8	1800	32.7
60	1200	20.0	2100	35.0
65	1200	18.5	2100	32.3
70	1500	21.4	2100	30.0

The final recommended dose derived from the model is modestly adjusted because of limitations in available dosing formulation. As the smallest available tablet is 150 mg the lowest daily dose was *up to* the nearest multiple of 300 mg daily dose. The highest maintenance dose was rounded *down to* the lowest daily 300 mg. All final pediatric dosing used the same regimen that has been approved for adults, i.e. twice daily. The rounding assured that the dosing would be within the modeled limits of efficacy.

Following the determination of recommended doses the Sponsor worked backwards and performed simulations using PK (dose/concentration) and PD (dose/response) models to determine distributions of patients of various heights and weights receiving the recommended high and low doses presented in the above table. Simulations first involved plugging the patient's weight, height and dose received into the PK model. The concentration received by the latter calculation would then be plugged into the PD model and response (percent seizure reduction) was obtained. The simulation generated 10,000 observations for each dose /weight set. The results of these simulations are presented in the two tables below (Tables 19 and 20). The mean change in seizure frequency for each weight/dose group is presented along with the distribution of the percent

changes in seizure reduction. It is notable that for the low dose 75% of patients are predicted to have 25 % reduction of seizures or better. Whereas 75 % of patients in the high dose are predicted to have 47% reduction of seizures or better. Both distributions are markedly skewed leading to the mean being markedly to the right of the median. The skew results in the fact that increases in seizures are observed in the upper 10 % of the distribution and the mean response is minimal (i.e. -11.6% to 7.2). The skew is far greater in the low than the high doses. The increases in seizures observed in the high dose in the model is not explained and must represent an artifact of the chosen model. The Sponsor compares the values here with those obtained from previous meta-analysis that included pediatric patients contained in 8 controlled (active and placebo) trials. 67 patients taking 10-20 mg/kg/day and 65 patients taking 20-55 mg/kg/day all experienced a median reduction of 100%. The Sponsor notes that the 82-95% in the tables, therefore, does not appear "overly optimistic." The Sponsor performs a similar analysis for the adult population and finds substantially less skewness.

*Table 19 Simulated distribution for percent change in seizure frequency by weight for the lower recommended doses*

Weight (kg)	Dose (mg/day)	Percentiles and Mean of Distribution					
		10%	25%	50%	Mean	75%	90%
20	600	-100	-100	-82.9	6.3	-25.1	133.2
25	900	-100	-100	-88.1	-11.6	-40.8	91.8
30	900	-100	-100	-86.2	-5.1	-35.1	107.1
35	900	-100	-100	-84.3	0.8	-29.9	120.9
40	900	-100	-100	-82.8	6.0	-25.3	132.5
45	1200	-100	-100	-86.9	-7.6	-37.4	102.0
50	1200	-100	-100	-85.6	-3.4	-33.6	110.5
55	1200	-100	-100	-84.4	0.4	-30.4	120.0
60	1200	-100	-100	-83.3	3.9	-27.2	128.4
65	1200	-100	-100	-82.4	7.2	-24.2	134.8
70	1500	-100	-100	-85.8	-4.0	-34.2	109.8

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**Table 20 Simulated distribution for percent change in seizure frequency by weight for higher recommended doses**

Weight (kg)	Dose (mg/day)	Percentiles and Mean of Distribution					
		10%	25%	50%	Mean	75%	90%
20	900	-100	-100	-90.5	-18.8	-47.1	74.2
25	1200	-100	-100	-93.9	-28.5	-55.9	51.4
30	1200	-100	-100	-91.7	-22.6	-50.3	65.7
35	1500	-100	-100	-94.3	-30.0	-57.2	46.5
40	1500	-100	-100	-92.6	-25.5	-52.8	57.9
45	1500	-100	-100	-91.1	-21.2	-49.0	69.1
50	1800	-100	-100	-93.3	-27.9	-55.1	51.5
55	1800	-100	-100	-92.3	-24.5	-52.1	60.1
60	2100	-100	-100	-94.2	-30.1	-57.3	46.0
65	2100	-100	-100	-93.1	-27.2	-54.5	53.3
70	2100	-100	-100	-92.2	-24.5	-52.0	59.9

Table 18 represents the final maintenance dose recommended in the new labeling for pediatric monotherapy use. In the final labeling the Sponsor recommends that Trileptal should be initiated at 8-10 mg/kg/day in both cases if initiation of monotherapy or conversion from another anticonvulsant to Trileptal monotherapy. This starting dose is similar to that which has been recommended for adjunctive use. While the upward titration in conversion and initiation therapy exhibit similar weekly rates the it is more frequent in initiation of therapy. Thus, conversion therapy recommends increases “as clinically indicated by a maximum increment of 10 mg/kg/day at approximately weekly intervals to achieve the desired clinical response.” The initiation of monotherapy treatment recommends increases of “5 mg/kg/day every third day to achieve the desired clinical response.” The above table 18 is referred to as a target dose in both forms of therapy: i.e. “based on extrapolation from adult monotherapy studies, daily doses of approximately 20-50 mg/kg/day as shown in the table.” The rate of dose titration is similar to the titration recommended for adult monotherapy under the conditions of initiation and conversion. Thus in the labeling for adults, a titration rate of 300 mg/day every third day recommended for monotherapy initiation and 600 mg/day every week is recommended for monotherapy conversion.

### 3.3.1 Preface to OCPB’s Analysis and Reviewer’s Commentary

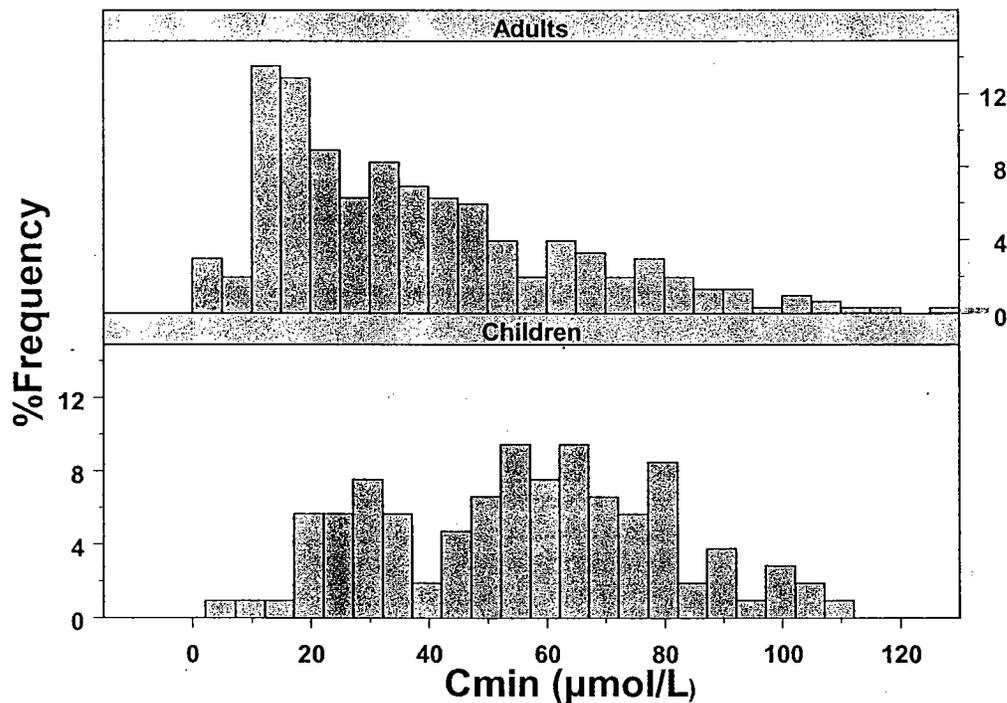
A preliminary comment is necessary regarding the following discussion of OCPB’s and this reviewer’s critique of the Sponsors dosing analysis. Upon initial review, OCPB did not concur with the Sponsors initial analysis and recommendations. This reviewer, however, agreed with the Sponsor and critiqued OCPB’s commentary. OCPB subsequently revised their review to concur with this reviewer’s arguments. The present review, however, was

written prior to this change. This reviewer feels that a number of interesting points and counterpoints were raised by OCPB and this reviewer. For this reason the initial comments will remain in the review and are presented in the following sections.

### 3.3.2 OCPB's Evaluation of Dosing

OCPB concurs with the way the present dose recommendations were derived. However, they argue against particular aspects of the Sponsors final recommended dosing. They argue that there is limited experience in adjunctive adult (OT/PE1) and pediatric (011) trials for  $C_{min}$ s above 110  $\mu\text{mol/L}$ . Dr Duan, the OCPB reviewer, justifies this by the following histograms of the distribution of mean  $C_{min}$ s from these studies.

*Figure 4 Distribution of  $C_{min}$ s in adults and pediatrics after adjunctive therapy.*



Dr Duan notes that it appears that the adjunctive patients experience lower concentrations and suggests this is a result of potential drug interaction (i.e. enzyme induction from other anticonvulsants). Using the above observation OCPB reviewer recommends a lower maximal maintenance dose than the one

recommended by the Sponsor. OCPB argues that a) the Sponsor's proposed dosing might lead to concentrations with limited experience in the clinical trials and b) the maintenance dose for monotherapy in children should be more or less similar to that in adjunctive therapy. This reviewer, however, would note that the adult patents tolerated high monotherapy doses (2400 mg/day) far better than these same doses in an adjunctive therapy setting. OCPB also suggests that only an upper limit maintenance dose be recommended. The rationale that they give for this recommendation:

- From a clinical practice view-point they speculated that the maximum target dose is what is helpful for the prescribers, not the lower limit of the target. They note that when patient reaches target effect at a dose lower than the maximum maintenance dose no further up-titration would occur.
- They also note that this would be consistent with the present labeling

OCPB's recommended maintenance dose is presented in the table below:

*Table 21 OCPB's recommended maintenance dose*

Weight in kg	Dose (mg/day)	Dose/body wt. (mg/kg/day)
20	900	45.0
25	900	36.0
30	1200	40.0
35	1200	34.2
40	1800	45.0
45	1800	40.0
50	1800	36.0
55	1800	32.7
60	1800	30.0
65	1800	27.7
70	1800	25.7

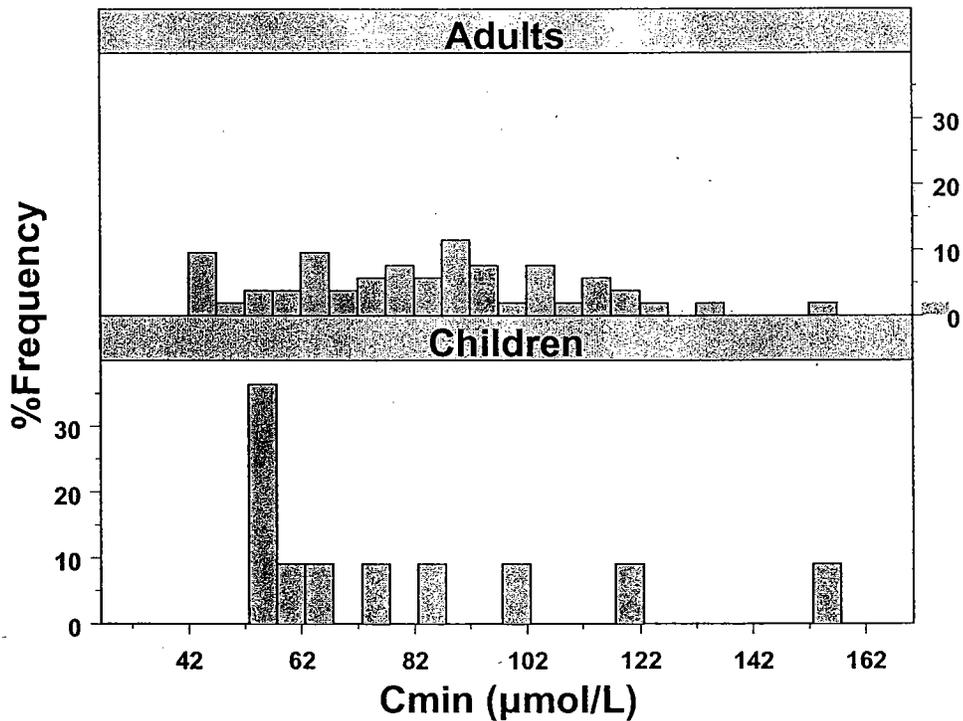
OCPB, however, concurs with the Sponsors recommended initiation dose and titration schedule.

### 3.3.3 Reviewer's Comment

Unlike OCPB's recommendation this reviewer agrees with the recommended dosing presented by the Sponsor. OCPB's argument against the Sponsors recommended dose would now be critiqued.

OCPB recommends lower maximal recommended doses than that suggested by the Sponsor. They note that there is limited experience with concentrations above 110  $\mu\text{mol/L}$ . The Sponsor uses 112  $\mu\text{mol/L}$  to estimate the maximal recommended dose. While as OCPB's point is well taken regarding adjunctive treatment it is less so regarding monotherapy. Thus, Figure 6 presents OPBC's histogram serum concentration for data from monotherapy trials. While it is true there are fewer patients above 110  $\mu\text{mol/L}$ , proportionally there are more than that observed in monotherapy trials. From trials where blood levels were available at least 15% of patients in adult monotherapy studies and 18% of patients in pediatric monotherapy studies had levels greater than 112  $\mu\text{mol/L}$ . This may not represent a large number of patients the proportionality is not unreasonable for the basis of a *maximal* maintenance dose recommendation.

*Figure 5 Distribution of Cmins in adults and pediatrics after monotherapy therapy.*



Another way to examine this issue is to use information provided by the Sponsor in from the previous labeling supplement. This information is presented in Tables 24-26. The tables present exposure demographics stratified by age.

and dose in 3 study populations. All epilepsy patients participating in trials are presented in Table 24. Patients in controlled monotherapy studies who were not previously treated with AEDs represented in Table 25. Lastly patients in controlled adjunctive therapy and monotherapy studies who were previously treated with AEDs are presented in Table 26. Safety information for all these patients was reviewed in the original NDA. Although the dosing information in these tables is stratified by age, the Sponsor's present dose recommendations are stratified by weight (Table 20). This reviewer performed the following manipulations so that a comparison could be made between the historical information and the present dose recommendations. The data presented in these table uses year 8 as a division point between two pediatric age groups. Consequently, this reviewer determined through examination of growth/weight charts (see Appendix A) that greater than 90% of patients below age 8 years are less than 30 Kg. According to the present dosing recommendations the maximal maintenance dose for patients less than 30 Kg, or younger than 8 years, will vary from 900 to 1200 mg/day. The maximal maintenance dose for greater than 30 Kg, or older than 8 years, will vary from 1500 to 2100 Kg/day. These doses can then be directly compared to demographics on the above safety information.

**Table 22 Summary of duration of exposure to study drug by maximum daily dose (mg/day) and age for all OXC-treated patients with epilepsy**

Duration of exposure (months)	Age <8 years N=141							
	Maximum daily dose (mg/day)							
	≤600		>600-1200		>1200-2400		>2400	
	n	%	n	%	n	%	n	%
≤ 1	7	14.9	4	6.0	0	0	0	0
>1 - 3	10	21.3	6	9.0	1	4.2	0	0
>3 - 6	10	21.3	10	14.9	0	0	1	33.3
>6 - 12	6	12.8	9	13.4	1	4.2	0	0
>12 - 24	6	12.8	15	22.4	12	50.0	0	0
>24 - 36	6	12.8	12	17.9	7	29.2	0	0
>36 - 48	2	4.2	4	6.0	3	12.5	0	0
>48	0	0	7	10.4	0	0	2	66.7
<b>TOTAL</b>	<b>47</b>	<b>100.0</b>	<b>67</b>	<b>100.0</b>	<b>24</b>	<b>100.0</b>	<b>3</b>	<b>100.0</b>
	Age 8-16 years N=431							
	n	%	n	%	n	%	n	%
≤ 1	18	31.6	16	10.7	14	7.7	3	7.0
>1 - 3	8	14.0	15	10.0	16	8.8	3	7.0
>3 - 6	5	8.8	21	14.0	11	6.1	2	4.7
>6 - 12	3	5.3	14	9.3	20	11.0	5	11.6
>12 - 24	7	12.3	23	15.3	43	23.8	15	34.9
>24 - 36	13	22.8	41	27.3	50	27.6	10	23.3
>36 - 48	3	5.3	13	8.7	19	10.5	4	9.3
>48	0	0	7	4.7	8	4.4	1	2.3
<b>TOTAL</b>	<b>57</b>	<b>100.0</b>	<b>150</b>	<b>100.0</b>	<b>181</b>	<b>100.0</b>	<b>43</b>	<b>100.0</b>

*Table 23 Summary of duration of exposure to study drug by maximum daily dose (mg/day) and age for patients in controlled monotherapy studies who were not previously treated with AEDs*

Duration of exposure (months)	Age <8 years N=26						Age 8-16 years N=103					
	Mean daily dose (mg/day)											
	≤600		>600-1200		>1200-2400		≤600		>600-1200		>1200-2400	
	n	%	n	%	n	%	n	%	n	%	n	%
≤ 1	2	9.1	1	25.0	0	0	4	12.1	3	4.8	1	12.5
>1 - 3	4	18.2	0	0	0	0	3	9.1	6	9.7	3	37.5
>3 - 6	2	9.1	1	25.0	0	0	1	3.0	9	14.5	0	0
>6 - 12	2	9.1	0	0	0	0	0	0	1	1.6	2	25.0
>12 - 24	12	54.5	2	50.0	0	0	25	75.8	43	69.4	2	25.0
<b>TOTAL</b>	<b>22</b>	<b>100.0</b>	<b>4</b>	<b>100.0</b>	<b>0</b>	<b>0</b>	<b>33</b>	<b>100.0</b>	<b>62</b>	<b>100.0</b>	<b>8</b>	<b>100.0</b>

*Table 24 Summary of duration of exposure to study drug by maximum daily dose (mg/day) and age for patients in controlled adjunctive therapy and monotherapy studies who were previously treated with AEDs*

Duration of exposure (months)	Age <8 years N=31						Age 8-16 years N=120					
	Mean daily dose (mg/day)											
	≤600		>600-1200		>1200-2400		≤600		>600-1200		>1200-2400	
	n	%	n	%	n	%	n	%	n	%	n	%
≤ 1	2	22.2	2	10.0	0	0	5	31.3	1	2.1	8	14.3
>1 - 3	0	0	1	5.0	0	0	3	18.8	2	4.2	4	7.1
>3 - 6	7	77.8	17	85.0	2	100.0	5	31.3	42	87.5	41	73.2
>6 - 12	0	0	0	0	0	0	3	18.8	3	6.3	3	5.4
<b>TOTAL</b>	<b>9</b>	<b>100.0</b>	<b>20</b>	<b>100.0</b>	<b>2</b>	<b>100.0</b>	<b>16</b>	<b>100.0</b>	<b>48</b>	<b>100.0</b>	<b>56</b>	<b>100.0</b>

The following table presents the total number of patients presented in the above table and groups them according to doses received for the different types of studies. The shaded doses represent cases of patient exposures from prior studies where doses overlap with that recommended by the Sponsor in the present labeling. From this table it can be appreciated that there is some degree of experience with these approximate doses.

**Table 25 Total Number of Patients Studied in Clinical Trials Stratified by Dose, Age and Type of Study**

	<8 years old (recommended dosing range of 900-1200 mg/day)				8-16 years old (recommended dosing range of 1500-2100 mg/day)			
	≤ 600	>600- 1200	>1200- 2400	Total n	≤ 600	>600- 1200	>1200- 2400	Total n
All studies	47	67	24	141	57	150	181	431
Mono- no Previous AEDs	22	4	0	26	33	62	8	103
Mono/ Adjunctive- previous AEDs adjunctive	9	20	2	31	16	48	56	120

This reviewer also disagrees with OCPB recommendation to only include the maximal maintenance dose. It is routine in clinical epilepsy to start at the lower tolerated dose known to be efficacious and to titrate upward as needed.

In summary this reviewer finds the final dose recommendations of the Sponsor adequate.

#### 4. Issues Regarding the Meta-analyses

A number of different meta-analyses were performed by the Sponsor in the previous submissions. The initial analysis performed used the small number pediatric patients that were included in the original pivotal monotherapy trials (004, 025, 026 and 028). This analysis was included in the Sponsors response (11/15/99) to the first approvable letter for the NDA. The Sponsor included additional meta-analysis in the previous labeling supplement. This analysis included patients from the aforementioned trial as well as a new pediatric double-blind, placebo-controlled trial (006) that was discontinued because of slow recruitment. For a complete review of this analysis the reader is referred to this reviewer's previous report on the supplement. Included in that submission was a second meta-analysis patients from previous placebo-controlled trials 005, 006, 025, 026 and 028 as well as those from active control trials. This reviewer's

criticism of these meta-analyses included: 1) The analysis involved the post hoc use of a non-primary endpoint; 2) The placebo and control populations appear rather different with the later having a greater than three-fold mean baseline seizure frequency than the former; 3) a very small number of young children (<8 years old) were included. This reviewer therefore concluded that although the meta-analysis is suggestive of a monotherapeutic effect it is not proof of such an effect or does help establish recommendations for dosing in populations that may exhibit different clearance<sup>4</sup>. For these reason this division requested the PK/PD bridging.

The approvable letter to the supplement noted that "(In this regard, however, it is interesting to note that your meta-analysis of the pediatric patients from the adult monotherapy studies plus the pediatric patients from Study 006, with a total sample size of 47 patients yielded a substantially greater p-value [p=0.08] than that from the analysis applied to just the original 4 studies [p=0.017 with a total sample size of 29])." In this submission the Sponsor argues that the p value increases with added numbers of patients not because of the addition of more patients but because of the fact that the original analysis included a slightly different population of patients than did the updated analysis that included study 006. Thus the original analysis of studies 005, 025, 026 and 028 defined the pediatric population as 8 to 17 years old whereas the updated analysis, which added study 006, used a pediatric population defined as 8-17. The Sponsor therefore argues that the difference in p value is "not due to the inclusion of Study 006." The Sponsor concludes that while the meta-analyses utilized data pooled from populations with different baseline seizure frequencies and different design paradigms... (it) provides strong evidence of the efficacy of oxcarbazepine given as monotherapy in pediatric patients." This reviewer does not disagree with the basic conclusion, although one might question the use of the term "strong." The limitations of meta-analysis must be kept in mind as well as the fact that while the meta-analysis was close to being statistically significant (p<0.05), it was not. In conclusion this reviewer stands by his original contention that while the meta-analysis is suggestive of a monotherapeutic effect it is not proof of such an effect or does help establish recommendations for dosing.

## 5. Safety

Submitted in the prior supplement was a summary of safety data that supported monotherapy use in pediatric patients. These data were compiled from data already submitted and reviewed by the agency in the form of the prior NDA, 120-safety update and Pre-approval Safety Update. As a result of the prior review Trileptal was considered safe for pediatric patients as adjunctive

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<sup>4</sup> According to the PI: "After a single-dose administration of 5 or 15 mg/kg of Trileptal, the dose-adjusted AUC values of MHD were 30%-40% lower in children below the age of 8 years than in children above 8 years of age. The clearance in children greater than 8 years old approaches that of adults."

treatment in epilepsy in the same age groups being proposed in the present application for monotherapy use. Moreover, the present recommended dosages are close to those that are considered safe and labeled for adjunctive pediatric treatment<sup>5</sup>. A total of 1059 pediatric patients ranging from 2 to 16 years old are included as part of this database. Of these 572 were included from clinical trials and 487 were from named patient programs. The clinical trials database was divided into 4 groups as follows: 1) all Trileptal treated pediatric patients (n=572); 2) monotherapy studies in pediatric patients not previously exposed to anticonvulsants (n=152); 3) monotherapy or adjunctive Trileptal patients treated who had previously been exposed to anticonvulsants (n=420); 4) studies in pediatric patients with steady state serum levels (n=286). While safety data for all these patients had previously been reviewed by this division it is noteworthy that specific information on patients from group 3 are presently included in the product labeling. For this reason much of the discussion that follows will compare groups 2 and 3. In the above section, along with Figures 4 and 5 and Tables 22 to 25, the amount of clinical trial experience in pediatric patients in general and those exposed to monotherapy in specific was discussed. In general this reviewer feels that there has been adequate exposure at the recommended dose levels.

Examination of data revealed no substantive difference in the types of adverse events experienced when comparing group 2 (monotherapy patients not previously exposed to anticonvulsant and group 3 patient (adjunctive/monotherapy patients previously exposed to anticonvulsant)). Indeed, the incidence of severe adverse events was lower in group 2 as compared to group 3 patients. Moreover, in the examination of group 2 data, the incidence of SAE were not different when patients <8 years old were compared to patients 8-16 years old. The incidence of withdrawals because of reasons of adverse events was also lower in group 2 patients as compared to group 3 patients.

While 2 patients were noted to die in group 3, from seizures, no deaths were reported in group 2 patients.

No clinically notable laboratory changes were observed for patients in any of the groups. Additionally, there was no clinically notable change in vital signs in patients from group 2.

When of group 4 were stratified by two serum concentrations of  $\leq 60$   $\mu\text{mol/L}$  and  $>60$   $\mu\text{mol/L}$ , there was little or no difference between the incidence of AEs, SAEs or withdrawals because of AEs.

No additional obvious signal was gleaned from named patient programs or post marketing database.

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<sup>5</sup> In most cases the maximal target monotherapy dose is very similar to that presented for adjunctive treatments. In a couple of cases of recommended dosing the weight dependant monotherapy dose is somewhat higher (16% and 33%). These differences are probably not sufficient to generate large differences in the adverse event profile. The fact that the dosing is based upon pharmacokinetic parameters further mitigates concern for potential adverse events.

The Sponsor concludes that the overall safety profile for Trileptal as monotherapy is similar and maybe perhaps better then that for adjunctive treatment.

This reviewer concurs with this conclusion. The fact that the recommended dose for monotherapy are similar to those for adjunctive treatment is further assurance. Moreover, it has already been demonstrated in adult studies that adult patents better tolerate Trileptal treatment when administered as monotherapy then as adjunctive therapy. The recommended regimen of pediatric monotherapy administration (i.e. in form of a dosage titration) should further contribute to the safety of for the monotherapeutic pediatric use of Trileptal.

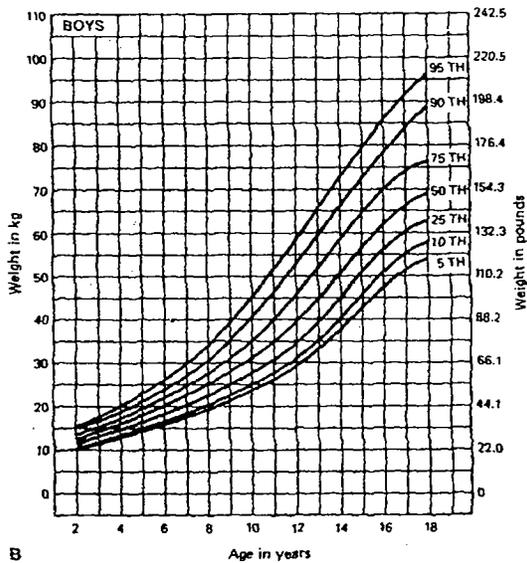
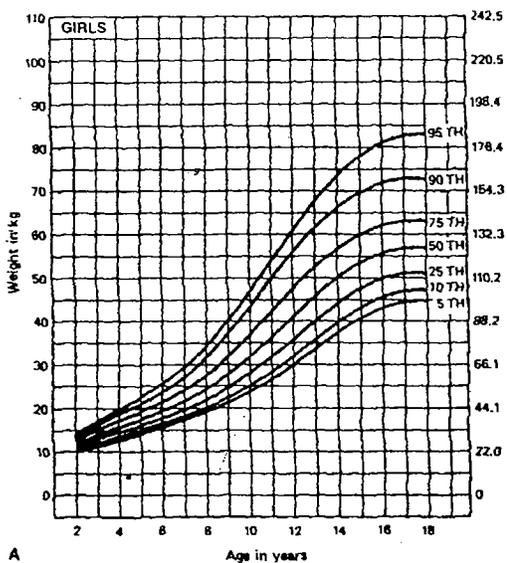
## 6. Final Conclusions

In conclusion, the Sponsor has constructed a cogent rational for the use of Trileptal as monotherapy. While each argument may not stand alone, they collectively, with previously submitted meta-analysis, make a strong argument for approval. The dosage recommendations appear adequate. Furthermore, it is reassuring that recommended doses of high weight pediatric patients (45 to 70 kg) are rather close to the dosages studied in the limited number of pediatric patients that were included in the adult studies. The final recommended doses were based upon sound pharmacokinetic and pharmacodynamic principles. There are no additional safety concerns. This reviewer recommends approval.

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# Appendix A

## Weight/growth Charts



Approved by  
Dr. [Signature]

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**This is a representation of an electronic record that was signed electronically and  
this page is the manifestation of the electronic signature.**  
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/s/

-----  
Norman Hershkowitz  
8/7/03 12:00:24 PM  
MEDICAL OFFICER

John, My final Trileptal, Norm

John Feeney  
8/7/03 12:50:37 PM  
MEDICAL OFFICER  
See my memo

## MEMORANDUM

NDA 21-014/S-005 Trileptal (oxcarbazepine)

**FROM:** John Feeney, M.D.  
Neurology Team Leader

**SUBJECT:** Supplement for Pediatric Monotherapy

**DATE:** December 12, 2001

In the Approval Letter for Trileptal, DNDP introduced an alternative approach to traditional pediatric monotherapy studies that might lead to a pediatric monotherapy claim. If the plasma levels associated with seizure control in adult adjunctive therapy were similar to the plasma levels associated with seizure control in pediatric adjunctive therapy, "...it would be reasonable to conclude that plasma levels associated with seizure control in adults during Trileptal monotherapy would be similar to those that would provide seizure control in pediatric patients during Trileptal monotherapy." Then dosing recommendations would need to be developed to produce those levels during pediatric monotherapy.

The pros and cons of this approach were discussed with the sponsor in a subsequent meeting on April 24, 2000.

Dr. Norman Hershkowitz has performed the medical review of the current submission. The biopharm review was performed by Dr. Vanitha Sekar with input from Drs. Ramana Uppoor and Jogarao Gobburu.

### **Current Submission**

#### *Meta-analysis*

The sponsor previously conducted 4 monotherapy trials. These studies included predominantly adults, but also enrolled small numbers of pediatric patients. The sponsor has pooled the pediatric data from these trials and performed a meta-analysis. Dr. Hershkowitz has outlined the problems with this analysis.

First, even pooling the data, the overall numbers are very small. There are only 24 drug-treated patients and 23 controls. There are only 2 drug-treated patients less than 8 years of age.

Second, Dr. Hershkowitz points out that patients across the different trials were different. The inclusion/exclusion criteria differed; outcomes for the placebo groups also differed. Therefore, the poolability of these patients is questionable.

Third, even having pooled the data, the p-value is only 0.08.

For these reasons, the results of this meta-analysis cannot be relied upon to support the new claim. The results do suggest an effect of Trileptal in pediatric monotherapy, however.

#### *Similarity of Observed Concentrations in Adult and Pediatric Adjunctive Therapy Trials*

Two trials of adjunctive therapy contribute to this analysis performed by the sponsor: Study OTPE 1 and Study 011. Study OTPE 1 enrolled predominantly adults. Study 011 enrolled patients less than 18 years of age. In Study 011 (pediatric), patients were titrated to an optimum daily dose defined as the lowest dose that provided seizure control with acceptable tolerability. In Study OTPE 1 (adult, with few pediatric patients), patients were randomized to placebo or 1 of 3 dose groups.

The sponsor has created a scattergram of the trough concentrations (either observed or modeled from patients' random concentrations) in these trials and found a great degree of overlap. The sponsor then chose particular dose groups to compare across adult and pediatric experience.

Dr. Hershkowitz points out that the component missing from the analysis is the pharmacodynamic linkage of dose/concentration. Without this linkage, the sponsor's comparisons of particular adult and pediatric dose groups seems particularly arbitrary.

Absent well-conducted concentration-controlled trials, it is impossible to identify a "therapeutic range" of concentrations for a drug. However, by constructing concentration-response curves in adult and pediatric populations and exploring the full PK/PD relationship, we might build confidence in the efficacy of pediatric monotherapy if the curves were the same.

#### **FDA Analyses.**

The first problem addressed by the biopharm reviewers was the identification of a suitable pharmacodynamic variable for comparison between adult and pediatric experience. The strongest evidence in support of efficacy, controlled trials, gauges efficacy by between-group differences. In constructing concentration-response curves, the question arises how to account for efficacy in terms of the control (placebo) group. Should each observed outcome be adjusted similarly or differently to allow comparison to other observed outcomes, either from the same trial or from a different trial ?

The answer to this question is not obvious. Our biopharm reviewers began to address the question by comparing the placebo outcomes between the adult and pediatric studies. The cumulative distribution functions suggest almost complete overlap for percent change in seizure frequency.

I do note that for the placebo patients who show improved seizure frequency in the studies, the curves suggest that more pediatric patients than adult patients are likely to show any given degree of improvement. Thus, there is this suggestion of a stronger placebo response in the pediatric study. While FDA analyses incorporate placebo response into PK/PD modeling, it remains a question whether to adjust and how best to adjust for placebo effect. How big a difference in the placebo distributions would be acceptable to warrant further comparison of adult and pediatric concentration-response curves ?

### *The Model*

The following linear function was developed:

$$\begin{aligned} \text{EFF} &= \text{EO} + \text{SLOPE} * \text{CONC}, \text{ where} \\ \text{EO} &= \text{INT}(0) + \text{SLOPE}(0) * \text{TIME} \end{aligned}$$

The first term calculates the PD effect for drug treated patients, while the second term, EO, calculates the PD effect for placebo patients. Thus, the adult and pediatric placebo responses are incorporated into the model, with their effects apparently weighted on the intercept rather than the slope of the drug effect.

In the first model, each patient has a single average trough concentration at steady state and a single average 28 day seizure frequency. A linear model with varying slope and intercept is developed using all the data for both adults and pediatric patients (including placebo data). When the addition of adult vs pediatric group is added as a covariate to the model, the fit is not significantly affected. Likewise, if the model is developed separately for adults and pediatric patients, there is no significant difference between the 2 lines (testing for both intercept and slope).

In the second model, a repeated measures model, each patient has a single average trough concentration at steady state and a different 28 day seizure count for each visit during the study. Again, a linear model with varying slope and intercept is developed using all the data. Again, the addition of adult vs pediatric group does not significantly improve the model fit. If the model is developed separately for adults and pediatric patients, there is no significant difference between the 2 lines (testing for both slope and intercept).

In addition to modeling the concentration-response data for adult and pediatric adjunctive therapy, the FDA biopharm reviewers modeled the monotherapy experience for adult and pediatric experience. Because the number of drug-

treated pediatric patients in these monotherapy exercises is so small (n=12), I do not believe these models contribute significantly to our understanding of the issue.

Having shown no difference between the modeled concentration-response relationships between adult and pediatric adjunctive experience in the 2 trials, the review team still believes further discussion is needed prior to approval. They point out that a finding of no difference is not the same as pharmacodynamic equivalence between the two populations. The acceptable difference between the two curves needs further discussion.

## Discussion

While the models developed by our own internal experts suggest that the concentration-response relationship for adult adjunctive therapy is not different than that for pediatric adjunctive therapy, we must recognize the limitations of our own approach.

First, because the models are developed post hoc, we are limited by the data collected. In one study, 011 (pediatric), patients were titrated to an optimum daily dose defined as the lowest dose that provided seizure control with acceptable tolerability. In the other study, OTPE1 (adult and limited pediatric), patients were randomized to placebo or 1 of 3 dose groups. Therefore, we began our endeavors with good adjunctive therapy dose-response data in adults and no such dose-response data in pediatrics. Only late in the process (after the modeling had been completed) did the entire FDA review team recognize the importance of this point.

Before creating a valid *concentration-response* curve for pediatric adjunctive therapy, it is a sine qua non that there exist *dose-response* data. Within the range of doses used in Study 011, we cannot predict which are effective. Any concentration observed has the potential to be confounded by multiple other factors related to outcome.

Second, it is not at all clear in modeling whether an appropriate efficacy measure exists. In placebo-controlled trials, effect is the difference between group response. FDA's models incorporate points with observed outcomes linked to a concentration. Placebo data is incorporated into the model similarly, with points with observed outcomes linked to a concentration of zero. Both types of data points are artificial in their own way. That placebo data points should be put into the model this way is not obvious.

Third, the statistical tests performed in the FDA models do not establish the equivalence of 2 concentration-response relationships. One test demonstrated that the 2 fitted lines are not significantly different (based on slope and intercept).

The other test demonstrated that adding group, adult vs pediatric, to the overall model did not significantly improve the fit of the model. Given the limited amount of information, the question remains: what difference was the model powered to show? Is that difference one that would be clinically acceptable?

Fourth, because concentrations were only collected at steady state during the maintenance period in these trials (and not during dose escalation), it is worth noting that we have data on only a limited expanse of the real concentration-response curves. If future exercises like this were planned, it might be informative to collect concentration-response data during dose escalation to fill in information at lower concentrations.

### **Recommendations**

The sponsor should be sent an Approvable Letter outlining the FDA analyses and the questions raised by those analyses. The sponsor should address these issues.

Crucial to the further development of this approach for Trileptal, the sponsor should be asked to supply dose-response data for pediatric adjunctive therapy if such data exists. Without that data, this approach may not be possible in the case of Trileptal.

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John Feeney  
12/12/01 11:16:37 AM  
MEDICAL OFFICER

APPROVED FOR SIGNATURE  
ON 12/12/01

**MEMORANDUM**

DATE: December 12, 2001

FROM: Director  
Division of Neuropharmacological Drug Products/HFD-120

TO: File, NDA 21-014/S-003

SUBJECT: Action Memo for NDA 21-014/S-003, for the use of Trileptal (oxcarbazepine) as monotherapy in pediatric patients

NDA 21-014, submitted by Novartis Pharmaceuticals Corporation, is approved for use in the treatment of partial seizures in adults as adjunctive and monotherapy, and in pediatric patients as adjunctive therapy. In the Approval letter of 1/14/00, the Agency informed the sponsor that it might be possible to obtain a claim for Trileptal's use as monotherapy in the pediatric population without a controlled trial in this setting.

Specifically, the Agency informed the sponsor that if plasma levels shown to be effective in adults and pediatric patients in the adjunctive setting were similar, it would be reasonable to conclude that plasma levels associated with seizure control in adults as monotherapy would be associated with seizure control in pediatric patients as monotherapy. In this case, the sponsor would need to be able to identify a dosing regimen in pediatric patients that could reliably achieve these levels.

The sponsor has submitted this supplement on 2/9/01, in an attempt to provide the requested information, and thereby obtain a claim for use of Trileptal in pediatric patients as monotherapy.

The submission has been reviewed by Dr. Vanitha Sekar, Office of Clinical Pharmacology and Biopharmaceutics (review dated 11/30/01), Dr. Norman Hershkowitz, medical officer (review dated 12/12/01), and Dr. John Feeney, Neurology Team Leader (memo dated 12/12/01). The sponsor has provided several approaches to the problem.

First, the sponsor has provided meta-analyses of pediatric monotherapy data.

As Dr. Hershkowitz describes, the sponsor combined the pediatric experience from the adult monotherapy studies with patients from a separate pediatric study, which had been terminated because of slow enrollment. The p-value for this comparison was  $p=0.08$  on the outcome variable time-to-exit.

They also performed an analysis of these combined patients for the outcome

percent change in seizure frequency (not the protocol specified outcome in any of the studies), which yielded a p-value of 0.019.

Finally, the sponsor performed a meta-analysis in which they combined the previous data with data from 3 additional active controlled trials, and calculated a p-value of the Trileptal-control contrast of 0.002.

With regard to the primary, kinetic issues raised in the Approval letter, as the review team notes, the sponsor's submission primarily consists of a plot of plasma level (of MHD, the active moiety into which oxcarbazepine is rapidly converted) versus dose in the adjunctive controlled trials in adults and pediatric patients. These plots show considerable overlap in both populations, from which the sponsor concludes that the plasma levels associated with effectiveness are similar in both age groups. The sponsor then went on to calculate "effective" plasma levels in children as monotherapy based on the levels seen in adults as monotherapy, and then a dosing regimen to achieve these levels in pediatric patients. However, as the review team explains, the sponsor has not attempted to compare the pharmacodynamic responses between adults and pediatric patients, and, therefore, their analyses are inadequate.

In an attempt to adequately address the pharmacokinetic questions raised in the Approval letter, our Clinical Pharmacology consultants have performed extensive analyses.

Briefly, in these analyses, trough plasma concentrations of MHD at steady state in the adult and pediatric adjunctive studies were plotted against 28 day seizure frequency, and regression lines for each population were drawn. The slopes of these lines were not statistically significantly different.

However, these plots do not adequately account for placebo effect (an appropriate accounting of which is necessary for determination of drug response). For this reason, histograms and cumulative distribution functions of the placebo response in the adult and pediatric adjunctive studies were generated. Again, these plots were not statistically significantly different, which lent credence to the conclusions drawn from the previous concentration-response curves.

Given these results, Dr. Sekar provisionally concluded that the first requirement of the Approval letter had been met; that is, the plasma concentration-response relationships were not different in adults and pediatric patients in the adjunctive setting. Given this, one could conclude that the relationship would hold for the monotherapy setting as well. To support this conclusion, Dr. Sekar demonstrated that the concentration-response relationship for the few pediatric monotherapy patients studied was not statistically different from that of adults.

## COMMENTS

I have a few comments, most of which have been made by the review team.

First, Dr. Hershkowitz has largely identified the primary concerns about the various meta-analyses performed by the sponsor. In particular, large baseline differences between (and within) treatment groups across studies, large differences in the between-treatment differences seen across studies, as well as different distributions of ages within treatments across studies suggest that the studies are not easily "poolable". The addition of data from active control trials without assay sensitivity is also problematic. Particularly interesting is the sponsor's finding of a p-value of 0.08 for the analysis including pediatric patients from the 4 adult monotherapy studies plus the one study terminated early (total N=47), while their original meta-analysis, which included patients only from the 4 adult studies (total N=29) yielded a p-value of 0.017.

For these reasons, I agree with Drs. Hershkowitz and Feeney that the meta-analyses, while certainly suggestive of, and consistent with, Trileptal's effectiveness in the pediatric population as monotherapy, do not adequately support this conclusion.

Regarding the kinetic analyses, it is critical to note, at the outset, that the trials were not designed to be analyzed in this manner.

Specifically, in these trials, patients were not randomized to plasma concentration. Such a design is ideally (perhaps only) suited to support reliable conclusions about a concentration-response analysis. The adjunctive trial performed in adults was a fixed-dose response study; that is, patients were randomized to one of 3 fixed doses and placebo. Such a design is not, theoretically, suited to establishing a concentration-response relationship, but one could attempt to justify constructing such a relationship from this sort of data, given that there is a reasonably predictable relationship between dose and concentration (that is, an argument could be made that a fixed-dose trial is similar to a fixed-concentration trial, although, of course, they are not identical).

However, critically, the pediatric adjunctive study randomized patients to a flexible dose range. Such a study cannot, by design, support even a dose-response relationship, let alone a concentration-response relationship, because dose can be confounded with response. In such a study, the patient's final dose is determined by a number of unknown factors, but is in part determined by the patient's overall response. Patients who are very well controlled, and who are tolerating the dose, may be titrated to the maximum allowable dose, even though they may have responded equally well to the lowest allowable dose. For similar reasons, any relationship seen between dose and response (in particular, a monotonically increasing linear relationship) may be spurious. When one determines a linear concentration-response, the implication is that it is the

increasing concentration that is responsible for the increasing effectiveness; in this design, such a conclusion is not necessarily warranted, given that we cannot even draw this conclusion for the dose-response relationship.

In my view, then, it is problematic to compare the concentration-response relationships in adults and pediatric patients, given my concerns about the propriety of constructing such a relationship for the pediatric patients (as I noted above, it is even problematic to do so for the adult patients, but it is more justifiable, in my view).

Dr. Sekar has attempted to address this concern by analyzing the concentration-response relationship of the few (N=18) pediatric patients included in the adult adjunctive therapy study; apparently, the relationship in these pediatric patients is not significantly different from that in the adults.

Even if we were to accept the appropriateness of constructing such a relationship for pediatric patients, we would still be left with the problem of determining whether or not the relationships were the "same" in adults and pediatric patients. As the review team has noted, a lack of a statistically significant difference between the curves is not synonymous with equivalence of the curves. Indeed, we have no experience with how best to determine the "equivalence" of concentration-response relationships. This issue applies to the placebo responses between adults and pediatric patients as well. Further, even if the slopes were "equivalent", this does not necessarily imply that the location of the data points is similar in both populations. That is, one could generate 2 regression lines with identical slopes and intercepts, but these lines could be generated by concentrations considerably different for adults and pediatric patients.

Finally, and importantly, even if the concentration-response relationships could be determined to be essentially identical in the two populations, we are left with the problem of determining the concentration range associated with effectiveness. One cannot conclude that all concentrations that resulted from the administration of effective doses are effective. The establishment of a concentration-response relationship does not, in my view, unambiguously determine the lower bound of effective concentrations. It should be noted, as Dr. Hershkowitz does, that the sponsor has attempted to address this question. Specifically, they have considered the effective range to be the entire range of C<sub>min</sub> values achieved in the adult studies. It is not immediately obvious, as noted above, that this is an appropriate way to determine a therapeutic range. The sponsor should provide a justification for this choice.

The analyses performed (including the sponsor's meta-analyses) provide, in my view, a strong suggestion that Trileptal is effective as monotherapy in the pediatric population, and that the doses effective in adults are likely to be effective in pediatric patients. However, for the reasons stated above, I do not

believe that the sponsor has made a convincing case. Before we may conclude that they have identified an appropriate dosing regimen that will yield effective concentrations in the pediatric monotherapy setting, they must:

- 1) justify the construction of a concentration-response curve from the pediatric adjunctive study, given that the design was that of a flexible dose regimen;
- 2) address the question of how to determine the equivalence of any concentration-response relationships determined for pediatric and adult adjunctive therapy
- 3) if the first 2 points can be adequately addressed, address the question of the absolute effective concentration range, and
- 4) if this can be done, develop dosing regimens in pediatric patients that will reliably yield these concentrations.

Should the sponsor be granted a claim for pediatric monotherapy on the basis of these analyses, it will represent the first time in this division (to my knowledge) that a claim has been extended to the pediatric population on the basis of data other than that obtained in adequate controlled trials. Given the potential precedent that this may set, we should be clearly convinced that the analyses to support such an extension are appropriate and comprehensive. For this reason, I will issue the attached Approvable letter.

Russell Katz, M.D.

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Russell Katz  
12/12/01 08:33:18 AM  
MEDICAL OFFICER

APPROVED AND  
ON ORIGINAL

## Review and Evaluation of Clinical Data

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NDA (Serial Number)	21-014(SE5-003)
Sponsor:	Novartis
Drug:	Trileptal® (oxcarbazepine)
Proposed Indication:	Seizure Monotherapy in Children
Material Submitted:	Reanalysis of existing data
Correspondence Date:	2/7/01
Date Received / Agency:	2/12/01
Date Review Completed	1/11/01
Reviewer:	Norman Hershkowitz MD, PhD

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### 1. Introduction

While the FDA approval letter granted Trileptal labeling in adult monotherapy and adult and pediatric adjunctive therapy, its monotherapeutic pediatric use was specifically not included because of the absence of clinical trials that directly examined its therapeutic efficacy under this condition. The original NDA contained 6 adequate pivotal placebo controlled trials. Four examined monotherapy in a predominately adult population (004, 025, 026 and 028) whereas the remaining two studies examined adjunctive therapy in adults and in children (OT/PE1 and 011, respectively). In response to an approvable letter the Sponsor has requested pediatric monotherapy labeling. The request was based upon a 3-point argument: 1) The recommendation by the ILAE that states "because the efficacy of AEDs seems to be the same in childhood...partial epilepsy...there is no obvious reason to repeat controlled efficacy studies of childhood partial epilepsy previously performed in adults," 2) The Sponsor's meta-analysis of children who participated in the original monotherapy adult studies that demonstrated some degree of efficacy; 3) The claim that that PK differences were not sufficiently large to require dosage adjustments based upon age. In the approval letter this division noted that while meta-analysis came close to addressing the question of pediatric monotherapy an insufficient number of patients (17 drug and 12 placebo) were included to provide a compelling argument to justify labeling dose recommendations.<sup>1</sup> This division also did not agree with the Sponsors claim that PK differences were not large enough to require a specific consideration of potential dosing differences between ages. Studies had previously demonstrated a 30-40% increase in clearance in children less than 8 years old.

This division suggested an alternative approach that is described as follows. "This would consist first, of comparing the plasma levels associated with a dose giving seizure control in the adjunctive setting in adults and pediatric patients. If these levels were similar, it would be reasonable to conclude that plasma levels associated with seizure control in adults during Trileptal

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<sup>1</sup> This was particularly true for the youngest patients. Thus, there were a total of 3 placebo and 3 drug treated patients between ages 6 and 11 years old.

monotherapy would be similar to those that would provide seizure control in pediatric patients during Trileptal monotherapy. Then, a dosing regimen in which these exposure levels could be reliably achieved when Trileptal is given to pediatric patients as true monotherapy could be determined." The present submission includes an attempt at performing the requested analysis.

## 2. Sponsors Analysis

### 2.1 Meta-Analysis

Along with the pharmacokinetic/pharmacodynamic (PK/PD) analysis the sponsor has performed a number of permutations of meta-analyses to "confirm effectiveness" of Trileptal in a monotherapeutic pediatric setting.

The first meta-analysis used is similar to one already submitted by the Sponsor in their response to an approvable letter (11/15/99). The meta-analysis performed in the latter submission used the small number of pediatric patients (17 drug and 12 placebo or low dose control) who were enrolled in predominately adult pivotal placebo-controlled trials (004, 025, 026, 028). The primary endpoint of time to exit was used in this analysis and a p value of 0.0172 was observed with the Sponsor concluding a significant therapeutic effect. This reviewer, however, argued that such an analysis was complicated by issues such as the differences in patient population, resulting from differences in inclusion/exclusion criteria that were reflected in a disparate mean time to meet required exit criteria in the placebo groups amongst the different studies (1.25 to 28 days). This was further complicated by the fact that patients in placebo and control groups were not equally represented for similar age ranges in a given study. The new analysis examines patients previously evaluated but also adds patients from a placebo-control study (006) that attempted to examine efficacy of Trileptal in newly diagnosed untreated pediatric patients<sup>2</sup>. This study used time to exit criteria as a primary endpoint although the exit criteria tended to be stricter than other studies; i.e. time to first partial seizure. This added an additional 9 drug and 13 placebo patients. This new meta-analysis appears to include fewer patients from the original pivotal trials. This is likely a result of the fact that the initial analysis characterized patients <18 as children whereas the new analysis defines this group as  $\leq 17$ .

This meta-analysis, which examines the original protocol primary endpoint (time to exit), is included in the following table.

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<sup>2</sup> This study was prematurely terminated because of slow patient recruitment.

**Table 3.1.-4. Meta-analysis of time to meeting protocol-specific endpoint in the five adequate and well-controlled monotherapy studies**

Treatment Group	N	Median (days)	IQ Range <sup>1</sup>	P-value
OXC (600-2400 mg/day)	24	NA	(46.0, NA)	0.0803
Control	23	42.0	(4.0, NA)	

Note: OXC (9 on 2400 mg/day, 3 on 1500 mg/day, 9 on 1200 mg/day, 2 on 900 mg/day, and 1 on 600 mg/day); Control group (4 on 300 mg/day, 19 on placebo)

<sup>1</sup>The interquartile (IQ) range represents the time-points at which 25% and 75% of patients met the protocol-specific endpoint (NA denotes that <75% of patients met the efficacy endpoint).

The p value was not statistically significant. This probably speaks more of issues related to meta-analysis and sample size than to the issue of efficacy and underscores the problems with such analysis. According to the Sponsor, however, this analysis "demonstrated trend toward better efficacy." This reviewer agrees with this statement.

The Sponsor performs another meta-analysis on this population of patients by comparing percent change in frequency from baseline between control and drug treated groups. These data are presented in the following table.

**Table 3.1.-5. Summary of the percentage change in seizure frequency relative to baseline for children (4 to 16 years of age) in the five adequate and well-controlled monotherapy studies**

Partial seizure frequency/28 days	OXC				Control				P-value
	N	Median	Min	Max	N	Median	Min	Max	
Baseline	24	3.3	0.3	70.0	23	0.8	0.3	112.0	0.0187
Post-baseline	24	0.0	0.0	45.6	23	0.7	0.0	123.7	
% change from baseline	24	-100.0	-100.0	111.7	23	-8.8	-100.0	1300.0	

Note: Control group (4 on 300 mg/day, 19 on placebo)  
 Denotes significance at a 0.05 level (two-sided) based Wilcoxon rank-sum test.

Data analysis revealed a statistically significant difference in the percent change in seizure frequency between groups. This meta-analysis demonstrates a median percent change from baseline of -100% for patients who received oxcarbazepine. This meant that at least 50% of patients in the drug treatment group were without seizures during the observation period. This is substantially different from the placebo median percent change of -8.8%. Other than the fact that this analysis involves the post hoc use of a non-primary endpoint, a problem exists with this analysis that can be gleaned from the table. The placebo and control populations appear rather different with the later having a greater than three-fold baseline seizure frequency than the former.

The Sponsor performs a meta-analysis that combines previous studies with additional double blind controlled studies (OT/F01, OT/F02 and OT/F04). These however were not used as pivotal trials because they compared Trileptal to an active control. As such this the analysis only adds additional observations

to the drug and not to the placebo group. These data are presented in the following table.

**Table 3.1.-6. Summary of the percentage change in seizure frequency relative to baseline for children (4 to 16 years of age) in all double-blind monotherapy studies**

Partial seizure frequency/28 days	OXC				Control				P-value <sup>2</sup>
	N	Median	Min	Max	N	Median	Min	Max	
Baseline	137	1.0	0.0	70.0	23	0.8	0.3	112.0	0.0024
Post-baseline	137	0.0	0.0	45.6	23	0.7	0.0	123.7	
% change from baseline	137	-100.0	-100.0	860.0	23	-8.8	-100.0	1300.0	

Note: Control group (4 on 300 mg/day, 19 on placebo).  
<sup>2</sup> Denotes significance at a 0.05 level (two-sided) based on Wilcoxon rank-sum test.

While the median seizure frequency was nearly equivalent the fact that this includes trials that were not even included as a pivotal trial detracts from the significance of such an analysis.

Simple demographics for studies used in all new meta-analyses are presented in the table below.

**Table 3.1.-1. Demographics by treatment in the pediatric monotherapy studies**

Demographic characteristic	OXC		Control	
	N	n (%)	n (%)	N
<b>Adequate and well-controlled monotherapy studies (004, 006, 025, 026, 028)</b>				
	N	24		23
Age (yrs)	< 8	2 (8.3)		8 (34.8)
	8 - 11	7 (29.2)		5 (21.7)
	12 - 16	15 (62.5)		10 (43.5)
	Mean (SD)	12.3 (3.1)		10.1 (3.5)
	Range	7-16		4-16
Weight (kg)	Mean (SD)	52.5 (20.7)		48.5 (28.3)
	Range	24.0-100.5		18.5-144.5
<b>All double-blind monotherapy studies (004, 006, 025, 026, 028, OT/F01, OT/F02, OT/F04)</b>				
	N	137		23
Age (yrs)	< 8	25 (18.3)		8 (34.8)
	8 - 11	48 (35.0)		5 (21.7)
	12 - 16	64 (46.7)		10 (43.5)
	Mean (SD)	11.3 (3.4)		10.1 (3.5)
	Range	5-16		4-16
Weight (kg)	Mean (SD)	41.8 (16.7)		48.5 (28.3)
	Range	17.0-100.5		18.5-144.5

Note: Control group (4 on 300 mg/day, 19 on placebo); the active control groups for OT/F01, OT/F02 and OT/F04 are not included.

Examination of this table reveals very few (n=2) young pediatric subjects (<8) were analyzed in placebo control trial meta-analysis. This is particularly pertinent when it is considered that children younger than 8 years old appear to exhibit a 30 to 40 percent greater clearance when compared to older children. There were more drug treated patients included when all controlled trials were included in the analysis. There was however no attempt made to stratify effects by age group. It remains a possibility that a marked effect in older children can potentially hide the absence of an effect in the younger age group where clearances may be greater.

Examination of the above table reveals a difference in age distribution between drug and placebo treated patients. Thus, 8 percent of all younger patients (<8 years old), received drug whereas 35 percent of this same age strata received placebo. This could theoretically effect results if the placebo effect varies with age.

The Sponsor presents statistical information on starting and maintenance doses for the 5 placebo controlled (adequate and well controlled) and all double-blind studies. These are presented in the following two tables.

**Table 3.1.-2. Initial dosage of OXC administered (mg/kg/day) in studies used in the meta-analysis**

Summary Statistic	Initial dose of OXC ( mg/kg/day)	
	Adequate and well-controlled monotherapy studies (n=24)	All double-blind monotherapy studies (n=137)
Mean (SD)	20.6 (11.5)	19.7 (7.9)
Median	22.8	18.0
Range	3.4 - 42.9	3.6 - 45.5

**Table 3.1.-3. Maintenance dosage of OXC administered (mg/kg/day) in studies used in the meta-analysis**

Summary Statistic	Maintenance dose of OXC ( mg/kg/day)	
	Adequate and well-controlled monotherapy studies (n=24)	All double-blind monotherapy studies (n=137)
Mean (SD)	30.9 (12.8)	21.9 (10.1)
Median	29.0	19.4
Range	6.6 - 68.6	6.4 - 68.6

This information would have been more pertinent had it been presented in an age stratified fashion along with seizure control outcome.

Although the meta-analysis is suggestive of a monotherapeutic effect it is not proof of such an effect nor does help establish recommendations for dosing

in populations that metabolize the drug differently. For these reason this division requested the PK/PD analysis described above. This reviewer feels that this new meta-analysis, with the above limitations, does not obviate the necessity of a PK/PD analysis.

## **2.2 Pharmacodynamic/Pharmacokinetic (PK/PD) analysis (Bridging Analysis)**

As noted above the Sponsor was asked to perform a PK/PD bridging analysis. The first step was to compare the pharmacodynamic similarity between children and adult populations by use of a concentration effect analysis from the two placebo-control adjunctive pivotal studies. Once this is determined, assuming sufficient pharmacodynamic similarity is demonstrated, an effective pediatric monotherapeutic dose was to be determined by first determining an effective adult concentration from available adequate double-blinded clinical trials. Pediatric PK information was to be used to estimate a dose that would achieve a similar concentration as that observed in adult efficacy trials.

Oxcarbazepine acts as a prodrug that is rapidly metabolized into its active metabolite, MHD. Serum MHD concentrations are therefore the subject of all of the following PK/PD analysis.

### *2.2.1 Pharmacodynamic Similarity Between Adult and Pediatric Populations in Pivotal Adjunctive Trials*

#### *2.2.1.1 Methods*

Patients used in this analysis were from the initial two pivotal trials; OT/PE1 with consisted of a predominately adult population and 011 that examined patients <18 years old. For their analysis, Novartis defined the pediatric age group as  $\leq 17$  years old<sup>3</sup> and adult age group as > 18 years old. Because OT/PE1 allowed recruitment from ages 15 to 65 and 011 allowed for recruitment of patients <18 years, subjects used in the analysis for each age group (adult or children) can be found from both studies. OT/PE1 and 011 also differed in design with regard to dosing. Thus, OT/PE1 examined three fixed doses, 600 mg/day, 1200 mg/day and 2400 mg/day (divided twice daily). A later amendment allowed for a reduction in maximal dose to 1800 mg when it was discovered that a large percent of patients were experiencing toxicity. Although protocol 011 specified a target dose of 30-46 mg/kg/day, investigators were permitted to adjust the dose for optimal therapeutic benefit. A final dosage range of 6.4 to 51.4 mg/kg/day (median 31 mg/kg/day; given BID) was used.

<sup>3</sup> This definition of the pediatric age groups is closer to that defined in the final rule (59 FR 64242) where the oldest child is defined as up to the 16<sup>th</sup> birthday.

Concentrations were observed at random times in Study 011 during the maintenance phase. The C<sub>min</sub> was calculated using population pharmacokinetic modeling. The model calculated the expected concentration 12 hours post-dose. While an attempt was made to maintain patients on a single dose throughout the maintenance period, patients dosage adjustments were allowed with approval of the trial monitor. In such cases the average dose was used in final analysis.

Only trough serum concentrations were observed in study OT/PE1. C<sub>min</sub> was calculated as the average trough observed during the maintenance phase. Only those "trough" concentrations collected 10-14 hours after last dose were used to calculate C<sub>min</sub>.

The Sponsor performs a comparison of concentrations achieved from adults and children in these two pivotal trials to prove pharmacodynamic similarity.

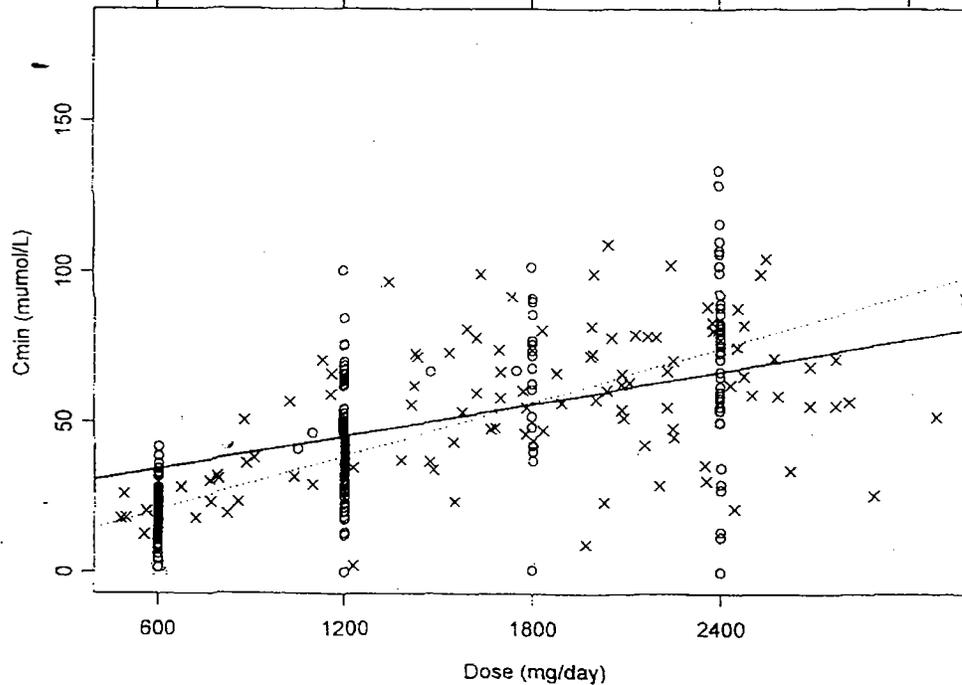
#### 2.2.1.2 Results

The Sponsor performs a number of comparisons of MHD plasma concentrations between pediatric and adult patients who participated in the two pivotal adjunctive trials. The assumption is that because a statistically significant therapeutic effect was demonstrated in these studies a sufficient overlap between blood concentrations observed would indicate sufficient pharmacodynamic similarity.

Novartis presents the following figure (Sponsor's Figure 3), which consist of a scattergram plot of dose Vs mean C<sub>min</sub> (actual or modeled) with least squares fitted regression lines. The Sponsor notes that this figure "reveals a high degree of overlap of C<sub>min</sub> values for adults and children over the respective ranges of effective doses." The Sponsor attempts to support their argument by noting that when the adult dosage groups 1200 and 2400 are compared to pediatric dosage groups of 8-30 mg/kg/day and 30-53 mg/kg/day, respectively, C<sub>min</sub> appear to have a rather similar distribution with "means, medians and lower quartiles differing by at most 12.2%." This conclusion is based upon the following table (Sponsor's Table 5) and figure (Sponsor's Figure 4) that presents distribution for the aforementioned groups.

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**Figure 3**  $C_{min}$  for adults and children at effective doses



Note: o = adults, referred to lower abscissa: the dashed represents a regression line fitted to the data for adults.

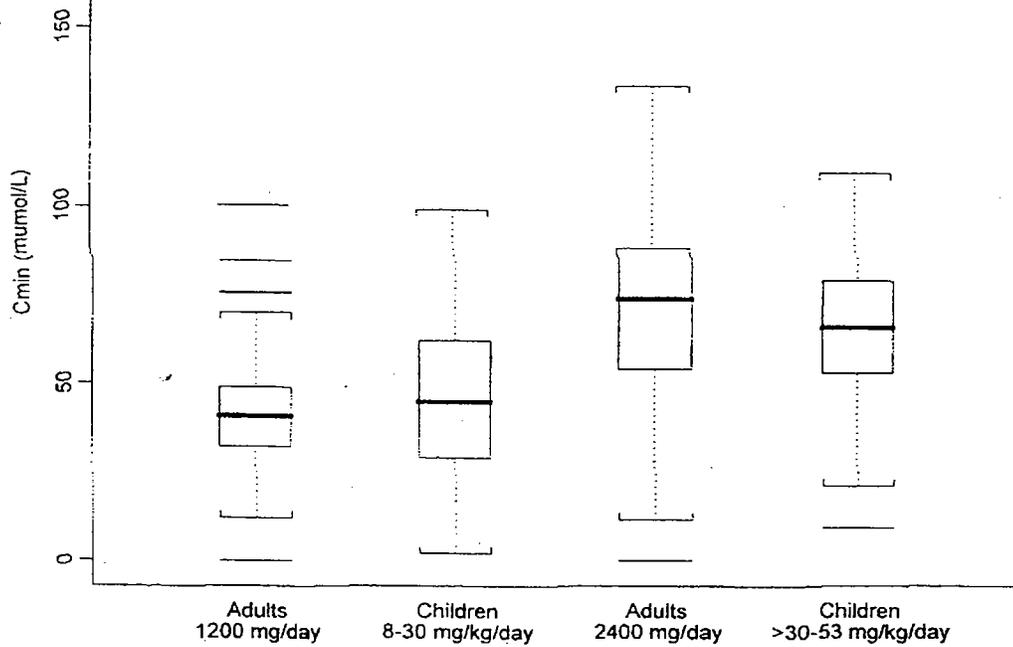
x = children, referred to upper abscissa: the solid line represents a regression line fitted to the data for children.

For purposes of display, 10 mg/kg/day is aligned with 600 mg/day.

**Table 5** Distribution of  $C_{min}$  at effective doses of oxcarbazepine in adults and children during adjunctive therapy

Summary Statistic	Children		Adults		
	8-30 mg/kg/day (n=50)	>30-53 mg/kg/day (n=56)	600 mg/day (n=123)	1200 mg/day (n=106)	2400 mg/day (n=47)
Maximum	99.0	109.2	41.9	100.2	133.6
95 <sup>th</sup> percentile	86.9	100.0	32.4	68.4	114.2
75 <sup>th</sup> percentile	61.7	78.7	22.7	48.8	87.1
50 <sup>th</sup> percentile (median)	44.9	65.7	17.0	40.8	73.8
25 <sup>th</sup> percentile	29.4	53.5	13.5	32.4	54.5
5 <sup>th</sup> percentile	17.9	24.9	8.3	17.7	12.1
Minimum	2.1	9.3	1.5	0	0
Mean	46.9	64.2	18.3	41.8	70.0
Standard Deviation	23.1	22.1	7.3	16.4	30.4

**Figure 4** Boxplots of  $C_{min}$  ( $\mu\text{mol/L}$ ) for children and adults at effective doses on adjunctive therapy



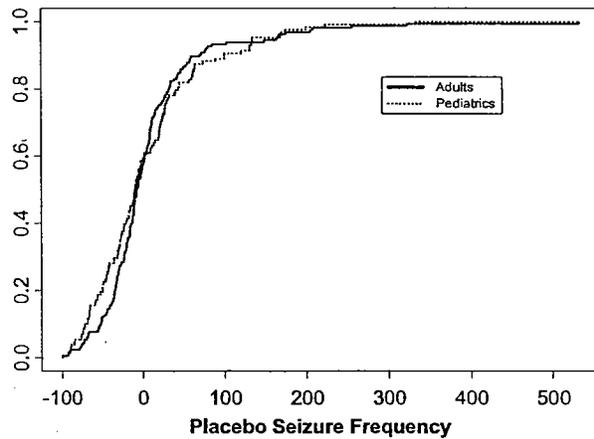
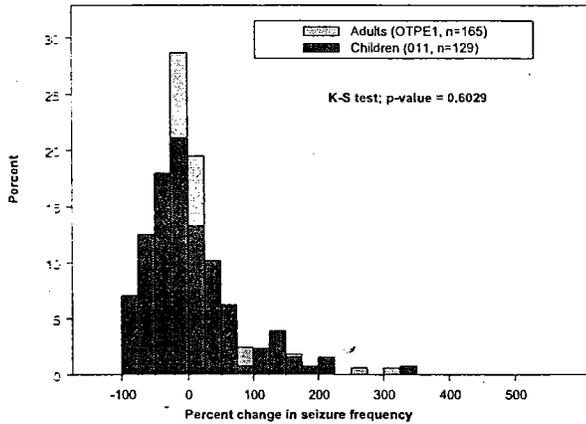
### 2.2.1.3 Analysis Critique

#### 2.2.1.3.1 PD Methodology

This is not a true pharmacodynamic analysis. Such an analysis would require a comparison of the concentration/response relationships between adult and pediatric populations. This analysis should include an examination of potential differential placebo effects between both populations. The specific comparison between the two highest adult dosages and the two dosage ranges is a completely arbitrary analysis. There is no justification as to why these particular dosage groups are compared. In fact if one compares the low adult dose to the low pediatric dose range a substantially different conclusion may follow (see Table 5 presented above). This underscores the need for a true concentration response analysis. These issues were presented to Dr. Sekar who performed an initial evaluation that is presented as follows (see the Clinical Pharmacology review for more details).

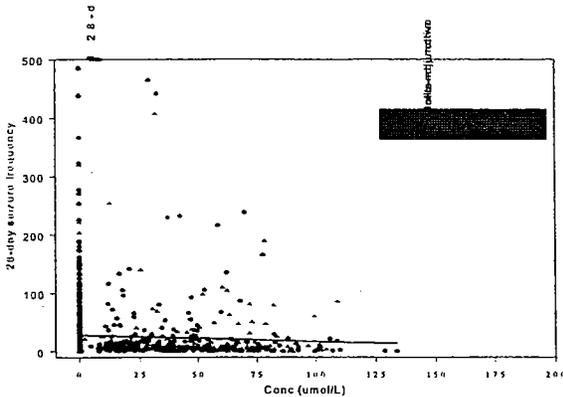
To compare placebo Dr. Sekar constructed histograms and CDF plots that compared percent change in seizure frequency with incidence of these changes. This is presented in the following two plots.

Distribution of response in placebo patients



The adult and pediatric curves were compared using the Kolmogorov-Smirnov goodness-of-fit test. This analysis revealed the distribution of placebo response was not different.

Dr. Sekar subsequently performed a PK/PD analysis. The primary endpoint in these studies was mean *percent reduction from baseline in seizure frequency* (number of seizures/28day) during baseline. Dr Sekar, however examined PD parameters by plotting the reduction in *seizure frequency* against serum concentration. This was done in two ways: 1) mean seizure frequency during the double-blind maintenance period or, 2) interim mean seizure frequency at each follow up during the maintenance period. The evaluation of mean seizure frequency during maintenance is presented below.



In her analysis Dr. Sekar notes:

- 1) The effects of MHD trough concentrations on the 28-day seizure frequency can be described using a linear function.
- 2) Because the clinical trials were designed to be *dose-effect* controlled trials a true serum concentration therapeutic range can not be established.
- 3) While relationship between PD effect and Cmin MHD concentrations is not strong the data shows a trend for increased effect with increasing MHD concentrations.
- 4) Baseline seizure frequency is a significant covariate in the model and affects the slope of the placebo response as well as the drug effect.<sup>4</sup>
- 5) The relationship between plasma MHD concentrations and the 28-day seizure frequency are not statistically different ( $\alpha=0.05$ )<sup>5</sup> between adults and children in the adjunctive therapy setting. This supported the assumption of pharmacodynamic similarity in these two populations.
- 6) Pharmacodynamic similarity between populations were also supported by a similar PD analysis that compared adults and children who were enrolled in the monotherapy studies 004, 006, 025. Thus, no statistical ( $\alpha=0.05$ ) difference was observed between pediatric and adult subjects in plots of plasma concentrations of MHD versus 28-day seizure frequency. However the number of children in this analysis was small, n=12, on drug with only 1 subject under the age of 8. Moreover, monotherapy trials were designed to measure time to meet exit criteria and not simple seizure frequency.
- 7) The analysis of the concentration-response relationship for patients on adjunctive and monotherapy suggests that this relationship is not statistically different between adults and children. However, this is not the same as stating that there is "pharmacodynamic equivalence" between the two populations. The applicant will be requested to submit a justification regarding the clinical relevance of this difference.

<sup>4</sup> Because of this reviewer suggested to Dr. Sekar that a percent change in seizure frequency may be a better value to follow (it was also the primary endpoint). This was attempted but without an obvious improvement in concentration/response relationship. Nonetheless the Sponsor should be asked to carry out a similar analysis.

<sup>5</sup> Log Likely Hood Ratio Test.

In summary the Sponsor has not provided this division with a true PD analysis. The analysis should have consisted of a concentration response comparison. An example of the analysis is presented above. This analysis suggests PD equivalence. The Sponsor should be asked to carry out a similar analysis, but also provide convincing argument for the appropriateness of its use. Two specific issues should be raised regarding this. Unlike OT/PE1, study 011 did not randomize patients to specific dose groups. Subject's dose were adjusted within a given range, and even permitted to be adjusted outside of the range, to a perceived optimal dosage. Ideally a PD evaluation would require patients be randomized to fixed concentration group, although randomization to different dosage groups may be acceptable. Study 011 goes beyond this and randomizes to effect. The Sponsor should be asked to justify this. The second issue involves the methodology of statistical comparison for equivalence. As this analysis involves a statistical comparison for equivalence the Sponsor should include a discussion of the margin (the smallest unacceptable inferiority and superiority) and the power (the probability of accepting equivalence when study populations are different) of the study.

#### 2.2.1.3.2 Demographic Equivalence between Adult and Pediatric Populations

The analysis should have also included a comparison of important inclusion and exclusion criteria and baseline seizure activity between adult and pediatric populations to confirm that the populations are analogous.

A comparison between the main inclusion criteria that are pertinent to severity of the seizure disorder is presented in the table below.

OT/PE1	011
Patients with a diagnosis of simple partial seizures and complex partial seizures with or without secondarily generalized seizures.	A diagnosis of partial seizures (including subtypes of simple, complex, and partial secondarily generalized).
Patients currently receiving treatment with 1 to 3 AEDs with at least 4 seizures per month on the average in the 8-week period prior to entry into the Baseline Phase.	Patients with poorly controlled seizures despite treatment with a stable dose 1 to 2 AEDs (defined as 8 partial seizures during the 56-day Baseline Phase, with at least 1 occurring during each 28-day period of the 56-day Baseline Phase).

The seizure inclusion criterion for seizure population is nearly identical between the two populations. Thus both populations will have an average of 4 seizures at

screening. Protocol OT/PE1 does allow for a greater maximal number of concomitant anticonvulsant medications (3 as opposed to 2).

There is no attempt to perform a demographic comparison between pertinent pediatric and adult baseline variables. This reviewer attempted a quick comparison based upon the original submitted NDA. This may not be a definitive analysis as some pediatric patients were contained in the predominately adult adjunctive trial and visa verse.

A quick analysis of baseline seizure frequencies is presented in the table below. The analysis indicates some similarity in median baseline seizure frequency.

***Baseline Median Frequency (seizures/28 days) for All Seizures of Partial Onset in Pivotal Adult and Pediatric Adjunctive Study***

OT/PE1 ("Adults")				011 ("Children")	
Placebo	600 mg/day	1200 mg/day	2400 mg/day	placebo	All doses
8.6	9.6	9.8	10.0	13.0	12.5

An analysis of the median baseline secondary generalized seizure frequency was slightly higher in adults than in children (see table below).

***Baseline Median Frequency (seizures/28 days) for Partial Secondarily Generalized Seizures for Pivotal Adult and Pediatric Adjunctive Study***

OT/PE1 ("Adults")				011 ("Children")	
Placebo	600 mg/day	1200 mg/day	2400 mg/day	placebo	All doses
3.5	3.5	2.0	2.4	0	0

This small difference may indicate some difference in severity of epilepsy between these populations, however it is unclear as to how this small difference may affect analysis.

The inclusion criteria permitted patients enrolled in OT/PE1 to be on 3 medications whereas 2 maximum of two medications are allowed in 011. A significant difference in the distributions of concomitant medication could potentially complicate the interpretation of the pharmacodynamic analysis. The Sponsor should provide this demographic information. This information was not included in this clinical reviewer's original NDA review.

The Sponsor does not perform a demographic comparison of sexual differences between analyzed groups. Analysis of the studies (see table below), derived from the original NDA, demonstrates similarity between the percent populations of male and females studied between both groups.

***Gender differences in study populations***

	OT/PE1 ("Adults")				011 ("Children")	
	Placebo	600 mg/day	1200 mg/day	2400 mg/day	Placebo	All Doses
% Male	44.5%	51.2%	45.2%	56.3%	55.0%	50.7%
% Female	55.5%	48.8%	54.8%	43.7%	49.3%	49.3%

- In summary, while a preliminary evaluation suggests that the pediatric patient population is similar to the adult population with regard to inclusion criteria and demographic variables, the Sponsor should carry out a more careful evaluation of pertinent baseline variables. This should include, but not necessarily be limited to, the following: 1) partial seizure frequency, 2) incidence and frequency of subtypes of partial seizures, 3) number of concomitant anticonvulsant medications, 4) gender differences.

#### *2.2.2 Pharmacokinetic Analysis: Determination of The Therapeutic Pediatric Dose*

This analysis, as noted above, consists of two steps: 1) determination of therapeutic serum concentrations in adult population; 2) calculation of a pediatric dose that will produce serum concentrations equivalent to those observed in step one. What follows is a review and analysis of this data. While some issues pertinent to the PK review can be found in Dr. Sekar's review, her review concentrated on the above PD issues. Much of the following conclusions are therefore those of the present reviewer. I, however, have utilized parts of Dr. Sekar's review were pertinent.

##### *2.2.2.1 Determination Therapeutic Serum Concentrations in Adult Monotherapy*

###### *2.2.2.1.1 Methods*

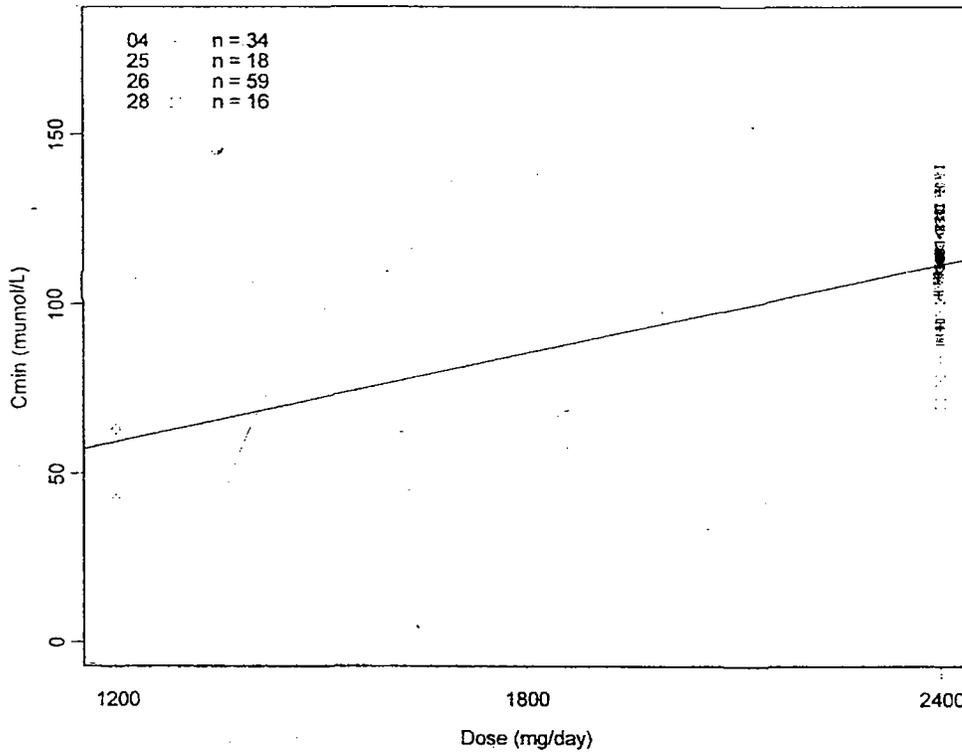
The four pivotal monotherapy trials (004, 025, 026 and 028) were used by the Sponsor for the determination of adult therapeutic serum concentrations. Because serum was collected according to different regimens in each study the C<sub>min</sub> for each study was determined in a different fashion. Only doses and serum concentrations occurring during the maintenance phase was used. In studies where 300 mg/day "low dose control" was used for comparison to higher therapeutic dose only data for the latter was included in this evaluation. Therapeutic doses used in protocols were 1200 and 2400 mg/day. Because data points from a single patient included more than one C<sub>min</sub>, the mean C<sub>min</sub> was used to determine the final therapeutic range in this study.

Protocol 004 measured early morning trough concentrations. Data points from this study were used only if serum collection occurred 10-14 hours following previous dose. Three patients in this study were allowed to have maintenance doses reduced. In this case mean dosage and associated concentrations were used as data points. Because serum concentrations were collected at random times in studies 025 and 026 the model used in study 011 was applied for the determination of a 12 hour post-dose serum concentration (C<sub>min</sub>). Random serum concentrations were also collected at random times in protocol 28. In this case up to 3 concentrations were collected for each patient during a 10-14 hour post dose period. These values were consequently used and modeling was unnecessary.

### 2.2.2.1.2 Results

A scattergram and resulting best-fit linear regression line for dose concentration curve is presented in the figure below<sup>6</sup>.

**Figure 5**  $C_{min}$  at effective doses of oxcarbazepine in adults during monotherapy (N=127)



A table presenting percentile distribution for the two major doses examined is presented in the table below.

<sup>6</sup> Many of the points cannot be observed. This is not a problem of the reproduced graph but one of the copies supplied by the Sponsor.

**Table 6 Distribution of  $C_{min}$  at effective doses of oxcarbazepine in adults during monotherapy**

Summary Statistic	Dose (mg/day)		
	1200 (n=18)	2400 (n=106)	1200-2400 (n=127 <sup>a</sup> )
Maximum	72.5	173.0	173.0
95 <sup>th</sup> percentile	71.4	139.0	137.9
75 <sup>th</sup> percentile	63.7	122.9	120.4
50 <sup>th</sup> percentile (median)	59.1	112.3	109.4
25 <sup>th</sup> percentile	47.0	95.9	88.6
5 <sup>th</sup> percentile	42.7	80.4	53.4
Minimum	42.2	70.7	42.2
Mean	57.0	111.0	103.3
Standard Deviation	10.14	19.2	26.1

This table demonstrates that mean concentrations were relatively tightly disturbed around the median dose with 5 to 95% of the observed concentration occurring at concentrations within a range of 17% to 28% of the median observed concentration. Values in this table are used by the Sponsor to draw conclusions as to what might be considered an acceptable monotherapeutic concentration range for a pediatric population (see below).

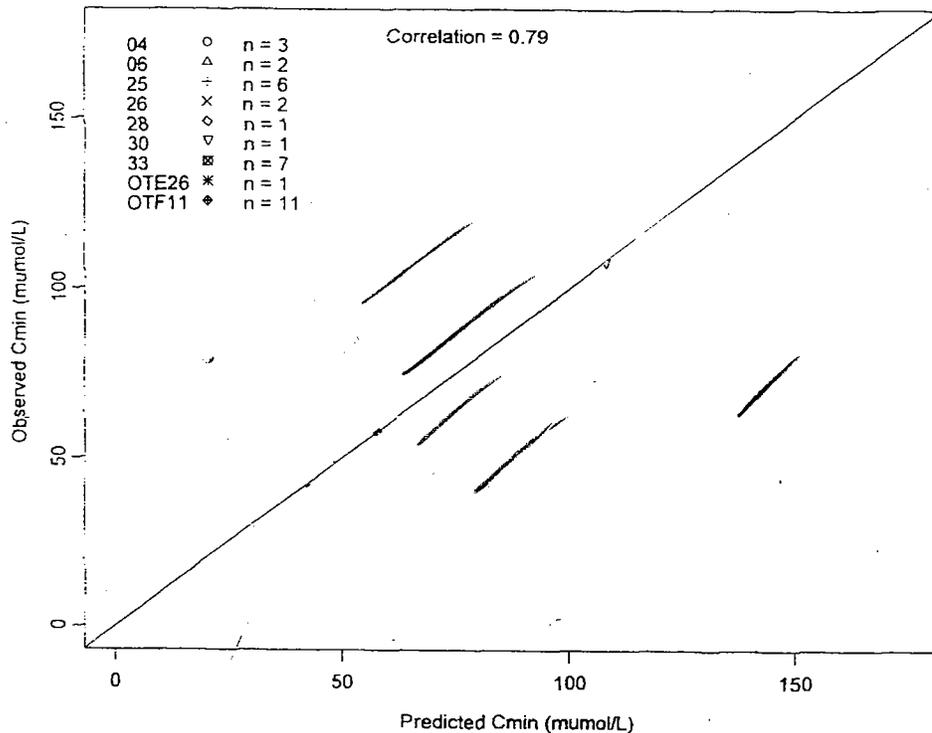
2.2.2.1.3 Critique of Adult Monotherapy PK Analysis

This reviewer found this analysis adequate. Clinical pharmacology's review did not directly comment on this analysis although the model used to calculate  $C_{min}$  values was considered adequate.

2.2.2.2 Calculation of Pediatric Dose in Monotherapy

The Sponsor utilizes the same model described above for protocol 011 to calculate the mg/kg dosage necessary to produce a concentration that was observed to produce a therapeutic effect in adults. Prior to this the Sponsor "validated" the model by comparing predicted  $C_{min}$  values in monotherapy trials with actual measured  $C_{min}$  values, where the latter was available. The dependent variable used in the estimation of the predicted  $C_{min}$  was dose in terms of body surface area. The figure below presents a graph of these data. The Sponsor notes that the slope is near 1 (i.e. "the line is a 45 degree line") although its value is not given.

**Figure 8** Observed vs predicted  $C_{min}$  values for patients on bid monotherapy



Little information is presented as to the ages of patients used to validate the model in monotherapy trials.

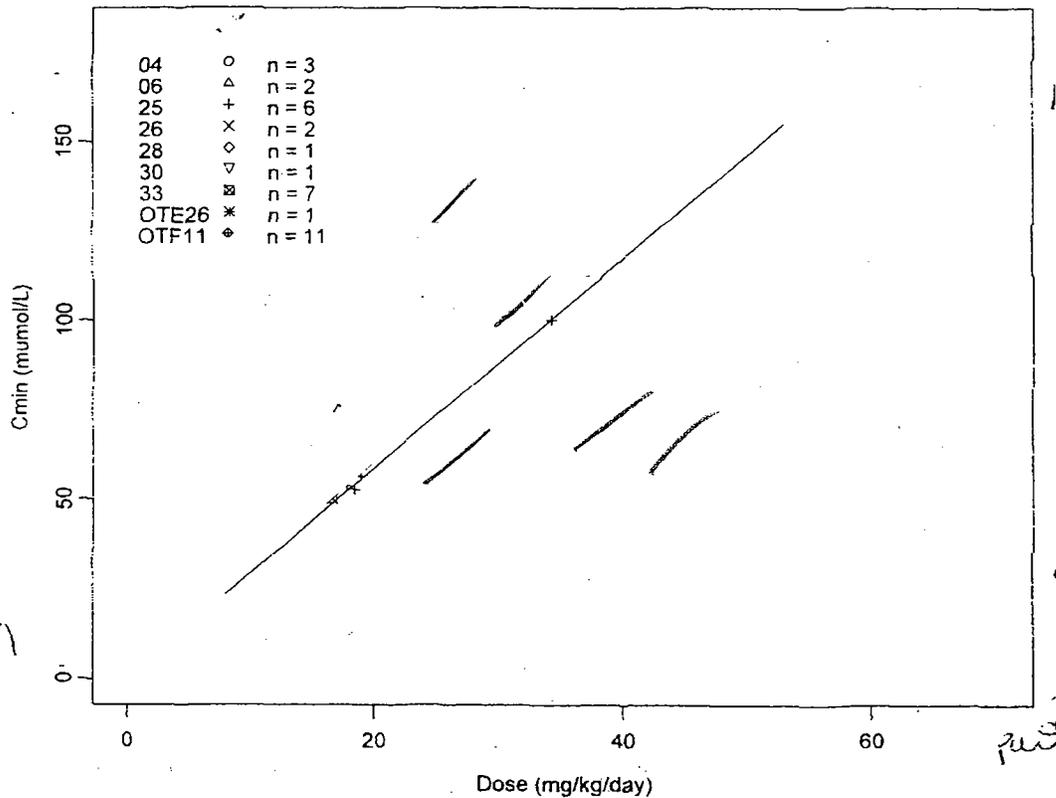
The model was modestly refitted to the monotherapy data following the latter analysis. This revision was performed to incorporate some of the differences in formulations utilized in all monotherapy studies and included factors that took bioavailability and absorption into consideration. A number of permutations of models were used (see table below).

Model
<b>Model 1. No formulation effects on either bioavailability or absorption rate</b>
<b>Model 2. Effects of all formulations on bioavailability</b>
<b>Model 3. Effect of only Oral Suspension on bioavailability (THETA(13)=THETA(14)=1, THETA(13) unconstrained)</b>
<b>Model 4. Effects of all formulations on absorption rate</b>

Model 1 (no formulation effect on bioavailability or absorption rate) was observed to be an "adequate." This model was subsequently used for the analysis.

Included in the modeling was an estimation of clearance based upon body surface area. Body surface area in turn can be expressed as a function of height and weight. The Sponsor derived a formula that describes height in terms of weight. Using this, the clearance, and therefore the  $C_{min}$ , can be derived only in terms of weight. As a test of the model the Sponsor compares predicted values of the model (solid line in the graph below) with actual data points in patients treated in monotherapy trials. These data are presented in the figure below.

**Figure 6**  $C_{min}$  vs Dose (mg/kg/day) of OXC in children during monotherapy (N=34) with superimposed predicted curve from the population PK model (N=121).



Note: The solid line represents a curve of predicted values from the population pharmacokinetic model computed at the mean height and weight

From this the Sponsor is able to calculate the dose necessary to achieve a given concentration for children of various weights. This was done for the minimum concentration in adults receiving 1200 mg/day in pivotal efficacy trials as well as the median serum concentrations for 1200 and 2400 mg/day dose groups (these concentrations were derived from the above Sponsors Table 6). This data is presented in the table below. The dose is presented in both mg per day and mg/kg/day for individuals of different weights.

**Table 7 Estimated doses of oxcarbazepine for children during monotherapy at  $C_{min}$  values corresponding to effective doses in adults during monotherapy**

Weight (kg)	MHD levels during monotherapy: $C_{min}$ ( $\mu\text{mol/L}$ )					
	42.2 (minimum concentration at effective doses in adults)		59.1 (median concentration at 1200 mg/day in adults)		112.3 (median concentration at 2400 mg/day in adults)	
	Dose (mg/day)	Dose (mg/kg/day)	Dose (mg/day)	Dose (mg/kg/day)	Dose (mg/day)	Dose (mg/kg/day)
20	410	20.5	575	28.7	1092	54.6
25	466	18.6	652	26.1	1240	49.6
30	520	17.3	728	24.3	1384	46.1
35	573	16.4	802	22.9	1524	43.5
40	623	15.6	873	21.8	1659	41.5
45	672	14.9	942	20.9	1789	39.8
50	720	14.4	1008	20.2	1916	38.3
55	766	13.9	1073	19.5	2039	37.1
60	811	13.5	1136	18.9	2158	36.0
65	855	13.1	1197	18.4	2275	35.0
70	897	12.8	1257	18.0	2388	34.1

A critique of this analysis is not presented by clinical pharmacology. This reviewer feels that such an analysis appears adequate although the Sponsor's should be asked, if possible, to include a separate analysis of the model validation at different age groups. Thus, is there a trend for the very young pediatric population to be outliers in the analysis in the Sponsor's Figure 6 presented above. An analysis by clinical pharmacology will be forthcoming following approval when labeling recommendations are to be considered.

### 3. Brief Statement on Labeling Changes

The following discussion does not include a definitive analysis of the labeling. Only issues that may need to be addressed in an approvable letter will be discussed. Monotherapy for children 4 to 16 years old has been added to the purposed indications of this drug. It is recommended that for conversion and initiation of monotherapy the drug should be started at a dose of 8-10 mg/kg/day, given in a bid regimen. The dose should then be increased. It is noted, from adult monotherapy extrapolation, that doses of 20-55 mg/kg/day achieve plasma concentrations in the effective range. These data can be observed in a table presented in the submission that is reproduced below. The table used the modeling described above to calculate serum concentrations expected with the administration of various doses (in mg/kg/day) to patients of differing weights.

The bolded entries represent values that fall between the minimum C<sub>min</sub> (42.2 umol/L) and Maximum C<sub>min</sub> (173 umol/L) of adults who received "therapeutic doses" (1200 and 2400 mg/day, respectively) in pivotal monotherapy trials. Note lower steady state concentrations occur in patients at lower weights but with the same mg/kg dosage. This is a result of the relationship between body surface area and clearance. This is consistent with the increased clearance observed in younger patients and described in the original labeling; i.e. children younger than 8 years of age experience a 30-40 increase in clearance.

Examination of the tables would suggest that 50 to 25 percent of patients between 20 and 30 kg, respectively, might not achieve sufficient theoretical serum concentrations to achieve seizure control. Examination of male and female pediatric growth curves presented below indicate that a majority of patients 8 years and younger have weights that is  $\leq$  30kg. This means that such patients are theoretically at risk of seizures if the recommended minimum therapeutic concentration is targeted. To further support the fact that a problem may exist with this dosage is the fact that in the present pediatric adjunctive labeling dosages of 31 to 45 mg/kg/day is recommended for adjunctive treatment in pediatric patients weighing 20 to 29 kg. This dosage is substantially higher than the recommended minimum monotherapeutic dosage of 20 mg/kg/day in this age range. This is particularly troublesome in that minimal adjunctive therapeutic dosages (600 mg/day) tend to be lower than monotherapeutic dosages (1200 mg) in the present labeling for adults. This in part may be an artifact of the design of the trial; i.e. patients had dose titrated to optimal dosages with some controlled at doses below the recommended targeted range. The Sponsor should explain this discrepancy. If this reaches final labeling a correction for the younger pediatric patients may be required.

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**Table 9 Distributions of simulated  $C_{min}$  values for children on mor**

a) 20 mg/kg/day

Weight (kg)	Percentiles ( $\mu\text{mol/L}$ )				
	5%	25%	50%	75%	95%
20	24.74	33.91	40.80	48.41	60.93
25	28.17	37.93	45.29	53.42	66.61
30	31.26	41.05	48.75	57.17	70.75
35	33.95	43.47	51.29	59.84	73.86
40	35.68	45.96	53.93	63.05	77.52
45	37.51	47.95	56.25	65.46	80.37
50	39.47	49.92	58.39	67.74	83.65
55	40.32	51.48	60.43	70.41	86.02
60	42.08	53.37	62.12	72.05	88.62
65	43.33	54.81	64.05	74.39	91.00
70	44.66	56.23	65.46	76.04	93.38

b) 30 mg/kg/day

Weight (kg)	Percentiles ( $\mu\text{mol/L}$ )				
	5%	25%	50%	75%	95%
20	37.4	50.7	61.4	73.1	92.7
25	42.3	56.5	67.0	79.2	98.8
30	47.1	61.3	72.7	85.1	105.5
35	50.1	65.0	76.9	89.7	110.7
40	53.9	68.9	80.9	94.3	116.5
45	56.1	71.5	84.1	97.6	120.7
50	59.2	74.5	87.6	101.7	125.1
55	61.3	77.4	90.7	104.8	129.7
60	63.1	80.1	93.4	108.4	133.2
65	65.7	82.4	95.7	111.3	137.4
70	67.0	84.6	98.4	113.6	139.6

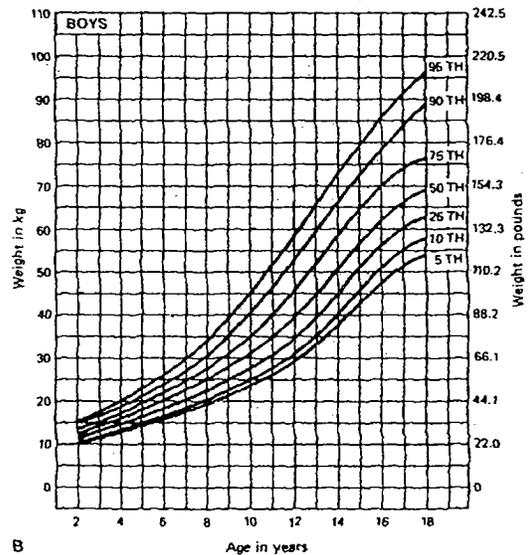
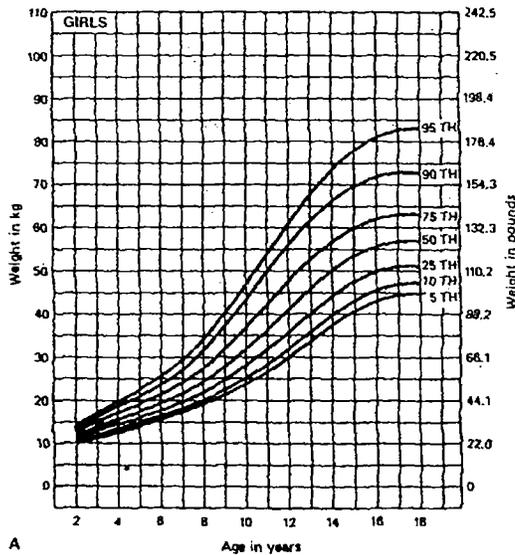
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c) 40 mg/kg/day

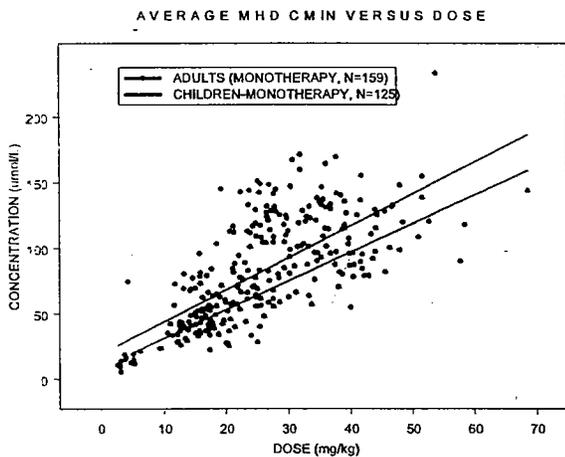
Weight (kg)	Percentiles (µmol/L)				
	5%	25%	50%	75%	95%
20	50.0	67.9	81.9	97.6	121.8
25	57.1	76.1	90.1	106.1	131.4
30	62.2	82.2	96.7	113.2	140.8
35	67.2	86.8	102.5	120.6	148.7
40	71.7	91.7	107.7	125.6	156.4
45	75.6	95.6	112.2	130.2	160.4
50	77.8	99.9	116.8	135.9	167.7
55	81.6	103.5	120.8	140.2	171.9
60	84.2	106.8	124.7	144.2	176.9
65	85.7	109.1	127.8	148.2	182.6
70	89.6	112.8	131.6	152.8	186.6

d) 50 mg/kg/day

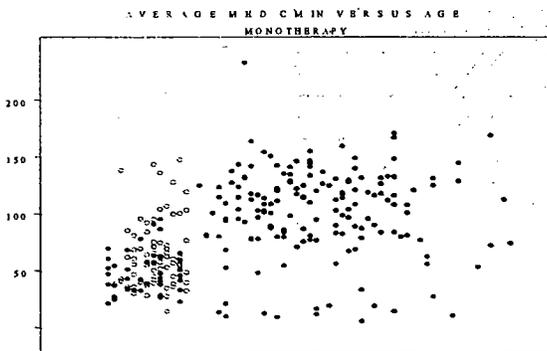
Weight (kg)	Percentiles (µmol/L)				
	5%	25%	50%	75%	95%
20	62.7	84.3	102.1	121.5	152.5
25	71.6	94.3	112.5	132.8	166.4
30	76.9	102.0	120.5	141.7	176.1
35	84.6	109.7	128.8	150.4	185.8
40	89.8	115.0	134.8	157.0	192.9
45	93.9	119.8	141.0	163.9	203.5
50	97.4	124.7	146.3	170.3	210.6
55	102.1	129.4	151.0	174.6	213.8
60	105.1	133.5	156.6	180.8	222.0
65	108.3	136.2	158.8	184.6	227.7
70	112.3	140.5	164.2	190.2	233.4



This above issue is founded on the fact that clearance appears to be dependent on body surface area and consequently differs with age. As noted above this is consistent with present labeling. Dr. Sekar indirectly addresses this issue in her review. Thus when Dr Sekar plotted dose Vs Cmin MHD serum concentration (see first figure below) in monotherapy trials, children appeared to have a lower serum concentration. However, a plot of age and body weight Vs Cmin (see second to figures below) did not reveal a significant relationship. This analysis is very preliminary and the disparity within these results and with modeling and labeling may need to be addressed in the future. It is noteworthy that a great deal of variability is apparent in older subjects (see figures below).



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ON 05/01/2011



## 4. Conclusions and Comments

The present application cannot be approved as submitted. There are certain clarifications that will need to be addressed before approval. These are discussed below.

### 4.1 *The Meta-analysis*

Although the meta-analysis is suggestive of a monotherapeutic effect it does not help establish recommendations for dosing in populations that metabolize the drug differently. This reviewer feels that even with the new meta-analysis a PK/PD bridging analysis is required.

### 4.2 *The PD Analysis*

#### 4.2.1 *Major Issues*

The Sponsor has not provided this division with a true PD analysis. The analysis should have consisted of a concentration response comparison. An example of one such an analysis was performed by Dr. Sekar in Clinical Pharmacology. This analysis suggests PD equivalence. The Sponsor should be asked to carry out a similar analysis, but also provide a discussion of the appropriateness of the particular analysis. Two particular issues should be addressed. Unlike OT/PE1, study 011 did not randomize patients to specific dose groups. Subject's doses were adjusted within a given range, and even permitted to be adjusted outside of that range, to a perceived optimal dosage. Ideally a PD evaluation would require patients be randomized to fixed concentration groups, although randomization to different dosage groups may be acceptable. Study 011 goes a step beyond this and randomizes to effect. The Sponsor should be asked to justify this. The second issue involves the methodology of statistical comparison for equivalence. As this analysis involves a statistical comparison for equivalence the Sponsor should include a discussion of the margin (the smallest unacceptable inferiority and superiority) and the power (the probability of accepting equivalence when study populations are different) of the analysis.

#### 4.2.2 *Lesser Issues*

While a preliminary evaluation by this reviewer suggests that pediatric and adult adjunctive patient populations are similar with regard to inclusion criteria and demographic variables, the Sponsor should carry out a more careful evaluation of pertinent baseline variables. This should include, but not

necessarily be limited to, the following: 1) partial seizure frequency, 2) incidence and frequency of subtypes of partial seizures, 3) number of concomitant anticonvulsant medications, 4) gender differences.

#### **4.3 PK analysis in Adult Monotherapy**

This reviewer found this analysis adequate. Clinical pharmacology's review did not directly comment on this analysis although the model used to calculate C<sub>min</sub> values was considered an adequate model in the Clinical Pharmacology review.

#### **4.4 Calculation of Pediatric Dose in Monotherapy**

Clinical pharmacology did not critique this analysis. This reviewer feels that such an analysis appears adequate although the Sponsor's should be asked, if possible, to include a separate analysis of the model validation for different age groups. Thus, is there a trend in the very young pediatric population to be outliers in the analysis in the Sponsor's Figure 6.

#### **4.5 Labeling**

Examination of information presented in the Sponsors analysis and of pediatric growth curves would indicate a large number of pediatric patients  $\leq 8$  years old ( $\leq 30$ kg) may be insufficiently treated with the recommended minimal dose of 20 mg/kg/day. It is also noteworthy that the present pediatric adjunctive labeling calls for a target therapeutic dosage of 31 to 45 mg/kg/day in patients weighing 20 to 29 kg. This dosage is substantially lower than the targeted recommended monotherapeutic dosage of 20 mg/kg/day in this age range. This is particularly troublesome in that minimal adjunctive therapeutic dosage (600 mg/day) is lower than the minimal monotherapeutic dosages (1200 mg) in the present labeling for adults. The Sponsor should explain this discrepancy. If this reaches final labeling a correction for the younger pediatric patients may be required.

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

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