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*APPLICATION NUMBER:*

**21-014/S-003**

**ADMINISTRATIVE DOCUMENTS**

## MEMORANDUM OF MEETING MINUTES

**Meeting Date:** November 6, 2002  
**Application:** NDA 21-014/S-003; Trileptal (oxcarbazepine) Tablets  
**Indication:** Pediatric Monotherapy  
**Meeting Chair:** Russell Katz, M.D.  
**Meeting Recorder:** Melina Griffis R.Ph.

### FDA Attendees:

Russell Katz, M.D., Division Director  
Norman Hershkowitz, M.D., Medical Reviewer  
Jogarao Gobburu, Ph.D., Biopharm TL  
John Feeney, M.D., Team Leader  
Ramana Uppoor, Ph.D., Biopharm TL

### Novartis Attendees:

Jerry Nedelman      Audrey Wong      Joseph D'Souza  
Hai Jiang            Werner Schmidt      Mary Ann Karolchyk  
Greg Sedek           Mara Stiles

### Background:

Trileptal has been approved for mono and adjunctive therapy in adults and for adjunctive therapy in children (ages 4-16). Although placebo-controlled blinded studies have been performed examining the therapeutic efficacy of Trileptal in an adjunctive setting in children there have been no such monotherapeutic studies. A supplemental new drug application was submitted in Nov. 2000, which analyzed already preexisting data and attempted to make a pharmacokinetic/pharmacodynamic argument to justify Trileptal's monotherapeutic use in the pediatric population. This analysis was based upon previous discussions with this division. The submission was not found to be completely adequate and an approvable letter was issued on December 20, 2001. This meeting was convened to discuss the sponsor's proposed response to item #2 of the approvable letter (equivalence of PK/PD relationship).

The following bulleted points were raised by Dr. Katz:

- It is noted in the submission seizure control is dependent on baseline seizure frequency in adults but not in children. We have not performed a comparison between these groups. The sponsor should present information as to how they arrived at this conclusion. Moreover, the fact that this occurs may subvert the assumption that there is pharmacodynamic equivalence between the adult and pediatric population. The sponsor should discuss this issue.
- The concentration-response relation is stated to be linear. We believe this is the case but to document this the sponsor should present the data that lead to this conclusion.
- The general approach presented appears acceptable, however, a final conclusion will be a

matter of review. The f value of 0.67 appears to be on the high side but the final decision as to what value is acceptable is a review issue that will also be presented to others in the agency.

Minutes Preparer: \_\_\_\_\_  
Melina Griffis, R. Ph.

Chair Concurrence: \_\_\_\_\_  
Russell Katz, M.D.

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ON ORIGINAL

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/s/

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Russell Katz  
11/14/02 04:37:54 PM

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ON ORIGINAL

## MEMORANDUM OF MEETING MINUTES

**Meeting Date:** April 4, 2002 **Time:** 10:00 am **Location:** Woc II , Rm. 4023

**Application:** NDA 21-014/S-003; Trileptal (oxcarbazepine) Tablets

**Indication:** Pediatric Monotherapy

**Meeting Chair:** Russell Katz, M.D.

**Meeting Recorder:** Melina Fanari R.Ph.

### **FDA Attendees:**

Russell Katz, M.D., Division Director

Norman Hershkowitz, M.D., Medical Reviewer

Vanitha Sekar, Ph.D., Biopharm Reviewer

John Feeney, M.D., Team Leader

Ramana Uppoor, Ph.D., Biopharm TL

Jogarao Gobburu, Ph.D., Biopharm TL

### **Novartis Attendees:**

Joseph D'Souza

Jerry Nedelman

Mara Stiles

Mary Ann Karolchyk

Hai Jiang

Greg Sedek

Audrey Wong

Roy Dodsworth

### **Background:**

Trileptal has been approved for mono and adjunctive therapy in adults and for adjunctive therapy in children (ages 4-16). Although placebo-controlled blinded studies have been performed examining the therapeutic efficacy of Trileptal in an adjunctive setting in children there have been no such monotherapeutic studies. A supplemental new drug application was submitted in Nov. 2000, which analyzed already preexisting data and attempted to make a pharmacokinetic/pharmacodynamic argument to justify Trileptal's monotherapeutic use in the pediatric population. This analysis was based upon previous discussions with this division. The submission was not found to be completely adequate and an approvable letter was issued on December 20, 2001. The meeting was convened to discuss the sponsor's proposed response to the approvable letter and discuss a reapplication for this indication. Below are our responses to the sponsor's specific questions and proposals (see attachment #1).

Dr. Katz opened with a general comment that the responses were interesting and possibly acceptable. Much of that contained in the submission is novel. Considering this and the precedent setting approach for labeling in the pediatric population we will ultimately be presenting this to a larger interagency group. The only definite response that we can make to the questions posed in the submission is that the review will not take 2 months (Question 6 in the sponsor's submission). It will be performed over 6-months.

### **Point 1: Justification of PK-PD analysis**

The sponsor presented their rationale for justifying the PK-Efficacy analysis for Trileptal in study OTPE1 (fixed dose study in adults) and for study 011 (flexible dose study in children) as described in the meeting package (as Response 1). The sponsor attempted to address the question related to PK-efficacy relationships in the flexible dose design study (011) using a statistical approach. The sponsor should clearly present the data sets that were used in these analyses along with the number of patients who achieved or maintained their target doses as well as the number of

patients who received and were maintained on less than the target doses.

Although the arguments made by the sponsor appear reasonable, the analysis would need to be reviewed (especially for the flexible dose study in which the sponsor has attempted to perform additional modeling to address this issue). In addition, 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. 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) will be useful. The sponsor should submit all control streams, data sets and outputs from their modeling exercises electronically. Approaches used for model validation must also be presented.

**Point 2: Equivalence of the PK-PD relationship in adults and children**

The sponsor stated that since comparison of efficacy responses in children and adults at various concentrations were similar and that the difference between the PK-PD relationships in the two populations was as expected from inter-study variation within a population (14% difference), the PK-efficacy relationships of adults and children are essentially clinically equivalent. Although this response may attempt to address the issue of clinical relevance of the differences observed in the PK-PD relationship between the two populations, the issue of pharmacodynamic equivalence between children and adults remains to be addressed.

It was this division’s intention that the sponsor would 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.

**Point 3: Determination of Effective Concentrations**

The sponsor attempted to address the issue of determining effective concentrations in children by presenting a summary analysis that used the median Cmin associated with the lowest effective dose in adults in both adjunctive and monotherapy to determine the lowest effective dose in children during monotherapy. In addition to using this approach, the sponsor should attempt to use the established PK-PD model to propose a suitable dosing regimen in children. Simulations should be performed to assess the distribution of predicted response using the proposed dosing regimen.

Minutes Preparer: \_\_\_\_\_  
Melina Fanari, R. Ph.

Chair Concurrence: \_\_\_\_\_  
Russell Katz, M.D. (Designated Signatory)

## ATTACHMENT 1 (SPONSOR'S SUBMISSION)

### Topics for discussion

#### Point 1: Justification of PK/PD analysis

"First, as you recognize, the studies were not designed to permit analyses of the son wè (and you) have performed There are questions about the propriety of examining a concentration-effect relationship in studies in which patients have not been randomized to plasma concentration... 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."

#### Response 1:

##### a) Fixed Dose Study (Adults) -Study OT/PE1

We propose to justify the PK/Efficacy analysis for oxcarbazepine with the following:

1. Demonstrate that there is a reasonable correlation between dose and plasma concentration (Tables 1, 2 and Figure 1) in adults, as suggested by the FDA.
2. We recognize that there is a potential for bias in the PK/Efficacy relationship in a fixed dose study where patients were randomized to fix doses instead of fixed concentrations.

The potential bias may arise from factors (e.g., patient's disease severity) that may affect the patient's pharmacokinetics and pharmacodynamics (Holford NHG and Peck CC. Population pharmacodynamics and drug development. In: The in vivo study of drug action: principles and applications of kinetic-dynamic modeling. Editors: van Bortel CJ, Holford NHG, DanhofM, 1992. Amsterdam Elsevier Science Publishers, p. 401-13.). One way to help determine the existence of such a bias is to examine the mutual variation in concentration and response data. This will be done by examining a plot of residuals (observed -predicted values) from the regression of plasma concentration on dose versus the residuals from the regression of seizure response on plasma concentration (Figures 3, 4,5). The lack of correlation supports the absence of relationship between individual variation in pharmacokinetics and individual variation in efficacy response that may affect the legitimacy of the PK/Efficacy analysis. Therefore, for oxcarbazepine this fixed dose study can be used to determine the PK/Efficacy relationship.

##### b) Flexible dose study (Children) -Study 011

We recognize that there is a potential for bias in the PK/Efficacy relationship in a flexible dose study. We propose to justify the PK/Efficacy analysis as follows:

1. Demonstrate that there is a reasonable correlation between dose and plasma concentration (Tables 1,2 and Figure 2) in children, as in the fixed dose adult study.
2. As with the fixed dose study, demonstrate the lack of correlation in the residual plot, thereby supporting the absence of relationship between individual variation in pharmacokinetics and individual variation in efficacy response. This would alleviate the potential of bias in the PK/Efficacy analysis.
3. For this flexible dose study, the patients were titrated to the target dose based on their body weight. To justify the PK/Efficacy analysis for this study, we must verify that dose adjustments were made mainly for reasons of tolerability, and establish that safe and efficacy are independent at a given concentration.

- i) Review of the CRFs (and contact reports) verified that for those patients on oxcarbazepine who had documented dose reductions, all were due to tolerability (Table 3).

- ii) Demonstrate that the PK/Efficacy relationship is justified if the intersubject variation in safety and the intersubject variation in efficacy are independent at a given concentration. This will be demonstrated by examining partial correlations between the percent change in seizure frequency and key safety variables, after accounting for concentration (Table 4 for Study II; Table 5 for Study OT/PEI), and by examining correlations within concentration tertiles (Figures 7a-g for Study 011; Figures Sa-g for OT/PEI). The lack of correlation in both Study OT/PEI and Study 011 supports this hypothesis of independence.

4. Demonstrate that the inferred PK/Efficacy relationship in Study 011 does not depend on whether patients achieved or maintained their target doses. This will be demonstrated by fitting the PK/Efficacy model with an additional term ( $\gamma$ ) indicating whether patients deviated from their target doses (Table 6). The lack of significance of this-additional term supports that the PK/Efficacy relationship does not depend on whether patients achieved or maintained their target doses.

All the above evidence from Studies 011 and OT/PEI strongly supports the validity of the PK/Efficacy analysis for Study 011. Therefore, for oxcarbazepine this flexible dose study can be used to determine the PK/Efficacy relationship.

Question 1 :

Will these responses adequately address Issue 1 ?

Point 2: Equivalence of PK/PD relationship in adults and children

Next, while we have concluded that the PK/PD relationships in adults and pediatric patients do not differ statistically, this is not the same as concluding that they are the same. You will need to provide a convincing argument that these relationships are, indeed, essentially equivalent, and not just not statistically significantly different.

Response 2:

We will assess the magnitude of the differences between the adult and children response curves with respect to clinical relevance by the following:

1. Demonstrate that at various plasma concentrations, the difference in efficacy response between adults and children is relatively small during adjunctive therapy. This will be determined by estimating the difference in the fitted values from the PK/Efficacy models for adults and children across the range of median C<sub>min</sub> values observed at oxcarbazepine doses of 600, 1200, 1800, and 2400 mg/day in Study OT/PE1 (Table 7).

The difference in response (percent change in seizure frequency) between adults and children, expressed as percentage of the adult response is small ( 14-15% ) for placebo and at all median C<sub>min</sub> values observed at doses of 600, 1200, 1800, and 2400 mg/day). Also, the difference in slopes of the fitted regression lines between adults and children is small (14%). To assess the clinical relevance of the observed difference in response, consider a child and an adult who have a baseline seizure frequency of 10 seizures per month (the average baseline seizure frequency observed in adults), and both of whom achieve a C<sub>min</sub> of 40.8  $\mu\text{mol/L}$  (the median C<sub>min</sub> for adults on 1200 mg/day). The child would expect to have a decrease in seizure frequency to an average of 6.3 seizures per month, and the adult would expect to have a decrease in seizure frequency to an average of 5.7 seizures per month. These expected seizure frequency reductions with a difference of 0.6 seizures per month are essentially equivalent.

2. Demonstrate that the observed PK/Efficacy relationships of adults and children are as similar as one would expect by conducting two identically designed studies in identical patient populations. This will be demonstrated by randomly dividing the 473 patients (placebo + patients with C<sub>min</sub> from Study OT/PE1 into two groups, stratified by dose. Each of the two

groups will be considered as representing patients from identically designed studies in identical patient populations. A PK/Efficacy model will be fitted to each group separately, and the percent difference between the two estimated slopes will be determined. This will be done 500 times (Table 8). The median difference in slopes of the fitted regression lines between the two randomly selected groups is 14%. The similarity of this value with the observed 14% difference in slopes between the adult and children studies (see above) demonstrates the equivalence of adults and children with respect to PK/Efficacy. Since the efficacy responses at various concentrations are similar between adults and children, and the difference between the two PK/Efficacy curves is as expected from inter-study variation, the PK/Efficacy relationships of adults and children are essentially clinically equivalent.

Question 2:

Will these responses adequately address Issue 2?

Point 3: Determination of effective concentrations

Another issue relates to the establishment of the effective range of concentrations. You have proposed that the effective MHO concentration range in pediatric patients as monotherapy is identical to the range of concentrations seen in adults at effective monotherapy doses. In our view, it is not immediately obvious that this is the appropriate manner in which to construct a therapeutic range. In particular, it is not obvious that the lowest plasma levels achieved at the lowest effective dose are, in fact, effective. You should provide a justification for your proposal.

Response 3:

In the previously submitted sNDA, the recommended dose for children during monotherapy was established as follows:

1. We demonstrated that the concentrations associated with the effective dose in adults and children during adjunctive therapy are similar.
2. Distributions of  $C_{min}$  values were then determined for adults on monotherapy at the effective doses (1200 and 2400 mg/day).
3. The median  $C_{min}$  (59.1  $\mu\text{mol/L}$ ) associated with the effective dose of 1200 mg/day for adults during monotherapy was used to determine the lower limit of the recommended dose range for children, using an established pharmacokinetic model.

Regarding the comment whether the lowest plasma levels achieved at the lowest effective dose are effective, the lowest plasma level was not used in the sNDA to determine the recommended dose for children on monotherapy (Table 9, previously submitted in the sNDA). In fact, the lowest plasma level associated with an effective dose was only included for completeness and to provide an estimate for a starting dose for children in monotherapy. The minimum recommended dose for children was based on the median  $C_{min}$  (59.1  $\mu\text{mol/L}$ ) associated with the effective dose of 1200 mg/day for adults.

To justify the use of the median  $C_{min}$  associated with the lowest effective dose we will demonstrate that for adjunctive therapy, the concentrations achieved with the lowest effective dose in the adults provide an effective concentration range for both adults and children.

The interquartile interval (25th -75th percentiles), 13.5 - 22.7  $\mu\text{mol/L}$ , centered around the median  $C_{min}$  ( 17.7  $\mu\text{mol/L}$  ) as associated with the lowest effective dose of 600 mg/day in adults will be used in the evaluation of efficacy. This will be established by evaluating the percent change in seizure frequency in patients (primary efficacy variable) with  $C_{min}$  within the interquartile interval from the two placebo-controlled adjunctive studies in adults and children (OT/PE1, 011). The concentration range based on the interquartile interval (13.5 - 22.7  $\mu\text{mol/L}$  ) is shown to be effective compared to placebo in both adults and children (Table 10).

The above the analyses confirm that the interquartile interval centered around the median C<sub>min</sub> associated with the lowest effective dose in adults, is an effective concentration range in both adults and children during adjunctive therapy. Also, it has been shown in the sNDA, that children and adults during monotherapy had similar distributions of C<sub>min</sub> at corresponding doses, as with adjunctive therapy. Therefore, it is appropriate to use the median C<sub>min</sub> associated with the 1200 mg/day in adults on monotherapy to determine the lowest dose recommended for children during monotherapy.

Question 3:

Will this response adequately address this issue?

Point 4: Meta-analyses of efficacy

As noted in the Approval Letter regarding the previously performed meta-analyses, the new meta-analyses also combined data from populations that were apparently different. While the results of these analyses are consistent with the conclusion that Trileptal is effective as monotherapy in pediatric patients, we do not consider them definitive.

Response 4:

The previously performed meta-analyses (as noted in the Approval Letter) combined all pediatric patients 8-17 years of age from four adequate and well controlled monotherapy studies (004, 025, 026, 028). The new meta-analyses performed in the sNDA combined all pediatric patients 8-16 years of age from these four adequate and well controlled monotherapy studies with the addition of Study 006. Though Study 006 was prematurely terminated due to slow patient recruitment, this study is well-controlled and appropriate for inclusion in the meta-analysis. The results are consistent with or without Study 006 if the same pediatric age group is considered (Tables 11-14). For 8-17 year olds, without Study 006, the p-value was 0.0172; with Study 006, the p-value was 0.0244. For 8-16 year olds, the p-value was 0.0648 without Study 006, and 0.0803 with Study 006. Hence, the apparent difference is not due to the inclusion of Study 006. Even though data were combined from populations with different baseline seizure frequency, different design paradigms (placebo/active controls), the meta-analyses that included both primary and secondary efficacy measures provides evidence that is strongly suggestive of the effectiveness of oxcarbazepine given as monotherapy in children. While we agree these analyses are not definitive, we continue to regard them as supportive.

Question 4:

Will this response adequately address this issue?

Question 5:

Will the FDA approve the pediatric monotherapy supplement for ages 4-16 based on our response which will consist of material presented in this Briefing Book?

Question 6:

Will the FDA agree to provide a two-month review for the response of this Approvable Letter?

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/s/

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

**CORRESPONDENCE**



NDA 21-014/S-003

**PRIOR APPROVAL SUPPLEMENT**

Novartis Pharmaceuticals Corporation  
Attention: Mara Stiles  
Associate Director, Drug Regulatory Affairs  
59 Route 10  
East Hanover, New Jersey 07936-1080

Dear Ms. Stiles :

We have received your supplemental drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Trileptal<sup>®</sup> (oxcarbazepine) Tablets

NDA Number: 21-014

Supplement Number: S-003

Review Priority Classification: Standard (S)

Date of Supplement: February 9, 2001

Date of Receipt: February 12, 2001

This supplement proposes the following change(s): The use of Trileptal as monotherapy in the treatment of partial seizures in children ages 4-16.

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on April 12, 2001 in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be December 12, 2001 and the secondary user fee goal date will be February 12, 2002.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). If you have not already fulfilled the requirements of 21 CFR 314.55 (or 601.27), please submit your plans for pediatric drug development within 120 days from the

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Food and Drug Administration  
Rockville MD 20857

date of this letter unless you believe a waiver is appropriate. Within approximately 120 days of receipt of your pediatric drug development plan, we will review your plan and notify you of its adequacy.

If you believe that this drug qualifies for a waiver of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of 21 CFR 314.55 within 60 days from the date of this letter. We will make a determination whether to grant or deny a request for a waiver of pediatric studies during the review of the application. In no case, however, will the determination be made later than the date action is taken on the application. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at [www.fda.gov/cder/pediatric](http://www.fda.gov/cder/pediatric)) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" (PPSR) in addition to your plans for pediatric drug development described above. We recommend that you submit a Proposed Pediatric Study Request within 120 days from the date of this letter. If you are unable to meet this time frame but are interested in pediatric exclusivity, please notify the division in writing. FDA generally will not accept studies submitted to an NDA before issuance of a Written Request as responsive to a Written Request. Sponsors should obtain a Written Request before submitting pediatric studies to an NDA. If you do not submit a PPSR or indicate that you are interested in pediatric exclusivity, we will review your pediatric drug development plan and notify you of its adequacy. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity. FDA does not necessarily ask a sponsor to complete the same scope of studies to qualify for pediatric exclusivity as it does to fulfill the requirements of the pediatric rule.

Please cite the application number listed above at the top of the first page of any communications concerning this application. All communications concerning this supplemental application should be addressed as follows:

U.S. Postal Service:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Neuropharmacological Drug  
Products, HFD-120  
Attention: Division Document Room 4008  
5600 Fishers Lane  
Rockville, Maryland 20857

Courier/Overnight Mail:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Neuropharmacological Drug  
Products, HFD-120  
Attention: Division Document Room 4008  
1451 Rockville Pike  
Rockville, Maryland 20852-1420

If you have any questions, call Melina Fanari, R.Ph., Regulatory Management Officer, at (301) 594-5526.

Sincerely,

*{See appended electronic signature page}*

John S. Purvis  
Chief, Project Management Staff  
Division of Neuropharmacological Drug Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

APR 10 2003  
08:00

/s/

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Melina Fanari  
3/5/01 03:04:19 PM  
Signed for John Purvis

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