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APPLICATION NUMBER:
21-014/S-003

APPROVABLE LETTER



Food and Drug
Administration
Rockville MD 20857

NDA 21-014/S-003

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

Dear Ms. Stiles:

Please refer to your supplemental new drug application dated February 9, 2001, received February 12, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Trileptal (oxcarbazepine) Tablets.

We acknowledge receipt of your submissions dated November 6, 2001, and November 20, 2001 and November 28, 2001.

This supplemental new drug application proposes the use of Trileptal as monotherapy in the treatment of partial seizures in children ages 4-16.

We also refer to the January 14, 2000 approval letter for Trileptal Tablets (N21-014) in which we described the criteria required for approval of this indication.

We have completed the review of this application, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to address the following.

We acknowledge your attempt to identify a plasma concentration range associated with effectiveness in the adjunctive setting in adults and pediatric patients as the first step in being able to provide monotherapy dosing recommendations in pediatric patients. However, your analyses fail to address the relationship between plasma concentrations and effectiveness (we believe a simple comparison of the plasma levels achieved at doses shown to be effective in clinical trials, such as you have performed, is not an adequate assessment of the pharmacokinetic/pharmacodynamic relationship that would necessarily underlie any appropriate approach to the questions raised in our Approval letter). For this reason, we have performed several analyses designed to examine this question. We have included a separate attachment to this letter containing several graphs that we believe will help clarify our comments.

First, we have plotted steady-state C_{min} values (including observed and predicted, using your model for the latter) vs 28 day seizure frequency from the adjunctive controlled trials in adults and

pediatric patients (see enclosed graph 1). The regression lines plotted are not statistically significantly different ($p > 0.05$). We have attempted to account for the placebo response (which we believe is necessary) in several ways. In the graphs, we have also plotted the placebo response by concentration (concentration=0). Alternatively, we have produced histograms and cumulative distribution functions of the placebo response in adults and pediatric patients (see enclosed graphs 2, 3, and 4); these, too, are not statistically significantly different. We have also examined these relationships in the few pediatric patients treated with monotherapy and compared them to the adult data; these also do not differ significantly.

These analyses suggest that the pharmacokinetic/pharmacodynamic relationship is similar in adults and children, but there are still several unanswered questions you will need to address before any definitive decisions can be made.

First, as you recognize, the studies were not designed to permit analyses of the sort we (and you) have performed. For this reason, they must be justified.

In particular, there are questions about the propriety of examining a concentration-effect relationship in studies in which patients have not been randomized to plasma concentration, because any such relationships seen might be spurious. 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.

Next, while we have concluded that the PK/PD relationships in adults and pediatric patients do not differ statistically (with the caveat expressed in the previous section), this is not the same as concluding that they are the same. Indeed, we have no experience with any systematic approach to determining the **equivalence** of two PK/PD relationships. You will need to provide a convincing argument that these relationships are, indeed, essentially equivalent, and not just not statistically significantly different.

Another issue relates to the establishment of the effective range of concentrations. You have proposed that the effective MHD 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.

We recognize that you have already constructed a dosing regimen for pediatric patients that should

result in plasma levels that fall within the range you have proposed. Obviously, depending upon your answers to the questions above, you may need to propose an alternative regimen.

We have also reviewed the various meta-analyses you have provided.

As noted in our comments in the Approval letter regarding the previously performed meta-analyses, the new meta-analyses also combined data from populations that were apparently different (e.g., different baseline seizure frequency within a treatment group across studies, different between-treatment baseline differences across studies, etc.), included analyses of secondary outcome measures, and included data from active control trials. 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. (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 [$p=0.17$ with a total sample size of 29]).

While we continue to believe that the evidence is strongly suggestive of Trileptal's effectiveness as monotherapy in pediatric patients, we have concluded that the analyses done to date do not yet adequately support definitive dosing recommendations in these patients. A complete and comprehensive response to the questions raised above will be necessary before such recommendations can be made.

Within 10 days after the date of this letter, you are required to amend the supplemental application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

This product may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with this change prior to approval of this supplemental application.

Under 21 CFR 314.102(d) of the new drug regulations, we encourage you to request an informal meeting or telephone conference with this division to discuss what further steps need to be taken before the application may be approved.

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Figure 1

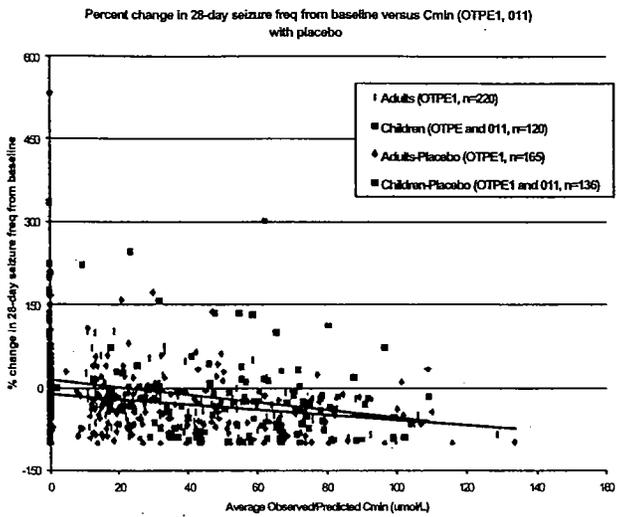


Figure 2

Distribution of response in placebo patients OTPE1 (adults, n=165)

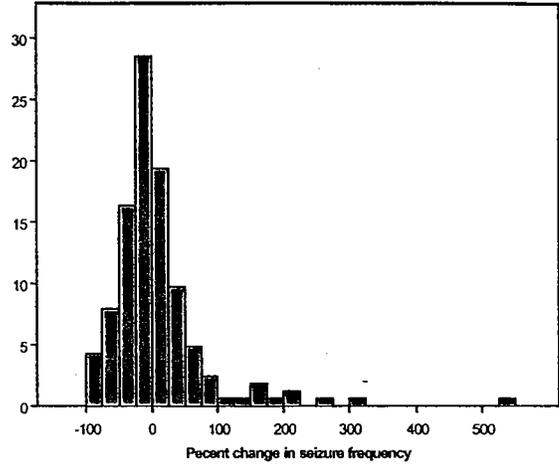


Figure 3

Distribution of response in placebo patients Study 011 (children, n=129)

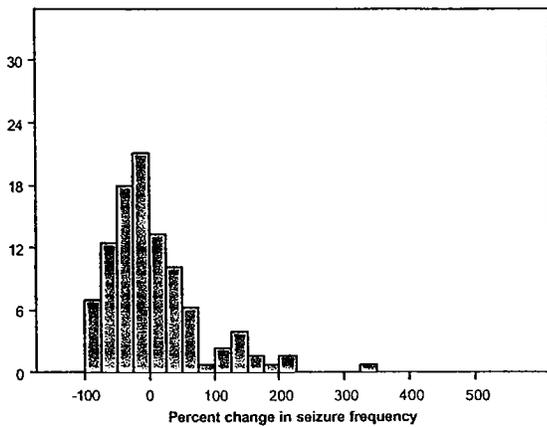
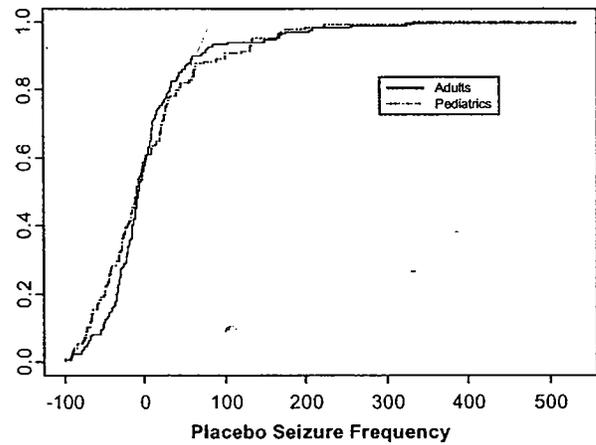


Figure 4



APPLIED MEDICAL
CORPORATION

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

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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