NDA 21-014

Novartis Pharmaceuticals Corporation
Attention: Michael J. Macalush
Associate Director, Drug Regulatory Affairs
59 Route 10
East Hanover, New Jersey 07936-1080

Dear Mr. Macalush:

Please refer to your new drug application (NDA) dated September 25, 1998, received September 25, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Trileptal (oxcarbazepine) Tablets.

We acknowledge receipt of your submissions dated: September 20, 1999
November 18, 1999
December 15, 1999
December 21, 1999
December 23, 1999
January 10, 2000

Your submission of November 15, 1999 constituted a complete response to our September 24, 1999 approvable action letter.

This new drug application provides for the use of Trileptal (oxcarbazepine) Tablets for use as monotherapy or adjunctive therapy in the treatment of partial seizures in adults with epilepsy and as adjunctive therapy in the treatment of partial seizures in children ages 4-16 with epilepsy.

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon enclosed labeling text. Accordingly, the application is approved effective on the date of this letter. We do, however, have the following comments.

Clinical

1. [ ]

2. For purposes of post marketing surveillance all hepatic, hematologic and skin hypersensitivity reactions, as well as all cases of hyponatremia, should be treated as unlabeled events. Any of these events determined to be serious should be submitted as 15 day reports.

3. We urge you to create and maintain a registry of women who were exposed to Trileptal during their pregnancy. The value of this registry lies primarily in its capacity to prospectively enroll registrants before they are aware of fetal outcome. Our staff will be happy to discuss with you the specific design elements of this registry.

Chemistry

1. Please submit for our review the actual-sized carton and container labeling with the changes agreed upon during the January 7, 2000 teleconference. This revised labeling should be implemented for your next printing.

2. Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

Biopharmaceutics

1. Please adopt the following dissolution methodology and specifications for 150, 300 and 600 mg tablets strengths of Trileptal:

Apparatus:	USP Apparatus 2 (paddles)
Medium:	Water + 1% Sodium Dodecyl Sulfate (SDS)
Volume:	900 ml
Agitation:	60 rpm
Temperature:	37°C±0.5°C
Specification:	Q[ ] in 30 minutes; Q[ ] in 60 minutes

2. We remind you of your Phase 4 commitment, specified in your submission dated January 10, 2000, to conduct an in-vitro drug interaction study to evaluate the potential interaction of diazepam and omeprazole with oxcarbazepine and MHD. Based on the results from this in-vitro study, an in-vivo drug interaction study may or may not be required.

   Protocols, data, and final reports should be submitted to your IND for this product and a copy of the cover letter sent to this NDA. If an IND is not required to meet your Phase 4 commitments, please submit protocols, data and final reports to this NDA as correspondence. In addition, under 21 CFR 314.82(b)(2)(vii), we request that you include a status summary of each commitment in your annual report to this NDA. The status summary should include the number of patients entered in each study, expected completion and submission dates, and any changes in plans since the last annual report. For administrative purposes, all submissions, including labeling supplements, relating to these Phase 4 commitments must be clearly designated "Phase 4 Commitments."

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved NDA 21-014." Approval of this submission by FDA is not required before the labeling is used.

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). We note that you have not entirely fulfilled the requirements of 21 CFR 314.55 (or 601.27). We are deferring submission of further pediatric studies, [ ] in patients between 2 months and 4 years. Please submit your pediatric drug development plans within 120 days from the date of this letter unless you believe a waiver is appropriate.

If you believe that this drug qualifies for a waiver of any of the deferred 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 notify you within 120 days of receipt of your response whether a waiver is granted. 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. We are waiving the pediatric study requirement for pediatric patients less than 2 months.

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) for details. We note your February 22, 1999 submission containing a proposed pediatric study request and describing a plan to [ ].

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

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

Sincerely,

Robert Temple, M.D.
DirectorOffice of Drug Evaluation I
Center for Drug Evaluation and Research)