CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-014

APPROVAL LETTER

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,

/S/

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

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-014

APPROVABLE LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

NDA 21-014

SEP 24 1999

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) 150 mg, 300 mg and 600 mg Tablets.

We acknowledge receipt of your additional correspondences and amendments dated:

Nov. 11, 1998	May 3, 1999	June 23, 1999	July 23, 1999
February 8, 1999	May 18, 1999	June 24, 1999	July 26, 1999
April 5, 1999	May 21, 1999	July 2, 1999	August 6, 1999
April 23, 1999	June 1, 1999	July 7, 1999	August 16, 1999
April 29, 1999	June 14, 1999	July 16, 1999	August 24, 1999
April 30, 1999	June 16, 1999	July 22, 1999	Sept. 2, 1999

The user fee goal date for this application is September 25, 1999.

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 submit draft labeling revised as follows:

Labeling

The attachment to this letter provides a draft of the labeling that the Agency asks you to adopt for Trileptal™ tablets upon approval. Although sections of this proposal are taken verbatim from the labeling proposed by you in the NDA, other sections have been revised. Please note that we have embedded several "Notes to Sponsor" in the text of the attached draft labeling, requesting further revisions or clarifications. If additional information relating to the safety or effectiveness of this drug becomes available, revisions of the labeling may be required.

Warnings Section

1. Hyponatremia

We have proposed language in the draft labeling for a warning statement describing the risk of hyponatremia that is clearly associated with oxcarbazepine use. The warning statement recommends that patients using oxcarbazepine undergo routine monitoring of serum sodium and that use be discontinued when the serum Na falls below 125. We realize you do not consider monitoring necessary but note possible excess seizures in patients with hyponatremia as well as the fact that all patients in trials were monitored.

To clarify some aspects of the risk of hyponatremia, additional analyses are necessary. Because sodium levels change over time, analyses of the effect of such factors as oxcarbazepine dose, the frequency of electrolyte monitoring, and preceding sodium level on the risk of developing clinically significant hyponatremia (sodium less than 125), and, in general, the risk over time, are not straightforward. We would suggest that you conduct a proportional hazards (Cox) style analysis focusing on a sodium less than 125 as the event of interest. In addition to examining the factors already mentioned, also consider the effects of such other factors as age, gender, and concurrent medications on the risk of hyponatremia.

In the NDA, you conducted an analysis to see if any adverse events (AEs) were associated with hyponatremia. However, this analysis confounded the time of the AE with the timing of hyponatremia. For many patients, AEs used in the analysis preceded the drop in Na. Please reconsider this question by looking at selected AE risk after patients reach selected sodium levels. You could, for example, look at AE risk within 1 week of reaching a Na of 130, 125, etc.

For each patient who developed a Na level less than 125, provide a plot of sodium level (on the y axis) against time (on the x axis) where time begins at randomization. Note on the figure or separately all AEs, concurrent medications and when the oxcarbazepine was stopped.

Finally, it is not clear whether some or all protocols used a discontinuation rule for patients reaching a specified sodium level. Please clarify this.

2. Cognitive/Neuropsychiatric Adverse Events

CNS adverse events were more frequent on oxcarbazepine than placebo, including both neurologic effects and changes in mental status. Specifically, there were increases in the risks of ataxia and gait abnormalities, with some of these events serious in nature, and diplopia, and nystagmus. These neurological effects were sometimes accompanied by confusion but there were also increases in the risks of confusion and such events as "thinking abnormal", "concentration impaired", "depression", and "psychosis" without ataxia.

In the labeling we have included a Warnings statement that seeks to enumerate, using clinically meaningful terminology, the kinds of mental status change that have been observed and their incidence. In general, there are appear to be three broad categories of these events: 1) psychiatric symptoms, including depression and psychosis, 2) psychomotor slowing and difficulty with concentration, and 3) somnolence. Since oxcarbazepine causes hyponatremia, which could be contributing to these events, the warning statement also recommends that sodium level be checked if any of these events occur.

To provide information for this warning, you need to first identify any patient who has suffered any kind of mental status change. You will need to document, in detail, the strategies, methods and procedures you used to identify, evaluate and classify individual patients presenting with mental status changes. Also provide the serum Na values for each patient having such an event.

This search of the database should not be based on a restricted set of COSTART terms but should be based on all terms that might possibly identify a patient with a mental status change. Once these cases are identified, you will need to characterize, in clinically understandable terms, the mental status changes seen. This description will probably require reclassification of the AEs under some broader term, as it is not clear that confusion, thinking abnormal, psychosis, etc., represent distinct events.

Other Safety Issues

1. Hepatic Risk

We have some degree of concern that oxcarbazepine may have an increased risk of hepatic injury. Based on the outlier analysis from the laboratory dataset, in the monotherapy initiation trials, 4 of the 405 patients on oxcarbazepine developed an AST greater than 100 compared to none of the 63 placebo patients. In the adjunctive therapy trials, 10 of 1204 patients on oxcarbazepine had an AST greater than 100 compared to 0 of 347 on placebo. There were no increases in ALT in either laboratory dataset. Of course, we are aware of 1 patient in the adjunctive trials who had hepatic necrosis with corresponding increases in ALT and AST.

We would like you to consider this question in more detail addressing the discrepancy in findings between AST and ALT, and also addressing the following questions. Did any patients other than the one with hepatic necrosis have concurrent increases in LFTs and bilirubin? Are there more details about the patient with hepatic necrosis regarding the course in the hospital? For example, was a liver biopsy performed? Did the patient have an altered mental status?

Based on the results of these additional analyses, labeling may need to include relevant language.

2. Hematological Risk

We also have significant concern that oxcarbazepine use is associated with aplastic anemia. There was 1 case in the primary database, 1 case of pancytopenia (no bone marrow) in the compassionate use program and 4 potential cases from post-marketing surveillance. Please conduct a risk assessment of this issue and propose labeling to describe the risk, if appropriate.

3. Extent of Use

You have proposed an upper dose limit of 2,400mg per day in labeling, but the extent of experience at doses greater than 1,800mg/day is not well defined. Provide a duration by dose table (using the same format as exhibits 4.2.2.-1 and 4.2.3.-1 in the ISS) that stratifies the experience by: >1,800mg/day to <2,400mg/day, and at 2,400mg/day. In one study, the protocol was amended to limit the maximum dose to 1800 mg/day because of AEs. Please separately examine the safety experience in patients reaching doses greater than 1800 mg and justify recommending a maximum dose of 2400 mg/day. Also describe the extent of use at these doses separately for pediatric patients.

4. More General Issues:

a) Patient 011EUSAM0230N107 had an AE listed as uremia but did not appear to have abnormal BUN or Creatinine results in the CRT dataset. Please explain what occurred with this event, including pertinent lab results, workup, and outcome.

b) Patients 004EUSAM8459P101 and 026EUSAM8706P111 both had jaundice listed as AEs but did not appear to have elevated bilirubin in the CRT dataset. Please explain what transpired with these patients including pertinent lab results, workup, and outcome.

c) There was a large percentage of patients lost to follow-up in some trials. Please explain this finding.

d) You will need to evaluate the lupus-like reactions observed with oxcarbazepine use and propose appropriate labeling.

e) There is a clear increase in edema and weight gain on oxcarbazepine. Please evaluate this issue and propose appropriate labeling. Are these events related to hyponatremia or the hypertensive AEs?

f) There seemed to be an increase in the number of patients with creatinine increases compared to placebo. Please summarize these patients and evaluate this issue.

g) In the primary database, there was a clear excess in AEs coded as hypertension. Please summarize patients having these events, specifically noting who were started on antihypertensive medications while they were receiving oxcarbazepine.

h) Please evaluate all patients in the NDA with skin reactions or sensitivity reactions for preceding carbamazepine use and propose labeling that describes the risk.

i) Conduct a risk assessment for serious rash, including the cases of SJS and TEN reported in the post-marketing experience.

j) Provide the rate of status for all treatment groups in the NDA.

k) You provided findings from analyses of the effects of oxcarbazepine on the QT interval for the 3 studies that used a central laboratory for reading the ECGs. There were 10 additional studies that also collected ECG data, but no analyses were presented for these studies. Please explain this approach. Why were these 3 studies selected for central reading? Were the ECG data in the other 10 studies also analyzed?

Pediatrics

We note your February 22, 1999 submission containing a proposed pediatric study request and

Chemistry, Manufacturing and Controls

1.

2. Please include one batch of the 300 mg strength tablets packaged in blisters in the post-approval stability commitment to cover all packaging configurations proposed for marketing.

Biopharmaceutics

1. Please provide a rationale for the proposed dissolution medium and the proposed dissolution specifications.

2. We have reviewed the individual dissolution data that was submitted on June 24, 1999 as well as dissolution data comparing profiles in different media

3.

Safety Update

Under 21 CFR 314.50(d)(5)(vi)(*b*), we request that you update your NDA by submitting all safety information you now have regarding your new drug. Please provide updated information as listed below. The update should cover all studies and uses of the drug including: (1) those involving indications not being sought in the present submission, (2) other dosage forms, and (3) other dose levels, etc.

1. Retabulation of all safety data including results of trials that were still ongoing at the time of NDA submission. The tabulation can take the same form as in your initial submission. Tables comparing adverse reactions at the time the NDA was submitted versus now will certainly facilitate review.

2. Retabulation of drop-outs with new drop-outs identified. Discuss, if appropriate.

3. Details of any significant changes or findings.

4. Summary of worldwide experience on the safety of this drug.

5. Case report forms for each patient who died during a clinical study or who did not complete a study because of an adverse event.

6. English translations of any approved foreign labeling not previously submitted.

7. Information suggesting a substantial difference in the rate of occurrence of common, but less serious, adverse events.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please send one copy to the Division of Neuropharmacological Drug Products and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-40
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Within 10 days after the date of this letter, you are required to amend the 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.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

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

Sincerely,

/S/ 9/24/98

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

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