CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 21-200

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-200

Novartis Pharmaceuticals Corporation
Attention: Donna Vivelo
Associate Director Regulatory Affairs
59 Route 10
East Hanover, NJ 07936-1080

Dear Ms. Vivelo:

Please refer to your new drug application (NDA) dated February 11, 2000, received February 11, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zelnorm™ (tegaserod maleate) Tablets.

We acknowledge receipt of your submissions dated February 28, June 11, 17, 18, 20, 24; July 01, 09, 12, 17, 18, 23 and, 2002. Your submission of February 28, 2002 constituted a complete response to our June 15, 2001 action letter.

This new drug application provides for the use of Zelnorm™ (tegaserod maleate) Tablets "for the short-term treatment of women with irritable bowel syndrome (IBS) whose primary bowel symptom is constipation. The safety and effectiveness of ZELNORM™ in men have not been established."

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.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert, text for the patient package insert, immediate container and carton labels). 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 the copies of final printed labeling (FPL) electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999). Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no 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 21-200." Approval of this submission by FDA is not required before the labeling is used.

We remind you of the telephone conferences held July 18, 2002, and July 23, 2002, in which you committed to submit reports of biliary tree-related adverse events and abdominal surgeries (including cholecystectomies), and pelvic surgeries as Postmarketing 15-Day Safety Reports according to the terms of 21 CFR 314.80. We agree to meet with you to reevaluate the need for these adverse event reports to be submitted as Postmarketing 15-Day Safety Reports after the Agency has had an opportunity to adequately assess the postmarketing safety profile of Zelnorm™.

We remind you of your postmarketing study commitments in your submission dated July 09, 2002. These commitments are listed below.

1. Commitment/Study Description: A randomized, double-blind, crossover, placebo-controlled study to assess the effects of tegaserod 6 mg b.i.d. on gallbladder motility and biliary tract diameter in healthy volunteers and of tegaserod 6 mg b.i.d. and tegaserod 12 mg b.i.d. on gallbladder motility and biliary tract diameter in female patients with IBS-C, as submitted February 28, 2002 (Gallbladder Mechanistic Study).

   Commitment Category: Clinical

   Protocol Submission (with amendment for 12 mg b.i.d. cohort): February 2002
   Study Start: Ongoing
   Final Report Submission: First Quarter 2003

2. Commitment/Study Description: Zelnorm™ Epidemiological Study, a prospective cohort postmarketing surveillance study, to evaluate the frequency of gallbladder surgeries and other abdominal and pelvic surgeries and procedures, as submitted February 28, 2002.

   Commitment Category: Clinical

   Protocol Submission: September 2002
   Study Start: Third Quarter 2002
   Final Report Submission: Third Quarter 2005

3. Commitment/Study Description: A randomized, double-blind, parallel group, placebo-controlled study to evaluate the intermittent and/or long-term efficacy of Zelnorm™.

   Commitment Category: Clinical

   Protocol Submission: October 2002
   Study Start: Second Quarter 2003
   Final Report Submission: First Quarter 2005

Submit clinical protocols to your IND for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and

314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments must be prominently labeled **"Postmarketing Study Protocol", "Postmarketing Study Final Report", or "Postmarketing Study Correspondence."**

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.

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 fulfilled the requirements of 21 CFR 314.55 (or 601.27). We are deferring submission of your pediatric studies until January 2, 2004. However, in the interim, please submit your pediatric drug development plans within 120 days from the 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 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.

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. 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.

(b)(4)

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 Gastrointestinal and Coagulation Drug Products and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Please submit one market package of the drug product when it is available.

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 Paul E. Levine, Jr., R.Ph., Regulatory Project Manager, at (301) 827-7310.

Sincerely,

{See appended electronic signature page}

Florence Houn, M.D., M.P.H., F.A.C.P.
Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

APPEARS THIS WAY
ON ORIGINAL

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

/s/

Florence Houn
7/24/02 09:42:12 AM

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 21-200

APPROVABLE LETTER

Levine

NDA 21-200

Novartis Pharmaceuticals Corporation
Attention: Donna Vivelo
Associate Director Regulatory Affairs
59 Route 10
East Hanover, NJ 07936-1080

AUG 11 2000

Dear Ms. Vivelo:

Please refer to your new drug application (NDA) dated February 11, 2000, received February 11, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for tegaserod hydrogen maleate tablets.

We acknowledge receipt of your submissions dated March 16, 22, 29, and 31; April 19; May 02, 04, 05, 17, 23, 24, 30, and 31; June 08, 09, 15, and 21; July 21; and August 3, 2000.

We also refer to your submission dated August 1, 2000. This submission has not been reviewed in our current review cycle. You may incorporate this submission by specific reference as part of your response to the deficiencies cited in this letter.

We have completed the review of this application, as amended, and it is approvable for the following indication: '[redacted]. The safety and effectiveness in men have not been established."

Before this application may be approved, however, it will be necessary for you to address concerns about the efficacy and safety of this drug, as follows:

1. Submit the results of a well-controlled, double-blind, randomized study of at least 300 persons per study arm and of at least 12 weeks duration. Assess drug efficacy in this study with the endpoints used in Study B301 entitled, "A randomized, double-blind, placebo-controlled, multicenter study to assess the safety and efficacy of SDZ HTF 919 at two dose levels and placebo in subjects with constipation-predominant irritable bowel syndrome."
2. Provide safety data from the study requested above and from any additional studies for which safety data has not been previously submitted.
3. Submit the results of a study of the $5HT_4$-receptor status of human appendix and non-gastrointestinal abdominal and pelvic organs compared to human intestinal samples.

Because final labeling will depend on the above studies for safety and efficacy, comments on your currently proposed draft label will be deferred until these data are received

Be advised that your proposed proprietary name, "Zelmac," is unacceptable. The use of this proprietary name, may lead to inaccurate interpretations due to the phonetic similarities between "Zelmac" and approved products (such as, Zomig, Zyrtec, and Zantac). We request that you submit a new proprietary name to the Agency for review prior to its implementation.

We remind you of the following Phase 4 commitments agreed to in your August 3, 2000, submission:

[

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Note that these commitments may be amended and/or additional Phase 4 commitments requested before the application is approved.

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.

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.

Under 21 CFR 314.102(d) of the new drug regulations, you may request an informal meeting or telephone conference with the Division of Gastrointestinal and Coagulation Drug Products to discuss what further steps need to be taken before the application may be approved.

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, call Paul E. Levine, Jr., R.Ph., Regulatory Health Project Manager, at (301) 827-7310.

Sincerely,

/S/

Florence Houn, M.D., M.P.H., F.A.C.P.
Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL