

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125290Orig1s000

OTHER ACTION LETTERS



Our STN: BL 125290/0

COMPLETE RESPONSE

Novartis Pharmaceuticals Corporation
Attention: Xin Du, Ph.D.
Sr. Associate Director, VP, Global Regulatory CMC
One Health Plaza
East Hanover, NJ 07936-1080

JUN 5 2009

Dear Dr. Du:

Please refer to your Biologics Licensing Application, dated May 6, 2008, received May 6, 2008, submitted under section 351 of the Public Health Service Act for Extavia (interferon beta 1-b) for the treatment of multiple sclerosis.

We acknowledge receipt of your amendments dated August 25, 2008, November 7 and 19, 2008, February 11, 13, and 23, 2009, March 23 and 30, 2009, April 10, 2009, and May 15 and 26, 2009.

We also acknowledge receipt of your amendment dated June 1, 2009, which was not reviewed for this action.

We have completed the review of your application, as amended, and have determined that we cannot approve this application in its present form. We have described below our reasons for this action and, where possible, our recommendations to address these issues.

LABELING

1. Submit draft labeling that incorporates revisions in the attached labeling. In addition, submit updated content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format as described at <http://www.fda.gov/oc/datacouncil/spl.html>.

When responding to this letter, submit labeling that includes all previous revisions, as reflected in the most recently approved package insert. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should include annotations with the supplement number for previously-approved labeling changes.

2. Please submit draft carton and container labeling revised as follows:

A. Extavia Vial Label (0.3 mg per vial)

1. Increase the prominence of the product strength (0.3 mg) by boxing, highlighting, using a different color, or some other means.
2. Add a statement regarding the total drug content per vial (e.g., 0.3 mg per vial) on the principal display panel.
3. Add a statement that the unused portion of Extavia should be discarded after use.
4. Add reconstitution instructions to the Extavia vial label if space permits.

B. Diluent Syringe Label

1. Each incremental dose marking on the syringe label should have an accompanying unit of measure (e.g., 0.25 mL, 0.5 mL, 0.75 mL, etc.) so that the reader is able to clearly identify the syringe marking to use for the proper dose.
2. Remove the trailing zero from the 1.0 mL marking on the syringe (use 1 mL instead) as trailing zeroes are error prone and can result in a ten fold overdose if misread.
3. Add a statement to the syringe label regarding the correct amount of diluent to use (1.2 mL).

C. Blister Package Label

1. Increase the prominence of the product strength (0.3 mg) by boxing, highlighting, using a different color, or some other means.
2. Add a statement regarding the total drug content per vial (e.g., 0.3 mg per vial) on the principal display panel.
3. Add a statement that the unused portion of Extavia should be discarded after use, and if not immediately used, it should be kept no longer than 3 hours if properly refrigerated.
4. The contents description should be updated to clearly and more completely identify the contents of the blister pack.
 - a. Include the amount of diluent contained in the syringe (1.2 mL).
 - b. State that the 'single ^{(b) (4)} vial for reconstitution' contains Extavia.

D. Carton Labeling

1. Increase the prominence of the product strength (0.3 mg) by boxing, highlighting, using a different color, or some other means.
2. Add a statement regarding the total drug content per vial (e.g., 0.3 mg per vial) on the principal display panel.
3. Add a statement that the unused portion of Extavia should be discarded after use and if not immediately used, it should be kept no longer than 3 hours if properly refrigerated.

4. The contents description should be updated to clearly and more completely identify the contents of the blister pack.
 - a. Include the amount of diluent contained in the syringe (1.2 mL).
 - b. State that the 'single (b) (4) vial for reconstitution' contains Extavia.
5. Delete the three bullets conveying (b) (4) (b) (4) (b) (4) because all three bullets contain information that is conveyed more prominently elsewhere on the principal display panel. We make this recommendation to decrease the redundancy of this information and improve readability on the principal display panel.
6. Consider relocating the net contents statement [15 single (b) (4) blister packs] to the space vacated by the three bullets to increase the prominence and readability of the net contents of the carton.
7. Although your labels and labeling contain the required statement to provide the Medication Guide with the product, we recommend the following language dependent upon whether the Medication Guide accompanies the product or is enclosed in the carton (for example, unit of use):
 - a. "Dispense the enclosed Medication Guide to each patient." or
 - b. "Dispense the accompanying Medication Guide to each patient."

E. Prescribing Information

1. Remove the trailing zeroes throughout the labeling (e.g., 0.50 mL and 1.0 mL) as trailing zeroes are error prone and can result in a ten fold overdose. Use '0.5 mL' and '1 mL' instead.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update. The safety update should include data from all nonclinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.
2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:
 - Present new safety data from the studies for the proposed indication using the same format as the initial submission.
 - Present tabulations of the new safety data combined with the initial data.
 - Include tables that compare frequencies of adverse events in the initial data with the retabulated frequencies described in the bullet above.
 - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.
4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.
5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the initial data.
6. Provide updated exposure information for the clinical trials (e.g., number of subjects, person time).
7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.
8. Provide English translations of current approved foreign labeling not previously submitted.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

We refer to our May 29, 2009 letter, requiring a Risk Evaluation and Mitigation Strategy (REMS) under section 505-1 of the Federal Food, Drug, and Cosmetic Act.

We note that your June 1, 2009 amendment contained a response to our May 29, 2009 letter; as noted above, this amendment was not reviewed for this action. Your application cannot be approved without an approved REMS in place. You must include your proposed REMS as part of your response to the deficiencies cited in this letter. The REMS, once approved, will create enforceable obligations.

Within one year after the date of this letter, you are required to resubmit or withdraw the application. If you do not take any of these actions, we will consider your lack of response a request to withdraw the application under 21 CFR 601.3(c). A resubmission must fully address all the deficiencies listed, and will start a new review cycle. A partial response to this letter may not be reviewed and will not start a new review cycle.

You may request a meeting or teleconference with us to discuss what steps you need to take before the application can be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA Guidance for Industry on *Formal Meetings With Sponsors and Applicants for PDUFA Products*, February, 2000 (<http://www.fda.gov/cder/guidance/2125fn1.htm>).

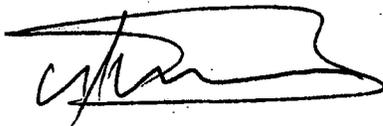
Please refer to <http://www.fda.gov/cder/biologics/default.htm> for information regarding therapeutic biological products, including the addresses for submissions.

If you have any questions, call James H. Reese, PhD, RAC, Regulatory Project Manager, at (301) 796-1136.

Sincerely,



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



Eric Bastings, M.D.
Deputy Director
Division of Neurology Products
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Enclosure