

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**125290**

**RISK ASSESSMENT and RISK MITIGATION  
REVIEW(S)**



**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology**

Date: July 9, 2009

To: Russell Katz, MD, Division Director  
**Division of Neurology Products (DNP)**

Through: Claudia Karwoski, PharmD, Director *Claudia B Karwoski*  
**Division of Risk Management (DRISK)**

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Subject: DRISK Review of Proposed Risk Evaluation and Mitigation Strategy (REMS)

Drug Name(s): EXTAVIA (interferon beta 1-b)

Application Type/Number: BLA 125290

Applicant/sponsor: Novartis Pharmaceuticals Corporation

OSE RCM #: 2008-1735

## 1 INTRODUCTION

This memorandum is in response to a request by the Division of Neurology Products (DNP) for the Division of Risk Management (DRISK) to review the proposed Risk Evaluation and Mitigation Strategy (REMS) for Extavia (interferon beta 1-b). Please send these comments to the Applicant and request a response within two weeks of receipt. Let us know if you would like a meeting to discuss these comments before sending to the Applicant. DRISK's review of the Medication Guide was sent to DNP under separate cover dated May 20, 2009.

## 2 MATERIAL REVIEWED

- EXTAVIA (interferon beta 1-b) Risk Evaluation and Mitigation Strategy (REMS) Notification Letter dated May 29, 2009.
- Proposed EXTAVIA (interferon beta 1-b) Risk Evaluation and Mitigation Strategy (REMS), dated May 29, 2009, submitted June 12, 2009.

## 3 CONCLUSIONS AND RECOMMENDATIONS

DRISK concurs with the elements of the REMS.

We have the following comments and recommendations for the Applicant with regard to the proposed REMS.

### **Comments to Novartis Pharmaceuticals Corporation:**

a. Revise the goal as follows:

The goal of this REMS is to inform patients about the serious risks with the use of Extavia.

- b. The Medication Guide distribution plan is generally acceptable. We have some editorial comments in this section of the proposed REMS.
- c. See the appended EXTAVIA REMS proposal (Appendix A) for track changes corresponding to comments in this review.
- d. The proposed timetable for submission of assessments (18 months, 3 years, and 7 years) is acceptable.
- You should specify the reporting interval (dates) that each assessment will cover and the planned date of submission to the FDA of the assessment. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. For example, the reporting interval covered by an assessment that is to be submitted by July 31st should conclude no earlier than June 1st.
- e. Regarding your proposal to conduct surveys to assess patients understanding of important messages contained in the Extavia Medication Guide:

- Do not send the Medication Guide to selected respondents. Re-educating the selected respondents by providing the Medication Guide biases the survey and will not allow for an adequate evaluation of the effectiveness of the REMS. The REMS should be evaluated based on the normal educational process of patients who take Extavia. The evaluation should assess if patients: received the Medication Guide when they filled their prescription, read the Medication Guide and can demonstrate that they understand the risks associated with Extavia.
- Prior to the Medication Guide questions provide a verbal description of the Medication Guide and how it differs from other printed information they may have received when they filled their prescription
- Submit for review the letter sent to respondents telling them about the survey
- Provide an estimated sample size
- Given that every patient who takes Extavia is eligible for the survey and given that this REMS does not have a restricted distribution or mandatory enrollment, clarify how TheraCom Inc can provide contact information for every patient.
- Clarify if respondents who complete the survey will be able to participate in future surveys
- Reword question #1 to read, "Have you taken Extavia during the last two months?"
- Remove questions #2, #2a, #2b and #10
- Reword question #4 to read "Again, thinking back to the last time you obtained a new or refilled prescription for Extavia, did you receive a copy of the Medication Guide?"
- Add questions about who provided the Medication Guide to the patient. For example:
  - Who gave you the Medication Guide for Extavia?
    - a) My doctor or someone in my doctor's office
    - b) My pharmacist or someone at the pharmacy
    - c) I did not get a Medication Guide
  - Did your healthcare provider offer to explain to you the information in the Medication Guide?
    - a) Yes
    - b) No

- c) I did not receive the Medication Guide
- Did you accept the offer? Yes or No
- Did you understand the explanation that was given to you?
  - a) All
  - b) Most
  - c) Some
  - d) None
- Did or do you have any question about the Medication Guide? Yes or No (If Yes, list your question below) Note: This is an open text field that should be grouped/coded by the sponsor prior to submitting to FDA
- Reword question #8 to read “While taking Extavia, if you feel noticeably sadder or helpless or feel like hurting yourself, you should (select all that apply):”; add an answer choice of “I don’t know”
- Reword question #9 to read “While taking Extavia, if you become pregnant you should (select all that apply):”; add an answer choice of “I don’t know”
- Add questions about the symptoms of allergic reactions and when they can occur. For example:
  - Which of the followings are signs of an allergic reaction? Select all that apply
    - a) Trouble breathing and swallowing
    - b) Rash
    - c) Headaches
    - d) Skin bumps
    - e) Blurry vision
    - f) I don’t know
  - An allergic reaction to Extavia will only happen with the first dose. True/False/I don’t know
- Reword question #11 to read “While taking Extavia, if you develop an allergic reaction such as a rash, itching, skin bumps, you should (select all that apply):”; add an answer choice of “I don’t know”
- Reword question #12. For example:

- Some signs of injection sites problems with Extavia are (select all that apply):
  - a) Redness
  - b) Pain
  - c) Swelling at the place where an injection was given
  - d) Fluid draining from it
  - e) I don't know
- Reword question #13. For example:
  - Extavia may cause which of the following (select all that apply):
    - a) Allergic reactions
    - b) Blindness
    - c) Thoughts of killing yourself
    - d) Headaches
    - e) Lose your baby (miscarry) or harm to your unborn child
    - f) Redness, pain or swelling at the injection site
    - g) I don't know
- Submit a revised methodology and survey instrument 90 days prior to implementation.

Please let us know if you have any questions.

3 pp withheld immediately after this page as (b)(4) draft labeling.

**Risk Evaluation and Mitigation Strategy (REMS) Memorandum**

**U.S. FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH  
Office of New Drugs  
Division of Neurology Products**

**NDA/BLA #s:** 125290  
**Products:** Extavia, Interferon beta 1-b, Subcutaneous Injection  
**SPONSOR:** Novartis  
**FROM:** Robert Temple, MD  
Office Director  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research  
**DATE:** 5/20/09

Title IX, Subtitle A, Section 901 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) amends the Federal Food, Drug, and Cosmetic Act (FDCA) to authorize FDA to require the submission of a REMS if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)). Section 505-1(a)(1) provides the following factors:

- (A) The estimated size of the population likely to use the drug involved;
- (B) The seriousness of the disease or condition that is to be treated with the drug;
- (C) The expected benefit of the drug with respect to such disease or condition;
- (D) The expected or actual duration of treatment with the drug;
- (E) The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug;
- (F) Whether the drug is a new molecular entity (NME).

After consultations between the Office of New Drugs and the Office of Surveillance and Epidemiology, we have determined that a REMS is necessary for Extavia (interferon beta 1-b) to ensure that the benefits of the drug outweigh the risks of potential complications after subcutaneous injection. In reaching this determination, we considered the following:

- A. Extavia (interferon beta 1-b) is indicated for multiple sclerosis. The estimated number of patients in the United States with multiple sclerosis is between 250,000 and 500,000. This estimate is based on figures from the National Multiple Sclerosis Society and the National Institute of Neurological Disorders and Stroke.
- B. Relapsing multiple sclerosis is characterized by repeated episodes of often progressive neurologic disability associated with multiple sclerosis plaque formation in the CNS.

- C. No clinical trials were submitted to BLA 125290. The sponsor relied, instead, on the right of cross-reference of Extavia (Novartis) to Betaseron (Bayer). It is to have the identical qualitative and quantitative composition as Betaseron of active substance and is to be manufactured in an identical fashion with identical materials. Betaseron has been shown to reduce the frequency of clinical exacerbations in patients with relapsing forms of multiple sclerosis.
- D. Extavia (interferon beta 1-b) is dosed as a single subcutaneous injection every other day and is expected to be used chronically.
- E. A review of the Betaseron label submitted by the sponsor (which will serve as the model for the Extavia (interferon beta 1-b) label) reveals numerous adverse events both during development and in the post-marketing period. These include leucopenia, lymphopenia, injection site inflammation (occasionally associated with site necrosis, mass, and edema), and flu-like symptoms occurring in 60% or more of patients during the clinical trials. More serious complications such as depression and suicide have occurred and, rarely, anaphylaxis has occurred. Patients require regular, ongoing monitoring of WBC counts, platelet counts, blood chemistries (including LFTs), and thyroid function while on therapy. Post-marketing adverse events are largely similar to those occurring in development, although a fatal case of capillary leak syndrome occurred, apparently in a patient who received this cytokine despite having a pre-existing monoclonal gammopathy.
- F. Extavia (interferon beta 1-b) is not a new molecular entity.

In accordance with section 505-1 of FDCA and under 21 CFR 208, FDA has determined that a Medication Guide is required for Extavia (interferon beta 1-b). FDA has determined that Extavia (interferon beta 1-b) poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of Extavia (interferon beta 1-b). FDA has determined that Extavia (interferon beta 1-b) is a product for which patient labeling could help prevent serious adverse effects, that it has serious risk(s) (relative to benefits) of which patients should be made aware because information concerning the risk(s) could affect patients' decisions to use, or continue to use, Extavia (interferon beta 1-b), and that the Medication Guide is important to health and patient adherence to directions for use is crucial to the drug's effectiveness.

The elements of the REMS will be a Medication Guide and a timetable for submission of assessments of the REMS.