

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**125290**

**OTHER 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 16, 2009

To:

Russell Katz, M.D., Director  
Division of Neurology Products

Through:

Carol Holquist, RPh, Director *C Holquist 7/16/09*  
Division of Medication Error Prevention and Analysis

From:

Laura Pincock, PharmD, Acting Team Leader *LP 7/16/09*  
Division of Medication Error Prevention and Analysis

Subject:

Label and Labeling Review

Drug Name(s):

Extavia (Interferon beta-1b) Lyophilized Powder for Injection  
0.3 mg per vial

Application Type/Number:

BLA STN 125290

Applicant:

Novartis Pharmaceuticals Corporation

OSE RCM #:

2009-1288

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## **1 INTRODUCTION**

This review was written in response to the receipt of revised labels and labeling for Extavia submitted on June 12, 2009. These revisions were made based on previous comments from DMEPA in OSE Review # 2007-1814 dated June 4, 2009.

## **2 MATERIAL REVIEWED**

DMEPA reviewed our labeling review for Extavia signed on June 4, 2009 (OSE Review# 2007-1814). See Appendices A through D for images of the labels and labeling.

- Extavia vial label: 0.3 mg
- Sodium Chloride 0.54% solution syringe label: 1.2 mL (Diluent)
- Blister package overwrap label
- Carton labeling: 15 count (single use blister packages)

## **3 DISCUSSION**

DMEPA reviewed the Applicant's labels and labeling which were revised according to our previous recommendations. They have addressed all of our concerns, with the exception of the request to add a statement to the diluent syringe label describing the correct amount of diluent to add (1.2 mL) to the drug vial. Ideally such a statement should be added to the syringe label, however, because the entire contents of the syringe are used (1.2 mL), and the amount of diluent for reconstitution is stated on the blister package overwrap label, we find the revised labels and labeling acceptable.

## **4 CONCLUSION**

The Applicant has satisfactorily revised the labels and labeling per our proposed recommendations in the June 4, 2009 DMEPA review.

If you have questions or need clarifications, please contact Laurie Kelley, OSE Project Manager, at (301) 796-5068.

**APPENDICES**

**Appendix A: Extavia Vial Label: 0.3 mg**



**Appendix B: Sodium Chloride 0.54% Solution Syringe Label: 1.2 mL (Diluent)**



**Appendix C: Blister Package Label: 0.3 mg**

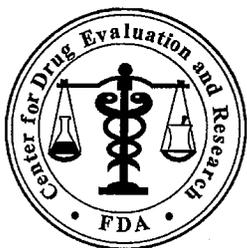


(b) (4)

**Appendix D: Carton Labeling: Contains 15 single use Blister Packages**

(b) (4)





**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 15, 2009

To: Russell Katz, M.D., Division Director  
**Division of Neurology Products (DNP)**

Through: Jodi Duckhorn, M.A., Team Leader *Jodi Duckhorn 7/15/2009*  
**Division of Risk Management (DRISK)**

From: Sharon R. Mills, BSN, RN, CCRP *Sharon R. Mills 7/15/2009*  
Patient Product Information Reviewer  
**Division of Risk Management (DRISK)**

Subject: DRISK Review of Patient Labeling (Medication Guide and Patient Instructions for Use; Review # 2)

Drug Name(s): Extavia (Interferon beta-1b)

Application Type/Number: BLA125290

Applicant/sponsor: Novartis Pharmaceuticals

OSE RCM #: 2008-1735

## 1 INTRODUCTION

This review is written in response to a request from the Division of Neurology Products (DNP) for the Division of Risk Management (DRISK) to review the Applicant's revised proposed Medication Guide (MG) and Patient Instructions for Use (IFU), submitted on June 15, 2009 as part of a Complete Response to a Complete Response action taken by DNP on June 5, 2009.

DRISK previously provided a detailed review of the Applicant's proposed MG and IFU on May 20, 2009. This review focuses only on the changes identified in the Professional Information, MG, and IFU.

## 2 MATERIAL REVIEWED

- Draft EXTAVIA Medication Guide (MG) and Patient Instructions for Use (IFU) submitted June 15, 2009
- Draft EXTAVIA Prescribing Information (PI) submitted June 15, 2009

## 3 DISCUSSION

The purpose of patient directed labeling is to facilitate and enhance appropriate use and provide important risk information about medications. Our recommended changes are consistent with current research to improve risk communication to a broad audience, including those with lower literacy.

Content and formatting revisions are made to ensure that the information is legible, clear, and patient-friendly. Patient Information that is well designed and clearly worded can help to maximize patient use and understanding of important safety information that is presented.

See the attached document for our recommended revisions to the MG and IFU. Comments to the review division are ***bolded, underlined and italicized***.

We are providing the review division a marked-up and clean copy of the revised MG and IFU.

All future relevant changes to the PI should also be reflected in the MG.

## 4 CONCLUSIONS AND RECOMMENDATIONS

**We have the following comments regarding the Medication Guide:**

1. In the section "What is the most important information I should know about Extavia?" the applicant revised language under "Injection site problems"

From: [REDACTED] (b) (4)

To: Although most skin reactions are not serious, you may need medical treatment if you develop a serious skin reaction.

We recommend revising this to state: “Most skin reactions are not serious, but you may need medical treatment if you develop a serious skin reaction.”

DNP should consider whether language about scarring should be added back to the MG since it is mentioned in PI section 5.2 as being associated with healing in most cases. We also recommend that DNP gain input from DDMAC on this.

2. In the section “How should I take Extavia?” in the second bullet, the applicant uses the word “instruct.” The word “instruct” implies verbal explanation about how to do something. Patients should be “shown” how to prepare and give the injection, and preferably demonstrate (return demonstration) that they can do so before being allowed to self-inject at home.
3. In the section “General information about Extavia?” the applicant should add their website information (if available) and toll-free number for patients to call for more information.

**We have the following comments on the Patient Instructions for Use:**

(b) (4)

Please let us know if you have any questions.

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

Cc List:

DNP:

Russell Katz

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**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: June 4, 2009

To: Russell Katz, M.D., Director  
Division of Neurology Products

Through: Denise Toyer, PharmD, Deputy Director  
Carol Holquist, RPh, Director *Carol Holquist 6/4/09*  
Division of Medication Error Prevention and Analysis

From: Laura Pincock, PharmD, Acting Team Leader *Laura Pincock 6/4/09*  
Division of Medication Error Prevention and Analysis

Subject: Label and Labeling Review

Drug Name(s): Extavia (Interferon beta-1b) Lyophilized Powder for Injection  
0.3 mg per vial

Application Type/Number: BLA STN 125290/0/0

Applicant: Novartis Pharmaceuticals Corporation

OSE RCM #: 2007-1814

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## **EXECUTIVE SUMMARY**

The Label and Labeling Risk Assessment findings indicate that the presentation of information and design of the proposed blister and container labels and carton labeling introduces vulnerability to confusion that could lead to medication errors. Specifically, we noted the use of trailing zeroes and an error prone abbreviation. Additionally, we recommended improvements to increase the prominence, consistency, and clarity of important information on the Extavia labels and labeling. These risks can be addressed and mitigated prior to drug approval. We provide recommendations in Section 5.2.

## **1 BACKGROUND**

### **1.1 INTRODUCTION**

This review is in response to a request from the Division of Neurology Products for assessment of the container label, carton, and insert labeling to identify areas that could lead to medication errors.

The proposed proprietary name, Extavia, was previously reviewed by DMEPA (OSE Consult # 2007-1814, dated November 21, 2008) without objection.

Interferon beta-1b [Betaseron (USA)/Betaferon (Europe)] was co-developed by both Chiron and Schering. Chiron held the US license for Betaseron (BLA 103471 approved by FDA on July 23, 1993) and Schering marketed it overseas as Betaferon. Subsequently, Bayer acquired Schering and Novartis acquired Chiron. As part of the subsequent co-development and legal agreement thereafter, Bayer now owns the Betaseron license and Novartis has now submitted their own new BLA, the BLA for this product.

### **1.2 PRODUCT INFORMATION**

Extavia is the proposed proprietary name for Interferon beta-1b. Extavia is intended for the treatment of relapsing forms of multiple sclerosis to reduce the frequencies of clinical exacerbations. Extavia is proposed to be marketed as a lyophilized powder for injection containing 0.3 mg of Interferon beta-1b, 15 mg Albumin (Human), USP, and 15 mg Mannitol, USP, in a single-use vial. A pre-filled syringe containing 1.2 mL of diluent (Sodium Chloride, 0.54% solution), two alcohol prep pads, and one vial adapter with attached 27 gauge needle are included for each vial of drug. The lyophilized powder and the diluent are for single use only and the unused portions should be discarded. Extavia should be stored at room temperature. After reconstitution, if the injection is not used immediately, it may be stored in the refrigerator for up to 3 hours. Any unused portions should be discarded.

The recommended treatment dose is 0.25 mg (1 mL reconstituted) injected subcutaneously every other day. Generally, patients should be started at 0.0625 mg (0.25 mL reconstituted) subcutaneously every other day, and increased over a six week period to 0.25 mg every other day. The full prescribing information contains the following schedule for dose titration:

	Recommended Titration	EXTAVIA Dose	Dose Volume
Weeks 1-2	25%	0.0625 mg	0.25 mL
Weeks 3-4	50%	0.125 mg	0.5 mL
Weeks 5-6	75%	0.1875 mg	0.75 mL
Weeks 7+	100%	0.25 mg	1 mL

To reconstitute Extavia, the pre-filled syringe containing the diluent should be attached to the Extavia vial using the vial adapter. 1.2 mL of diluent is slowly injected into the Extavia vial. The vial is gently swirled to dissolve the drug completely; it should not be shaken. Foaming may occur during reconstitution or if the vial is swirled or shaken too vigorously. If foaming occurs, the vial should sit undisturbed until the foaming settles. Keeping the syringe and vial adapter in place, the assembly should be turned over so the vial is on top. The appropriate dose of Extavia solution should be withdrawn. The vial should be removed from the vial adapter before injecting Extavia. Extavia is intended for use under the guidance and supervision of a physician. It is recommended that physicians or qualified medical personnel train patients in the proper technique for self-administering subcutaneous injections. Patients should be advised to rotate sites for subcutaneous injections. Extavia should be visually inspected for particulate matter and discoloration prior to injection.

## 2 METHODS AND MATERIALS

This section describes the methods and materials used by DMEPA staff to conduct a label, labeling, and/or packaging risk assessment (see 2.1 Container Label, Carton and Insert Labeling Risk Assessment). The primary focus of the assessments is to identify and remedy potential sources of medication error prior to drug approval. The Division of Medication Error Prevention and Analysis defines a medication error as any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer.<sup>1</sup>

### 2.1 AERS SELECTION OF MEDICATION ERROR CASES

Extavia will be another marketed brand of Interferon beta-1b. Interferon beta-1b is currently marketed as Betaseron. Any medication errors that are occurring with Betaseron may be indicative of medication errors that may occur with Extavia once the product is approved. Therefore, DMEPA performed a search of the FDA AERS database for medication errors involving the labels and labeling of Betaseron.

The MedRA High Level Group Term (HLGT) “Medication Errors” and Preferred Term (PT) “Pharmaceutical product complaint” were used as search criteria for Reactions. The

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<sup>1</sup> National Coordinating Council for Medication Error Reporting and Prevention. <http://www.nccmerp.org/about/MedErrors.html>. Last accessed 10/11/2007.

search criteria used for Products were active ingredient “Interferon be%”, trade name “Betas%” and verbatim substance search “Betas%”.

## **2.2 CONTAINER LABEL AND CARTON LABELING**

The label and labeling of a drug product are the primary means by which practitioners and patients (depending on configuration) interact with the pharmaceutical product. The carton labeling and container label communicate critical information including proprietary and established name, strength, dosage form, container quantity, expiration, and so on. The insert labeling is intended to communicate to practitioners all information relevant to the approved uses of the drug, including the correct dosing and administration.

Given the critical role that the label and labeling has in the safe use of drug products, it is not surprising that 33 percent of medication errors reported to the USP-ISMP Medication Error Reporting Program may be attributed to the packaging and labeling of drug products, including 30 percent of fatal errors.<sup>2</sup>

Because the Division of Medication Error Prevention and Analysis staff analyze reported misuse of drugs, we are able to use this experience to identify potential errors with all medication similarly packaged, labeled or prescribed. The DMEPA staff uses Failure Mode and Effects Analysis (FMEA) and the principles of human factors to identify potential sources of error with the proposed product labels and insert labeling, and provided recommendations that aim at reducing the risk of medication errors.

For this product the Applicant submitted blister container and carton labeling on February 2, 2009 for review (see Appendices A-D):

- Extavia vial label: 0.3 mg
- Sodium Chloride 0.54% solution syringe label: 1.2 mL (Diluent)
- Blister package overwrap label
- Carton labeling: 15 count (single use blister packages)
- Prescribing Information and Medication Guide (no images)

## **3 RESULTS AND DISCUSSION**

DMEPA notes that the proposed container labels, carton and insert labeling for Extavia are similar to the labels and labeling for the currently approved and marketed product Betaseron. Therefore, as part of the label and labeling review we conducted a search of the FDA AERS database for the product Betaseron to determine if there were any problem areas with Betaseron that may be applicable to this review.

The AERS search performed on May 21, 2009, yielded 156 reports. After identifying duplicate reports and reports that did not contain a medication error relevant to this review, only one case remained. The remaining case (ISR 3881273-0 dated March 11, 2002) involved a home health agency nurse who administered 1 mL (0.25 mg) of Betaseron instead of the proper initiation dose of 0.25 mL (0.0625 mg). The reason for the error was not provided. The patient experienced uncontrollable shakes, fever, and headache, and later on that day, tingling in the extremities and inability to move his legs.

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<sup>2</sup> Institute of Medicine. Preventing Medication Errors. The National Academies Press: Washington DC. 2006. p275.

The case was reported by the patient's mother and no outcome was provided. Therefore, the AERS search identified one issue with the currently marketed Betaseron product that has relevance to this product review (see Section 3.2).

Additionally, our analysis of the container labels and carton labeling noted several areas of needed improvement. They are as follows:

### 3.1 GENERAL COMMENTS

- 3.1.1 The prominence of the product strength (0.3 mg) is lacking on the Extavia vial label, blister label, and carton labeling. In general, the proprietary name, established name, and the product strength should be the most prominently communicated information displayed on the principal display panel so that the reader can clearly identify the contents. It is important for the reader to clearly identify the product strength to ensure they have the proper drug and strength of the drug for preparation and administration of the proper dose.
- 3.1.2 The total drug content per vial (e.g., 0.3 mg per vial) is not stated on the Extavia vial label, blister label, and carton labeling. It is important for the total drug content to be stated to decrease the potential for misinterpretation when the drug is being reconstituted and prepared for administration.
- 3.1.3 The abbreviation 'SC' for subcutaneous is used throughout the Extavia labels and labeling. DMEPA recommends against using abbreviations in FDA approved labels and labeling. When included in approved labeling, health care practitioners carry these abbreviations over to the prescribing world which may lead to errors. Abbreviations may not be commonly understood or may be misinterpreted when not written legibly. Additionally, the abbreviation 'SC' is included on ISMP's List of Error-Prone Abbreviations, Symbols, and Dose Designations<sup>3</sup> which states they should never be used when communicating medical information. To discourage the overall use of these abbreviations by healthcare practitioners, such abbreviations should not be used in labels and labeling approved by FDA. Thus the term 'subcutaneous' should be spelled-out rather than abbreviated.
- 3.1.4 We note that trailing zeroes are used in the prescribing information (e.g., 0.50 mL, 1.0 mL) and on the diluent syringe label (e.g, 1.0 mL). DMEPA recommends against using trailing zeroes after the decimal point (e.g., do not use 1.0 mL, use '1 mL' instead) in labels and labeling especially when associated with dosing recommendations. When included in approved labeling, health care practitioners carry this practice over to the prescribing world which may lead to errors. If the reader misses the decimal point, and reads the dose as 10 mL, a ten fold drug overdose can result. Although a 10 mL dose is not likely to be administered with this particular product, the use of trailing zeroes is an unsafe practice so we consistently discourage their use. Furthermore, use of trailing zeroes is included on ISMP's List of Error-Prone Abbreviations, Symbols, and Dose Designations<sup>4</sup> which states they should never be used when communicating medical information. As a result, they should not be used in FDA approved labels and labeling.

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<sup>3</sup> <http://www.ismp.org/Tools/errorproneabbreviations.pdf>, accessed 15APR2009.

<sup>4</sup> <http://www.ismp.org/Tools/errorproneabbreviations.pdf>, accessed 15APR2009.

3.1.5 The Extavia vial label, blister package label, and carton labeling lack the statement that “unused portions should be discarded”. This information is important to the person preparing and administering the dose, and may discourage patient or provider attempts to save reconstituted portions for later doses in an attempt to save money.

### **3.2 DILUENT SYRINGE LABEL**

We note that each incremental number marking on the syringe (except for 1 mL) lacks the measuring unit (mL). It is important for the user to determine that these markings represent the dose increments in milliliters rather than the milligram dose. This is especially important because there is a numerical overlap with two of the doses; 0.0625 mg has a volume of **0.25 mL**, whereas the **0.25 mg** dose has a volume of 1 mL. Confusion between the markings can result in the administration of the wrong dose. Although we cannot determine actual causality of the single medication error with Betaseron that we found in AERS (0.25 mg [1 mL] administered instead of 0.0625 mg [0.25 mL]), it could have been caused by misleading markings on the syringe. To reduce the potential for a user to misinterpret these markings and administer the wrong dose, each marking on the syringe should also convey the proper unit of measure (mL).

Additionally, a statement describing how much diluent to use should be included on the syringe to aid the person preparing the dose. It is important the correct volume of diluent is used otherwise the product will not be reconstituted properly and the patient will not receive an accurate dose.

### **3.3 BLISTER PACKAGE LABEL**

The contents description on the blister package label can be improved to more clearly identify the contents. As currently drafted, the contents description does not convey the amount of diluent contained in the syringe (1.2 mL). The contents description also does not state that the single use vial for reconstitution contains Extavia. It is important that the reader can clearly identify the contents of the blister package when preparing to reconstitute and administer the dose. In the event that the blister label is removed and the contents are incomplete or separated before the reader begins to prepare the dose, a complete contents description can ensure that the proper items are gathered and used for the dose.

### **3.4 CARTON LABELING**

As previously described in section 4.3, the contents description does not convey the amount of diluent contained in the package (1.2 mL) nor does it state that the single use vial contains Extavia. If the description is lacking and the contents are incomplete or separated before use, the reader may misinterpret or improvise the components during preparation which may result in a medication error.

Some of the important information is stated twice and is redundant on the principal display panel resulting in a crowded display of information. The three bullets conveying the product strength [0.3 mg (9.6 million IU)], the net contents [15 single use blister packs], and the route of administration [subcutaneous use] all contain information that is conveyed more prominently elsewhere on the principal display panel. To decrease the redundancy of this information and improve readability, DMEPA recommends removing

these three bullets. DMEPA also recommends that the net contents of the carton (15 single use blister pack) above the Medication Guide statement be relocated to the area vacated by the three bullets to improve the prominence and readability of the net contents of the carton.

Finally, we acknowledge the Applicant's inclusion of the statement for provision of a Medication Guide (i.e., 'Medication Guide for patients enclosed') However, we believe the statements should be revised to language that is more consistent with medication guide statements on other products' labels and labeling. See section 5 for our recommended wording.

### **3.5 MEDICATION GUIDE**

The vial contents should be stated accurately and with a consistent unit of measure for the strength (e.g, 0.3 mg) and not (b) (4). Using a different strength and different unit of measure in the Medication Guide is confusing to the reader who is accustomed to doses stated in milligrams and the vial contents as 0.3 mg in the remainder of the labels and labeling. Using a different strength and unit of measure in the Medication Guide may cause the reader to attempt unnecessary and incorrect dose calculations or conversions and may result in the administration of an incorrect dose.

The term (b) (4) is used in the Medication Guide rather than the term 'diluent' as stated in the full prescribing information which is inconsistent. Additionally, the full name of the diluent and the net quantity of diluent in the syringe (e.g., Sodium Chloride 0.54% Solution 1.2 mL Diluent) should be stated rather than (b) (4). For consistency and clarity, the same terminology and the complete name of the diluent should be used in all labels and labeling for Extavia.

A figure or graphic of a subcutaneous injection (e.g., pinched injection site showing needle inserted at 90° angle) would be helpful to health care providers who are instructing their patient on how to self-administer Extavia. A graphic would help patients ensure proper subcutaneous injection technique is utilized upon self-administration at home.

Finally, the Medication Guide lacks clear storage and stability instructions for reconstituted Extavia. The prescribing information (in section 16) states "after reconstitution, if not used immediately, the product should be refrigerated and used within three hours" and that "unused portions should be discarded". This information is also important to Patients who self-administer and should be included in the Medication Guide. Including this information in the Medication Guide will inform patients and may discourage patient attempts to save reconstituted portions for later doses in an attempt to save money. If a patient saves the unused portion of a dose and administers it at another time, adverse events can result.

## **4 CONCLUSIONS AND RECOMMENDATIONS**

The Label and Labeling Risk Assessment findings indicate that the information presented lacks prominence, is misleading and may introduce vulnerability to confusion that could lead to medication errors. Specifically, we noted the use of an error prone abbreviation and trailing zeroes. Additionally, we have recommended improvements to increase the prominence, consistency, and clarity of important information on the Extavia labels and labeling. The risks we have identified can be addressed and mitigated prior to drug

approval. We provide recommendations in Section 5.2 that aim at reducing the risk of medication errors.

#### **4.1 COMMENTS TO THE DIVISION**

We would be willing to meet with the Division for further discussion, if needed. Please copy or include DMEPA on any communication to the Applicant with regard to this review. If you have any questions or need clarification, contact Daniel Brounstein, OSE Project Manager, at 301-796-0674.

#### **4.2 COMMENTS TO THE APPLICANT**

Based upon our FMEA of the labels and labeling, DMEPA identified several areas of needed improvement. We request you revise your labels and labeling 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. Avoid the use of the abbreviation 'SC' to decrease the potential for misinterpretation and confusion. The abbreviation should be removed and the term 'subcutaneous' should be spelled out in all labels and labeling.
4. Add a statement that the unused portion of Extavia should be discarded after use.
5. 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. Avoid the use of the abbreviation 'SC' to decrease the potential for misinterpretation and confusion. The abbreviation should be removed and the term 'subcutaneous' should be spelled out in all labels and labeling.

4. 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.
5. 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 use 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. Avoid the use of the abbreviation ‘SC’ to decrease the potential for misinterpretation and confusion. The abbreviation should be removed and the term ‘subcutaneous’ should be spelled out in all labels and labeling.
5. 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 use vial for reconstitution’ contains Extavia.
6. Delete the three bullets conveying the product strength [0.3 mg (9.6 million IU)], the net contents [15 single use blister packs], and the route of administration [subcutaneous use] 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.
7. Consider relocating the net contents statement [15 single use blister packs] to the space vacated by the three bullets to increase the prominence and readability of the net contents of the carton.
8. 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.”
9. Sufficient numbers of Medication Guides should be provided with the product such that a dispenser can provide one Medication Guide with each new or refilled prescription. We recommend that each packaging configuration

contain enough Medication Guides so that one is provided for each “usual” or average dose. For example:

- a. A minimum of four Medication Guides would be provided with a bottle of 100 for a product where the usual or average dose is 1 capsule/tablet daily, thus a monthly supply is 30 tablets.
- b. A minimum of one Medication Guide would be provided with unit of use where it is expected that all tablets/capsules would be supplied to the patient of the net contents of the carton.

#### ***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.

#### ***F. Medication Guide***

1. The product strength of the Extavia vial should be stated as 0.3 mg in the list of blister pack contents. Stating the strength as (b) (4) is incorrect, confusing, and may cause the reader to attempt unnecessary and incorrect calculations or conversions resulting in the administration of an incorrect dose.
2. Change the term (b) (4) to ‘diluent’ to be consistent with the terminology used in all the other labeling.
3. The full name of the diluent and the quantity in the syringe (e.g., Sodium Chloride 0.54% Solution 1.2 mL Diluent) should be stated rather than (b) (4)
4. Consider including a figure or graphic of a subcutaneous injection (e.g., pinched injection site showing needle inserted at 90° angle) to be useful to health care providers who are instructing their patient on how to self-administer a subcutaneous injection. A graphic may help patients improve self-administration technique at home.
5. Include clear storage and stability instructions for reconstituted Extavia in the Medication Guide. Specifically, include information from the prescribing information which states “after reconstitution, if not used immediately, the product should be refrigerated and used within three hours” and that “unused portions should be discarded”. This information is important for patients who self-administer Extavia and will discourage patient attempts to save reconstituted portions for later use in an attempt to save money.

## REFERENCES

### *Adverse Events Reporting System (AERS)*

AERS is a database application in CDER FDA that contains adverse event reports for approved drugs and therapeutic biologics. These reports are submitted to the FDA mostly from the manufactures that have approved products in the U.S. The main utility of a spontaneous reporting system that captures reports from health care professionals and consumers, such as AERS, is to identify potential postmarketing safety issues. There are inherent limitations to the voluntary or spontaneous reporting system, such as underreporting and duplicate reporting; for any given report, there is no certainty that the reported suspect product(s) caused the reported adverse event(s); and raw counts from AERS cannot be used to calculate incidence rates or estimates of drug risk for a particular product or used for comparing risk between products.



Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research

Office of Biotechnology Products  
Federal Research Center  
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## Memorandum

### PROJECT MANAGER'S REVIEW

**Application Number:** STN 125290/0

**Name of Drug:** Extavia®

**Sponsor:** Novartis Pharmaceutical Corporation

**Material Reviewed:** Extavia® (interferon beta-1b) Carton and Container Labels

**OBP Receipt Date:** October 30, 2008

**Amendment Reviewed:** June 3, 2009

#### Background:

STN 125290/0 for interferon beta-1b is an original Biologic License Application (BLA) intended a treatment for relapsing forms of multiple sclerosis. The product is a sterile, white to off-white powder, for subcutaneous injection after reconstitution with the diluent supplied (sodium chloride, 0.54% solution. The manufacturing and establishment standards are identical to the currently licensed product, Betaseron®.

#### Labels Reviewed:

Extavia® (interferon beta-1b) Container Label

Vial label

Single blister

Diluent vial label

Extavia® (interferon beta-1b) Carton Label

Multi unit blister package

#### Review

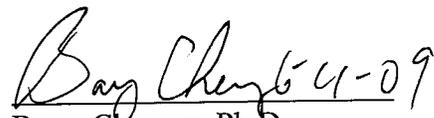
The carton and container labels for Extavia® (interferon beta-1b) were reviewed and found to be adequate under most of the following regulations: 21 CFR 610.60 through 21

- Based on the statement "Medication Guide for the patients enclosed" located on the blister pack carton, please clarify that a quantity of fourteen medication guides will be provided in the carton for each of the fourteen single use blister packs that could potentially be dispensed individually. There is no indication that the product is intended as a unit of use configuration per USP 31-NF 26 General notices-Preservation, packaging, storage, and labeling. Carton will indicate unit of use and contain one medication guide. Acceptable
- As per 21 CFR 610.60, include a reference to the Medication guide on the blister pack label. Not applicable. Carton will indicate unit of use and Medication guide statement.
- Consider removing the statement "9.6 million IU" from the carton and container labels to comply with the recommendation of the Institute of Safe Medication Practices' list for error-prone abbreviations, symbols, and dose designations. Change made and acceptable.
- Please provide font size configurations for all carton and container labels. Acceptable.

 6/3/09  
Kimberly Rains, Pharm.D  
Regulatory Project Manager  
CDER/OPS/OBS

Comment/Concurrence:

 4/2/09  
Ralph Bernstein, Ph.D.  
Product Reviewer  
Division of Therapeutic Proteins  
CDER/OPS/OBP

 4-09  
Barry Cherney, Ph.D.  
Deputy Director  
Division of Therapeutic Proteins  
CDER/OPS/OBP/DTP



**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: May 20, 2009

To: Russell Katz, M.D., Division Director  
**Division of Neurology Products (DNP)**

Through: Jodi Duckhorn, M.A., Team Leader *Jodi Duckhorn 5/20/2009*  
**Division of Risk Management (DRISK)**

From: Sharon R. Mills, BSN, RN, CCRP *Sharon R. Mills 5/20/2009*  
Patient Product Information Reviewer  
**Division of Risk Management (DRISK)**

Subject: DRISK Review of Patient Labeling (Medication Guide and Patient Instructions for Use)

Drug Name(s): Extavia (Interferon beta-1b)

Application Type/Number: BLA 125290

Applicant/sponsor: Novartis Pharmaceuticals

OSE RCM #: 2008-1735

## 1 INTRODUCTION

Novartis submitted an original Biologics Licensing Application, BLA 125290, for Extavia (interferon beta-1b) on May 6, 2008. The applicant is relying on right of reference to Bayer Healthcare Pharmaceuticals approved BLA 103471 for Betaseron.

This review is written in response to a request from the Division of Neurology Products (DNP) for the Division of Risk Management to review the Applicant's proposed Medication Guide.

## 2 MATERIAL REVIEWED

- Draft Extavia (Interferon beta-1b) Prescribing Information (PI) submitted on May 6, 2008 revised throughout the review cycle, and provided by the Review Division on April 15, 2009
- Draft Extavia (Interferon beta-1b) Medication Guide (MG) submitted on May 6, 2008, revised throughout the review cycle, and provided by the review division on April 15, 2009.

## 3 DISCUSSION

The purpose of patient directed labeling is to facilitate and enhance appropriate use and provide important risk information about medications. Our recommended changes are consistent with current research to improve risk communication to a broad audience, including those with lower literacy.

The draft MG submitted by the Applicant has a Flesch Kinkaid grade level of 8.2, and a Flesch Reading Ease score of 61.8%. To enhance patient comprehension, materials should be written at a 6<sup>th</sup> to 8<sup>th</sup> grade reading level, and have a reading ease score of at least 60% (60% corresponds to an 8<sup>th</sup> grade reading level). The reading scores as submitted by the Applicant are acceptable.

In our review of the MG, we have:

- simplified wording and clarified concepts where possible,
- ensured that the MG is consistent with the PI,
- rearranged information due to use of PLR format,
- removed unnecessary or redundant information
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20.
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006).

In 2008, The American Society of Consultant Pharmacists Foundation in collaboration with The American Foundation for the Blind published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. They recommend using fonts such as Arial, Verdana, or APHont to make medical information more accessible for patients with low vision. We have reformatted the MG document using the font APHont, which was developed by the American Printing House for the Blind specifically for low vision readers.

See the attached document for our recommended revisions to the MG. Comments to the review division are ***bolded, underlined and italicized.***

We are providing the review division a marked-up and clean copy of the revised MG. We recommend using the clean copy as the working document.

All future relevant changes to the PI should also be reflected in the MG.

#### 4 CONCLUSIONS AND RECOMMENDATIONS

**We have the following comments on the MG:**

1. The applicant should add the phonetic spelling of Extavia at the top of the MG.
2. We recommend that the review division consider revising the Betaseron MG to be consistent with the Extavia MG. Any recommended changes to Extavia that differ from the Betaseron MG reflect our current thinking about conveying safety information to patients in MGs.
3. The applicant uses both the terms “doctor” and “healthcare professional” in the MG. We recommend using either the term “doctor” or “healthcare provider” consistently throughout the MG, except at the end of the section “What are the possible side effects of Extavia?” where the term “doctor” is required. The term “healthcare professional” is too vague.
4. Use either the term “use” or “take” consistently throughout the MG with regard to either “using” or “taking” Extavia.
5. In the section “What is the most important information I should know about Extavia?”
  - Consult DDMAC regarding the first statement.
  - Under allergic reactions, swelling of the mouth or tongue seem like they would be symptoms of a more severe allergic reaction. The review division should clarify this and the information should be updated accordingly.
  - Additional information has been added to better inform patients regarding the severity of injection site reactions and the possible outcomes.
6. We added the standard MG section “What should I tell my doctor before taking Extavia?”
  - The bullet for “(b) (4)” was deleted because the basis of this information can not be found in the PI. The information in the MG must be consistent with the information in the PI. If the applicant or review division wishes to include this information in the MG, then it must first be added to the PI.
7. In the section “How should I take Extavia?” the instruction telling patients to take their injections (b) (4)  
(b) (4) We have deleted this information. If the applicant wishes to include this information in the MG, then it must first be added to the PI, such as in section 17. The information in the MG must be consistent with the information in the PI.
8. We deleted the section (b) (4) because it is redundant. Information about pregnancy is included in the section “What is the most important information I should know about Extavia?” Information about breast-feeding is included in the section “What should I tell my doctor before taking Extavia?”.
9. In the section “What are the possible side effects of Extavia?”

- In the bullet “liver problems” the review division should clarify whether there are other symptoms of liver problems that should be listed, such as right sided stomach area (abdominal) pain, and dark urine, and update as appropriate.
- If the applicant or review division wish to keep language in the MG telling patients that they should talk with their doctor regularly about their general health and that their doctor may want to watch them more carefully and request blood tests more often, this information should be first added to the PI, such as in section 17 Patient Counseling Information. The information in the MG must be consistent with the information in the PI.
- We have added the following statement to the end of the section, “What are the possible side effects of TRADENAME?”:

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

This verbatim statement is required for all Medication Guides.<sup>1</sup>

10. We added the standard MG section “How should I store Extavia?”
11. We revised the section “General information about Extavia to make it consistent with our recommended language for other MGs.
12. We added the standard MG section “What are the ingredients in Extavia?”

**We have the following comments on the Patient Instructions for Use:**

13. Under “Important safety information”:
  - In the 4<sup>th</sup> bullet, the applicant should clarify if they mean the seal on the blister pack, on the vial of Extavia, or both.
  - Regarding the 5<sup>th</sup> bullet, the applicant should add a labeled figure showing where the expiration date can be found.
14. Under “Gather your supplies?”
  - (b) (4) is not a common term that patients will be familiar with. We changed this to “diluent.”
  - Add a labeled figure showing the sharps container, cotton ball, and gauze. Many people may not know what a sharps disposal container is.
15. Under “Prepare for self-injection”
  - The 3<sup>rd</sup> bullet under “Important safety information” has information about (b) (4) [redacted]. This information is redundant and has therefore been deleted.
  - Regarding #3, the applicant should add a labeled figure showing the “well” and “trough” before the items are placed into them.
16. Under “Mix Extavia” the applicant should add additional labeled figures to show these steps. In particular,

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<sup>1</sup> 21 CFR 208.20 (b)(7)(iii)

- Regarding step #7, leaving the alcohol wipe on tip of the vial is not a required step; however, it is an acceptable technique. We defer to the review division regarding whether to include this information in the Patient Instructions for Use. If this step is deleted, then revise step 9 accordingly.
  - Regarding step #10, add a labeled figure showing the motion needed to remove the rubber cap.
  - Regarding step #12, add a labeled figure to indicate what is “diluent.”
  - Add a labeled figure to show step #18. In figure 7, change “1.0 mL” to “1 mL” to be consistent with the text in this instruction.
17. Under “Choose an Injection Site”:
- Regarding the second bullet, (b) (4), then this information should be moved up accordingly in the Patient Instructions for Use. If this is not important, the statement should be deleted from this paragraph.
18. Under “Injecting Extavia”, the applicant should add labeled figures to show these steps.
19. We deleted (b) (4) from the Patient Instructions for Use. (b) (4)

Please let us know if you have any questions.

26 pp withheld in full immed. after this page as (b)(4) draft labeling.

Cc List:

DNP:

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Billy Dunn

James Reese

OSE:

Claudia Karwoski

Mary Dempsey

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