

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
125290

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type BLA
Submission Number 125290/0

Submission Code Original

Letter Date 5/6/08
Stamp Date 5/6/08
PDUFA Goal Date 6/5/09

Reviewer Name Rob Harris, M.D.
Review Completion Date 6/5/09

6/5/09
Rob Harris
Billy Dennis
Team Leader
Health

Established Name Interferon beta-1b
(Proposed) Trade Name Extavia
Therapeutic Class Cytokine
Applicant Novartis

Priority Designation S

Formulation Injection
Dosing Regimen 0.25 mg every other day
Indication Multiple Sclerosis
Intended Population Patients with relapsing forms of multiple sclerosis

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Since this is the identical product to the previously approved Betaseron, it merits approval once the CMC issues discussed in this review are resolved. No new data were submitted for this NDA. The label for this product should be the last approved label for Betaseron, as updated to allow for PLR formatting and use of the name Extavia rather than Betaseron.

1.2 Risk Benefit Assessment

There are no new risk/benefit issues presented in the submission as the sponsor references Bayer HealthCare Pharmaceuticals, Inc.'s (Bayer) Biological License for Betaseron® (STN# 103471), also known as NVF233, as detailed below. Except for a smaller needle, the products are identical.

1.3 Recommendations for Postmarketing Risk Management Activities

None.

1.4 Recommendations for other Post Marketing Study Commitments

None.

2 Introduction and Regulatory Background

2.1 Product Information

Extavia, to be licensed by Novartis, is interferon beta-1b. It is the identical product to Betaseron, currently manufactured by Bayer. Novartis, the sponsor of this BLA, has obtained a letter of authorization to reference Bayer's Biological License for Betaseron® (STN# 103471), also known as NVF233. Novartis was the Biological License holder for Betaseron® until August 30, 2007 when this Biological License was transferred from Novartis to Bayer.

The product is a therapeutic protein marketed (as Betaseron) for the treatment of relapsing forms of multiple sclerosis (MS). It is supplied as a lyophilized powder containing 0.3 mg of Interferon beta-1b, 15 mgs human albumin USP, and 15 mg mannitol USP. The drug is packaged in a clear glass, single-use vial (3mL capacity). A pre-filled single-use syringe containing 1.2 mL of diluent (NaCl, 0.54% solution, 2 alcohol prep pads, and one vial adapter with an attached 27 gauge needle, are included for each vial of drug. Extavia and its diluent are single-use only.

2.2 Table of Currently Available Treatments for Proposed Indications

Table 1: Currently Approved Immunomodulator MS Treatments

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2.3 Availability of Proposed Active Ingredient in the United States

See sections 2.1 and 2.2

2.4 Important Safety Issues with Consideration to Related Drugs

No new data were submitted with this labeling NDA. In brief review, depression and suicide have been reported to occur with increased frequency in patients receiving interferon compounds, including Betaseron. As described in the Betaseron label, injection site necrosis (ISN) has been reported in 4% of patients in controlled clinical trials. Typically, injection site necrosis occurs within the first four months of therapy, although post-marketing reports have been received of ISN occurring over one year after initiation of therapy. Necrosis may occur at a single or multiple injection sites. Anaphylaxis has been reported as well.

Please see the attached Betaseron label for additional details.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

This product has a long and complicated regulatory history which was summarized for the Review Team by Dr. Ralph Bernstein of the Office of Biologic Products for this NDA.

Betaseron (USA) /Betaferon (Europe) were developed in the late 80's initially in Europe by Chiron and Schering. As part of their co-development agreement, Chiron had the US License for Betaseron and Schering sold it elsewhere as Betaferon (which is NOT approved for US). Although they co-developed the drug, there has been some drift in manufacturing in the last 10 or so years (Betaseron was approved in 93); Betaseron and Betaferon are not comparable from a CMC perspective.

At some point, Bayer acquired Schering. To further complicate the regulatory history, about 4 or 5 years ago, Novartis acquired Chiron. A year following the Novartis/Chiron acquisition, the co-

development/legal agreement between the former Schering (now Bayer) and the former Chiron (now Novartis) ended. The net result was:

(b) (4)



This NDA represents the latest chapter in the Regulatory History: Novartis now plans to market Extavia, which is identical in every respect to Bayer's Betaseron, except for a smaller needle used with Betaseron (27G vs. 30G) and product packaging. The CDRH review of the needle change issue for Betaseron is pending. The role of the clinical reviewer in this NDA has been one of labeling oversight as the sponsor has submitted no new clinical data for this NDA.

2.6 Other Relevant Background Information

See Section 2.5

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

Acceptable.

3.2 Compliance with Good Clinical Practices

Please see CMC review for a discussion of these issues.

3.3 Financial Disclosures

None provided. No clinical studies or investigations were submitted to this NDA.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Please see the CMC reviews for details of this biologic product's CMC considerations. No clinical studies have been done for this BLA (125290) as the sponsor has obtained a letter of authorization allowing the sponsor to reference the original Betaseron BLA (103471).

Dr. Ralph Bernstein has summarized the CMC issues. Please see his review for more details. There are no outstanding CMC issues.

4.2 Clinical Microbiology

Please see the Microbiology review. No clinical studies have been done for this BLA (125290) as the sponsor has obtained a letter of authorization allowing the sponsor to reference the original Betaseron BLA (103471).

4.3 Preclinical Pharmacology/Toxicology

Please see the Pharmacology/Toxicology review. No clinical studies have been done for this BLA (125290) as the sponsor has obtained a letter of authorization allowing the sponsor to reference the original Betaseron BLA (103471).

4.4 Clinical Pharmacology

Please see the Biopharmaceutics review. No clinical studies have been done for this BLA (125290) as the sponsor has obtained a letter of authorization allowing the sponsor to reference the original Betaseron BLA (103471).

4.4.1 Mechanism of Action

Unknown.

4.4.2 Pharmacodynamics

No new data submitted for this product cross-referencing Betaseron BLA 103471.

4.4.3 Pharmacokinetics

No new data submitted for this product cross-referencing Betaseron BLA 103471.

5 Sources of Clinical Data

5.1 Tables of Clinical Studies

No clinical studies have been done for this BLA (125290) as the sponsor has obtained a letter of authorization allowing the sponsor to reference the original Betaseron BLA (103471).

5.2 Review Strategy

No clinical studies have been done for this BLA (125290) as the sponsor has obtained a letter of authorization allowing the sponsor to reference the original Betaseron BLA (103471). Since there is no new data submitted, this review focused only on labeling for Extavia in comparison to Betaseron.

5.3 Discussion of Individual Studies

No clinical studies have been done for this BLA (125290) as the sponsor has obtained a letter of authorization allowing the sponsor to reference the original Betaseron BLA (103471).

6 Review of Efficacy

Efficacy Summary

No clinical studies have been done for this BLA (125290) as the sponsor has obtained a letter of authorization allowing the sponsor to reference the original Betaseron BLA (103471).

6.1 Indication

Treatment of relapsing forms of multiple sclerosis to reduce the frequency of clinical exacerbations.

7 Review of Safety

Safety Summary

No clinical studies have been done for this BLA (125290) as the sponsor has obtained a letter of authorization allowing the sponsor to reference the original Betaseron BLA (103471).

7.1 Additional Submissions

None.

8 Postmarketing Experience

None submitted for this BLA (125290) as the sponsor has obtained a letter of authorization allowing the sponsor to reference the original Betaseron BLA (103471).

9 Appendices

9.1 Literature Review/References

None.

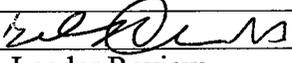
9.2 Labeling Recommendations

See attached labeling documents.

9.3 Advisory Committee Meeting

None.

Cross-Discipline Team Leader Review

Date	6/3/09
From	Billy Dunn, MD 
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	125290
Supplement#	0
Applicant	Novartis
Date of Submission	5/6/08
PDUFA Goal Date	6/5/09
Proprietary Name / Established (USAN) names	Extavia/Interferon beta-1b
Dosage forms / Strength	0.25 mg subcutaneous injection
Proposed Indication(s)	Relapsing multiple sclerosis
Recommended:	Complete response

1. Introduction

Extavia is a drug product proposed by Novartis for the treatment of relapsing forms of multiple sclerosis to reduce the frequency of clinical exacerbations.

Extavia will contain the same drug substance and, for all intents and purposes at the current time, will represent the same drug product as Betaseron, a drug that carries the identical indication to that proposed for Extavia. These two drug products are to be manufactured currently as a single entity with labeling representing their only physical differences. Upon approval, it is conceivable that this situation may change in the future should each product's manufacturing diverge from the other, as each product will have a distinct marketing license.

The review team for this submission included the following primary reviewers:

CMC – Ralph Bernstein, PhD
 Nonclinical – Barbara Wilcox, PhD
 Clinical Pharmacology – Jagan Parepally, PhD
 Microbiology – Bo Chi, PhD
 Clinical – Rob Harris, MD, PhD

I discuss below the key conclusions of each reviewer and provide my recommendations regarding this submission.

2. Background

Betaseron was approved in 1993 as the first interferon beta-1b for the treatment of multiple sclerosis. Due to various corporate maneuvers, Novartis has now reached an agreement with Bayer (holder of the Betaseron license) to jointly produce interferon beta-1b that will be branded either "Extavia" or "Betaseron" depending on the labeling applied. As noted above, these two branded products will represent, at the current time, identical drug products.

Novartis, the current applicant, has obtained and submitted an appropriate letter of authorization referencing the original Betaseron BLA. As the Extavia product does not currently differ in any regard from the Betaseron product, and the products are manufactured as a single entity, no new data was presented in this application and there has been no clinical development program for Extavia. In effect, this application simply requests the addition of another brand name to an extant product whose current brand name will continue to be marketed.

3. CMC/Device

Dr. Bernstein reviewed this submission and engaged the sponsor in a series of discussions and negotiations regarding appropriate quality assurance oversight over the manufacturing process and carton and container labeling. These have been resolved and there are no outstanding CMC issues. Upon approval, Dr. Bernstein is recommending a post-marketing commitment to develop an analytical test method for use in release and stability testing of the drug product to monitor the size and bioactivity of IFN/HSA complexes by Q1 2010.

4. Nonclinical Pharmacology/Toxicology

Dr. Wilcox reviewed this submission and found it acceptable. There are no outstanding nonclinical issues.

5. Clinical Pharmacology/Biopharmaceutics

Dr. Parepally reviewed this submission and found it acceptable. There are no outstanding clinical pharmacology issues.

6. Clinical Microbiology

Dr. Chi reviewed this submission and found it acceptable. There are no outstanding microbiology issues.

7. Clinical/Statistical- Efficacy

Dr. Harris reviewed this submission and found it acceptable. There are no outstanding clinical efficacy issues.

8. Safety

Dr. Harris reviewed this submission and found it acceptable. The application for Extavia included a Medication Guide, consistent with that used for the original Betaseron product. Accordingly, a Medication Guide-only Risk Evaluation And Mitigation Strategy (REMS) is required and was requested of the sponsor. This REMS has been submitted by the sponsor and is currently under review by the Division of Risk Management (DRISK). Otherwise, there are no outstanding clinical safety issues.

9. Advisory Committee Meeting

N/A

10. Pediatrics

N/A

11. Other Relevant Regulatory Issues

N/A

12. Labeling

The proposed label for Extavia is informed by the label of currently approved Betaseron, with appropriate changes.

Labeling negotiations with the sponsor have not been completed. The sponsor is currently reviewing the latest proposal. The primary issues of negotiation center on the sponsor's desire for absolute consistency and alignment with the current Betaseron label and on the sponsor's desire to include a statement in labeling indicating that [REDACTED] (b) (4) [REDACTED]. These issues remain outstanding.

13. Recommendations/Risk Benefit Assessment

I do not recommend approval of this application. A complete response letter should be issued to the sponsor indicating that it cannot be approved until an acceptable label has been negotiated. There are no other obstacles to approval.

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Eric Bastings, MD, Deputy Division Director, for Russell Katz, MD, Division Director
Subject	Division Director Summary Review
NDA/BLA #	125290
Supplement #	0
Applicant Name	Novartis
Date of Submission	5/6/08
PDUFA Goal Date	6/5/09
Proprietary Name / Established (USAN) Name	Extavia/Interferon beta-1b
Dosage Forms / Strength	0.25 mg subcutaneous injection
Proposed Indication(s)	Relapsing forms of multiple sclerosis
Action:	<i>Complete Response</i>

Material Reviewed/Consulted	Names of discipline reviewers
OND Action Package, including:	
Medical Officer Review	Robert Harris, MD, PhD
Pharmacology Toxicology Review	Barbara Wilcox, PhD
CMC Review/OBP Review	Ralph Bernstein, PhD
Microbiology Review	Bo Chi, PhD
Clinical Pharmacology Review	Jagan Parepally, PhD
DDMAC	Sharon Watson, PharmD
CDTL Review	Billy Dunn, MD
OSE/DMEPA	Laura Pincock, RPh
OSE/DRISK	Sharon Mills, BSN, RN, CCRP
Other	

Signatory Authority Review

1. Introduction

This application is for the marketing by Novartis of interferon beta-1b for the treatment of relapsing forms of multiple sclerosis. As discussed by the review team, this application relies on a cross-reference of the entirety of Bayer's license (103471) for Betaseron until Dec 2006. There are no new non clinical or clinical data in support of this application.

2. Background

Betaseron was approved in 1993 for the treatment of relapsing forms of multiple sclerosis. I reproduce below an (adapted) description by Dr. Bernstein of the regulatory history of Betaseron, preceding this cross-licensing agreement between Bayer and Novartis:

Betaseron was originally approved and licensed to Chiron (Emeryville CA) in 1993 under BLA 103471. Chiron and Germany based Berlex/Schering AG, co-developed Betaseron, but the two processes have diverged since that time. Schering's interferon beta-1b (proprietary name Betaferon) is manufactured in Germany, and is not licensed for distribution in the US. Schering was subsequently acquired by Bayer, and Chiron was acquired by Novartis in 2006. Novartis was briefly the license holder for Betaseron, until 13 Sept 07, wherein Bayer became the license holder. As part of the negotiations encompassing this arrangement, Bayer agreed to manufacture Betaseron for Novartis, under a separate BLA. Bayer has given Novartis the right (in a letter to the Agency dated 13 Sept 07) to "irrevocably" cross reference the entirety of Bayer's license (103471) until Dec 2006. In this BLA, Novartis has also submitted all changes subsequent to Dec 2006.

3. CMC/Device

Dr. Bernstein notes that there are currently no major CMC differences between Betaseron and Extavia. Bayer has filed a supplement (103471/5125, which was approved) to reduce the number of blister packs to 14 per carton, to change to a thinner 30 gauge needle (in part to differentiate Betaseron from Extavia's 15 per carton and 27 gauge needle) and to change the color of the (b) (4) vial adaptor. Dr. Bernstein believes that Novartis has sufficiently demonstrated adequate quality assurance oversight over Bayer's manufacturing of Extavia, which is an exact clone of Betaseron at the time of approval. Dr. Bernstein reviewed all changes subsequent to Dec 2006, and finds them acceptable.

Dr. Bernstein is recommending as a post-marketing commitment that Novartis commits to develop an analytical test method for use in release and stability testing of the drug product to monitor the size and bioactivity of interferon/HSA complexes. I concur.

Manufacturing site inspections were acceptable. There are no CMC outstanding issues.

4. Nonclinical Pharmacology/Toxicology

I concur with the conclusions reached by Dr. Wilcox that there are no outstanding pharm/tox issues that preclude approval.

5. Clinical Pharmacology/Biopharmaceutics

I concur with the conclusions reached by Parepally that there are no outstanding clinical pharmacology issues that preclude approval.

6. Clinical Microbiology

I concur with the conclusions reached by Dr. Chi that there are no outstanding clinical microbiology or sterility issues that preclude approval.

7. Clinical/Statistical-Efficacy

As discussed by Dr. Dunn, the application relies entirely on a cross-reference to the Betaseron license 103471 for efficacy, and there are no new clinical data submitted with this application. Betaseron is approved for the treatment of relapsing forms of MS.

8. Safety

Similarly, the application relies entirely on a cross-reference to Betaseron license 103471 for safety.

9. Advisory Committee Meeting

This product was not referred to an advisory committee meeting as, at the time of approval, it is identical to the already marketed Betaseron, and poses no new safety issue.

10. Pediatrics

PREA was not triggered. There is no pediatric plan.

11. Other Relevant Regulatory Issues

As part of a Risk Evaluation and Mitigation Strategy, the sponsor was required to dispense a medication guide with each prescription of Extavia. The sponsor was required to submit a timetable for assessments of the REMS, and an evaluation of the patients' understanding of the serious risks of Extavia. The sponsor submitted the requested REMS on June 1, 2009, and this could not be reviewed in this cycle.

12. Labeling

I concur with DMEPA's recommendation to accept the proprietary name "EXTAVIA".

Physician labeling is not resolved, as the sponsor has continuing disagreement on several issues. This are summarized in the following excerpt from a June 4, 2009 email from the sponsor:

[REDACTED] (b) (4)

It is for this reason we respectfully request that the agency consider as a minimum adding a sentence in section 11 stating that [REDACTED] (b) (4) As we mentioned in earlier presentations there is already precedent by the agency in allowing this sentence to be used for a biologic (e.g., the vaccine Engerix-B) when there are data supporting

[REDACTED] (b) (4)

The division believes that as Betaseron and Extavia may diverge in the future, any statement on [REDACTED] (b) (4) of the products is problematic. This and the other labeling disagreements will need to be resolved before an approval action can be taken.

The action letter will also communicate to the sponsor several carton and immediate container labels changes recommended by DMEPA (other changes recommended by CMC have already been communicated to and accepted by the sponsor).

As discussed above, a Medication Guide is required as part of a REMS.

13. Decision/Action/Risk Benefit Assessment

The division is taking a complete response action, as agreement could not be reached with the sponsor on physician labeling.

A post-marketing CMC commitment will be requested for the development of an analytical test method for use in release and stability testing of the drug product to monitor the size and bioactivity of interferon/HSA complexes.