European Medicines Agency
Evaluation of Medicines for Human Use

Doc.Ref.: EMEA/207265/2008

ASSESSMENT REPORT
FOR
EXTAVIA

International Nonproprietary Name:
INTERFERON BETA-1B

Procedure No. EMEA/H/C/933

Assessment Report as adopted by the CHMP with
all information of a commercially confidential nature deleted.

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TABLE OF CONTENTS

Page

1 BACKGROUND INFORMATION ON THE PROCEDURE

1.1 Submission of the dossier

The applicant Novartis Europharm Limited submitted on 04 October 2007 an application for Marketing Authorisation to the European Medicines Agency (EMEA) for Extavia, through the centralised procedure falling within the Article 3(1) and point 3 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMEA/CHMP on 26 April 2007.

The legal basis for this application refers to:
Article 10(c) of Directive 2001/83/EC, as amended – relating to informed consent from a the marketing authorisation holder, Bayer Schering Pharma AG, for the authorised medicinal product Betaferon (EU/1/95/003/003 – EU/1/95/003/006).

Scientific Advice:
The applicant did not seek scientific advice at the CHMP.

Licensing status:
The product was not licensed in any country at the time of submission of the application.

The Rapporteur and Co-Rapporteur appointed by the CHMP were Dr Ian Hudson (Rapporteur) and Dr Karl Broich (Co-Rapporteur)

1.2 Steps taken for the assessment of the product

- The application was received by the EMEA on 04 October 2007.
- The procedure started on 14 October 2007.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 16 November 2007. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 16 November 2007.
- During the CHMP meeting on 10-13 December 2007, the CHMP agreed on a list of outstanding issues to be addressed in writing and by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 08 February 2008.
- During the meeting on 17-19 March 2008, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Extavia on 19 March 2008.
- The applicant provided the letter of undertaking on the follow up measures to be fulfilled post authorisation in 2020.

2 SCIENTIFIC DISCUSSION

2.1 Introduction

Extavia has the same composition and the same pharmaceutical form as Betaferon, 250 microgram/ml, powder and solvent for solution for injection, which has been marketed by Bayer Schering Pharma AG since 1995 (Marketing Authorisation (MA) number EU/1/95/003/003-006 in November 1995). The last renewal date of Betaferon was 31 January 2006. A variation procedure EMEA/H/C/81/II/48, which started in June 2007, relates to the inclusion of results from a 3-year integrated analysis and first year of follow-up of an ongoing clinical study in patients with a single clinical event suggestive of multiple sclerosis. A positive opinion was issued on 15 November 2007; changes to the SPC resulting from this variation have been reflected in the SPC of Extavia in order to harmonise the SPCs of both products.

On 13 September 2007, Bayer Schering Pharma AG has acquired from Novartis Vaccines and Diagnostics Inc. the biologics manufacturing facility used to produce Betaferon and agreed to manufacture Extavia for Novartis.

2.2 Quality aspects

Since this application is an informed consent application of the Betaferon application, the quality data in support of Extavia application are identical to the up-to-date quality data of the Betaferon dossier which have been assessed and approved (including all post-marketing procedures).

Like Betaferon, Extavia is supplied as a vial with powder and either a 1.2 ml pre-filled syringe with 1.2 ml solvent or a 2.25 ml pre-filled syringe with 1.2 ml solvent and a vial adapter with needle.

Human albumin 12.5 mg is used as an excipient.

2.3 Non clinical aspects

In accordance with Directive 2001/83/EC and Guideline CHMP/SWP/4447/00, it has been accepted that there was no need to provide an environmental risk assessment, since the active interferon beta-1b is a recombinant equivalent of the antiviral human native cytokine interferon beta, a naturally occurring protein. Moreover, with a maximum daily dose of 250µg, the predicted environmental concentration in surface water (PECsw) is expected to be significantly below the trigger value of 10ng/L for a phase II environmental fate and effect analysis.

2.4 Clinical aspects

Not applicable.

2.5 Pharmacovigilance

Detailed description of the Pharmacovigilance system

Pharmacovigilance System

The Pharmacovigilance System as described by the Applicant fulfils the requirements and provides adequate evidence that the Applicant has the services of a qualified person responsible for Pharmacovigilance and has the necessary means for the collection and notification of any adverse reaction suspected of occurring in the Community or in a third country. Furthermore, the Applicant has satisfactorily addressed the issues raised by the CHMP in December 2007.

Risk Management Plan

In support of the application, a Risk Management Plan- which included a risk minimisation plan- was produced and submitted by Bayer Schering Pharma AG on behalf of Novartis, the Applicant. The Applicant satisfactorily addressed the issues raised by the CHMP in December 2007 and provided a letter of undertaking with a commitment to the activities outlined in the RMP.

Safety concern	Proposed pharmacovigilance activities	Proposed risk minimisation activities
Important identified risks:		
Hypersensitivity	**Routine Pharmacovigilance**	**Labelling: Contraindications, Warnings, Undesirable Effects**
Hepatotoxicity	**Routine Pharmacovigilance**	**Labelling: Contraindications, Warnings, Undesirable Effects**
Injection site necrosis	**Routine Pharmacovigilance**	**Labelling: Warnings, Undesirable Effects**
Blood disorders	**Routine Pharmacovigilance**	**Labelling: Warnings, Undesirable Effects**
Important potential risks:		
Depression / suicidal behaviour	**Routine Pharmacovigilance**	**Labelling: Contraindications, Warnings, Undesirable Effects**
Pregnancy outcomes	**Routine Pharmacovigilance, European pregnancy registry**	**Labelling: Contraindications, Warnings, Pregnancy and Lactation**
Capillary leak syndrome	**Routine Pharmacovigilance**	**Labelling: Warnings**
Pancreatitis	**Routine Pharmacovigilance**	**Labelling: Warnings, Undesirable Effects**
Seizure	**Routine Pharmacovigilance**	**Labelling: Warnings, Undesirable Effects**
Thyroid disorders	**Routine Pharmacovigilance**	**Labelling: Warnings, Undesirable Effects**
Worsening of concurrent cardiac disease by interferon-induced influenza-like symptoms	**Routine Pharmacovigilance**	**Labelling: Warnings, Undesirable Effects**
Immunogenicity	**Routine Pharmacovigilance**	**Labelling: Warnings**
Important missing information:		
Use in renal failure patients	**Routine Pharmacovigilance**	**Labelling: Warnings**

The CHMP, having considered the data submitted in the application, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information. The CHMP agreed that the PSUR cycle for Extavia will correspond to the one of Betaferon unless otherwise specified.

2.6 Overall conclusions, risk/benefit assessment and recommendation

Based on the review of the data from Module 1, and the submitted Risk Management Plan, the CHMP considers that the application for Extavia (interferon beta-1b) is approvable.

Risk-benefit assessment

Concerning safety and efficacy, as this was an informed consent application, no data were submitted and the risk/benefit balance is the same as for Betaferon.

A risk management plan was submitted. The CHMP, having considered the data submitted, was of the opinion that:

- routine pharmacovigilance was adequate to monitor the safety of the product.
- no additional risk minimisation activities were required beyond those included in the product information.

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the risk-benefit balance of Extavia in the treatment of patients

- with a single demyelinating event with an active inflammatory process, if it is severe enough to warrant treatment with intravenous corticosteroids, if alternative diagnoses have been excluded, and if they are determined to be at high risk of developing clinically definite multiple sclerosis.
- with relapsing-remitting multiple sclerosis and two or more relapses within the last two years.
- with secondary progressive multiple sclerosis with active disease, evidenced by relapses.

was favourable and therefore recommended the granting of the marketing authorisation.