EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

18 December 2013
EMA/176383/2014
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Rebif

International non-proprietary name: INTERFERON BETA-1A

Procedure No. EMEA/H/C/000136/II/0103

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. Background information on the procedure

1.1. Requested Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Merck Serono Europe Limited submitted to the European Medicines Agency on 2 October 2013 an application for a variation.

This application concerns the following medicinal product:

Medicinal product:	**International non-proprietary name:**	**Presentations:**
Rebif	INTERFERON BETA-1A	See Annex A

The following variation was requested:

Variation requested		**Type**
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	II

The MAH proposed the update of sections 4.2 and 4.8 of the Summary of Product Characteristics (SmPC) in order to add safety information relevant to the paediatric population. The Package Leaflet (PL) was proposed to be updated in accordance.

The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet.

Rapporteur: Bengt Ljungberg

1.2. Steps taken for the assessment

Submission date:	2 October 2013
Start of procedure:	20 October 2013
Rapporteur's preliminary assessment report circulated on:	22 November 2013
CHMP opinion:	18 December 2013

2. Scientific discussion

2.1. Introduction

Rebif (interferon beta-1a) was approved in Europe on 4 May 1998. Interferons (IFNs) are a group of endogenous glycoproteins endowed with immunomodulatory, antiviral and antiproliferative properties. Rebif (interferon beta-1a) shares the same amino acid sequence with endogenous human interferon beta. It is produced in mammalian cells (Chinese hamster ovary) and is therefore glycosylated like the natural protein.
Rebif is indicated for the treatment of
• patients with a single demyelinating event with an active inflammatory process, if alternative diagnoses have been excluded, and if they are determined to be at high risk of developing clinically definite multiple sclerosis (see section 5.1)

• patients with relapsing multiple sclerosis. In clinical trials, this was characterised by two or more acute exacerbations in the previous two years (see section 5.1).
Efficacy has not been demonstrated in patients with secondary progressive multiple sclerosis without ongoing relapsing activity (see section 5.1).

Multiple sclerosis (MS) is a chronic, inflammatory, demyelinating disease of the central nervous system (CNS) and is one of the most common causes of neurological disability in young adults. It is characterized by multifocal recurrent attacks (relapses) of neurological symptoms and signs with variable recovery. Eventually, the majority of subjects develop a progressive clinical course. Because the onset of MS is less common before the age of eighteen, most reports of MS in the pediatric population describe single cases or small groups without being able to define distinct characteristics of the disease in this age group.

The MAH performed a retrospective cohort study of Rebif use in pediatric MS patients (REPLAY, EMR200136-024) and conducted a review of paediatric cases captured in the company Global Drug Safety database. Consequently, with this type II variation the MAH proposed an update of the Product Information to add information relevant to the paediatric population.

2.2. Clinical Efficacy aspects

2.2.1. Methods – analysis of data submitted

Study EMR200136-024 (REPLAY) was a retrospective single cohort study of paediatric patients exposed to Rebif for treatment of demyelinating events. Data sources typically included hospital discharge files, medical records, ad-hoc clinical databases, administrative records, prescription drug files and biological measurements. This study was retrospective (historical) in that the exposure and outcomes had already been captured. However, all information on exposure, covariates and outcomes (including medical events) had been prospectively recorded in the patients' medical records at the centres as part of routine healthcare.
The study collected and reviewed medical records from 307 children and adolescents treated with Rebif. The study period began in 1997 and ended in 2009. The start of the observation period for each individual patient was the date of the first medical record available on site, e.g. a visit to the site during the first demyelinating event. For each outcome, patients were followed until the end of the observation period, defined as the last medical record available on site, or 31 Dec 2009, whichever occurred first. The following four periods of interest were defined:

Pre-Rebif Period (P1): All data collected from the first medical record until the initiation of Rebif treatment

Treatment Period (P2): All data collected from the initiation until the end of Rebif treatment

Observation Period (P3): All data collected from the initiation of Rebif treatment until the last medical record (or until 31 Dec 2009).

Post-Rebif Period (P4): All data collected from the end of Rebif treatment to the end of the study, for patients who stopped Rebif treatment.

The MS Analysis Set (MSAS), comprising all patients with a final diagnosis of MS, was used for efficacy analyses.

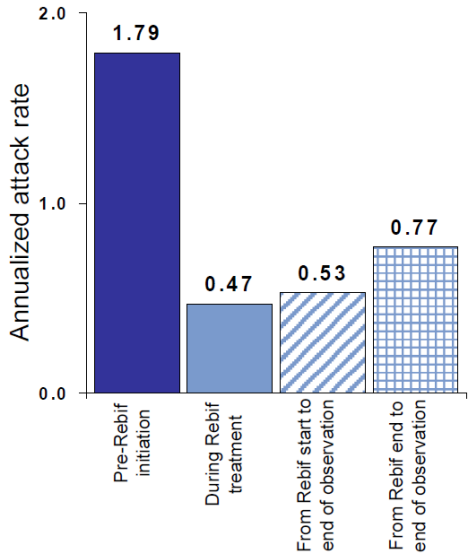
2.2.2. Results

The MSAS comprised 298 patients, with 50 patients who were <12 years of age at Rebif initiation and 248 who were 12 to <18 years of age. Overall, the mean (±SD) age at time of MS diagnosis was 13.3 (±3.1) years. The mean (±SD) age at time of MS diagnosis was 8.2 (±2.6) years for patients <12 years and 14.3 (±2.1) years for patients 12 to <18 years. 99.7% of patients had an initial MS course of RRMS. The median highest EDSS score pre-Rebif initiation was 3.0 for patients <12 years of age and 2.5 for patients 12 to <18 years. The percentage of patients with highest EDSS scores of ≥4 pre-Rebif initiation was higher among patients <12 years of age (32.0% [16/50]) than patients 12 to <18 years of age (11.3% [28/248]).

Annualized relapse rate

For all patients in the MSAS, the annualized attack rate was lower during Rebif treatment (P2) than during the pre-Rebif period (P1), which included the first demyelinating event; 0.47 attacks/ year vs. 1.79 attacks/year, respectively. For the period from start of Rebif treatment to end of study (P3), which included both patients who were still on Rebif treatment at the end of the study and patients who had discontinued Rebif, the rate was 0.53 attacks/ year. For the period from the end of Rebif treatment until the end of observation (P4), which included only patients who discontinued Rebif prematurely and either switched to another DMD or remained untreated, the rate was 0.77 attacks/year.

Figure 1 Medically Confirmed Clinical Attacks, MSAS



The annualized attack rate before Rebif initiation (P1) was 1.99 attacks/year for patients <12 years of age at Rebif initiation and 1.74 attacks/year for patients age 12 to <18 years. During Rebif treatment (P2), the annualized attack rate was lower in patients <12 years of age than patients 12 to <18 years of age (0.27 attacks/year vs. 0.54 attacks/year). The annualized attack rate during Rebif treatment was lower in patients who received 22 mcg tiw than in patients who received 44 mcg tiw at the initiation of Rebif treatment (0.35 vs. 0.68 attacks/year, respectively), although rates were similar before Rebif initiation (1.85 vs. 1.73 attacks/year, respectively) for these dose groups.

2.2.3. Discussion

The CHMP considered that the REPLAY study was a retrospective collection of data from the past medical records and thus, many potential confounding factors such as exposure to other medications, co-morbidities, gender, weight and age at the time of first Rebif injection potentially could impact the efficacy results. Other potential biases could have been introduced by differences in data collection practices and patient selection procedures, by the different Rebif exposures (different dosages and durations of treatment) and by missing data. Taken together, the MAH´s conclusion that the efficacy outcomes should be interpreted with caution because the study was not controlled and a number of biases could have influenced the outcomes was accepted by the CHMP. On the other hand, the CHMP took into consideration that symptoms and course of multiple sclerosis are very similar between the younger and the adult population and concluded that no additional separate studies with Rebif in children and adolescents were necessary to establish efficacy.

2.3. Clinical Safety aspects

2.3.1. Methods – analysis of data submitted

REPLAY study

The Total Analysis Set (TAS), comprising all patients included in the REPLAY study (EMR200136-024), was used for all safety analyses.

Due to the retrospective nature of the study, safety data collection was focused on any serious medical events regardless of their relatedness to Rebif, pre-specified medical events of special interest and any other medical events (regardless of seriousness) considered by the Investigator as related to Rebif treatment.

The pre-specified medical events of special interest were defined as all events regardless of seriousness and relatedness that were included in one of the following categories:

- Medical events known to be related to IFN-beta-1a treatment, such as injection site reactions (ISRs), FLS, blood cell disorders, hepatic disorders, allergic reactions and thyroid disorders
- Medical events under close monitoring with Rebif, such as malignancies, serious infections and autoimmune diseases
- Medical events most prone to occur in a pediatric population with or without MS, such as epilepsy and convulsive disorders and bone/epiphyseal and cartilage disorders.

Laboratory values were collected retrospectively from medical records and were available for the majority of patients. Due to the retrospective nature of the study, collection of laboratory data was not standardized, which meant that some patients had laboratory data collected regularly, whereas other patients had no or limited laboratory data recorded in their medical files.

Global Drug Safety database search criteria:

The Global Safety Database was searched with the following query:

- Suspected drug: Rebif/Interferon beta-1a
- All cases from patients aged between 0 years to 17 years (inclusive)
- All reporting sources (clinical trials solicited, spontaneous solicited and unsolicited and literature)

- Medically confirmed AND not medically confirmed

- Serious and non-serious

2.3.2. Results

Safety findings from REPLAY study

Serious Medical Events

The TAS comprised 307 patients, of whom 52 patients were 2 to <12 years of age at the time of Rebif initiation and 255 were 12 to <18 years of age. A total of 18 serious medical events (regardless of causality) were reported in 12 patients (3.9%). All serious medical events had single occurrences. There were no deaths during the period covered by this retrospective analysis.

Four of the 307 (1.3%) patients reported serious medical events that were considered by the Investigator as related to Rebif treatment. Four additional patients (1.3%) experienced serious medical events for which an 'unknown' causal relationship to Rebif treatment was assigned by the Investigator. Six of the 307 patients (2.0%) reported serious medical events that were considered not related to Rebif treatment.

With the exception of 'irritability', all serious medical events considered as related to Rebif, i.e. injection site reactions, hepatic enzyme elevations and thrombocytopenic purpura are known adverse reactions for Rebif and listed in the reference safety information of Rebif. The single case of irritability occurred in a 12-year-old female, 11 days after the first injection of Rebif. The event resolved following treatment discontinuation. A causal association between irritability and Rebif in this particular case could not be excluded due to the short latency and positive dechallenge.

Serious medical events with an 'unknown' relationship to Rebif, as per the Investigator, were autoimmune hepatitis, cholelithiasis, hypersensitivity, auditory hallucinations and suicidal behaviour.

All but one of the serious medical events considered related or of unknown causality to Rebif were reported in patients aged 12 to <18 years of age at the time of Rebif initiation. With the exception of hypersensitivity in a 9-year-old patient and irritability in a 12-year-old female, all other events occurred in patients aged from 16 to 18 years.

Serious medical events considered not related to Rebif by the Investigator included convulsion, epilepsy, appendicectomy, omentectomy, suicidal ideation, anaphylactic reaction and cellulitis. Each medical event was reported in just one patient each. All but three serious medical events that were considered not related to Rebif occurred in patients aged 12 to <18 years of age at the time of Rebif initiation. The serious medical events in patients <12 years of age at the time of Rebif initiation were epilepsy in a 9-year-old patient and appendectomy with omentectomy in another 9-year-old patient.

Pre-Specified Medical Events

At least one pre-specified medical event was reported in 54.7% (168/307) of patients. The most frequent pre-specified events were injection site reactions, in 27.7% of patients, and the most frequent injection site reactions were injection site erythema (15.6%) and injection site pain (11.1%). Flu-like symptoms (FLS) were reported in 24.4% of patients. Hepatic disorders were reported in 14.3% of patients and the most frequent medical events were ALT increase (4.2%), hepatic enzyme increase and liver function test abnormality (2.9% each). Fourteen patients (4.6%; 14/307) had medical events related to blood cell disorders; the most frequently reported were leukopenia or white blood cell count decreased in 2.9% (9/307) of patients and neutropenia or

neutrophil count decreased in 1.3% (4/307) of patients. All other pre-specified medical events were reported in less than 2% of patients.

Analysis by age group for the pre-defined medical events of special interest did not show significant differences between the <12 years and 12 to <18 years age groups. FLS and hepatic disorders were reported with a slightly higher frequency in the younger age group, whereas injection site reactions and blood cell disorders were reported more frequently in the 12 to <18 years age group.

Non-serious medical events considered by the investigator as related to Rebif

Any medical events, regardless of seriousness, considered by the Investigator as related to Rebif were collected. About half of patients (53.1%; 163/307) had at least one non-serious medical event that was considered by the Investigator as related to Rebif. The most commonly reported non-serious medical events (≥1% of patients) were headache, myalgia, pyrexia, fatigue, chills and depression.

Analysis by age group revealed slight differences in reporting patterns in the medical events: pyrexia was reported more frequently in the younger age group (<12 years), whereas headache was reported more frequently in the 12 to <18 years age group. Depression was reported exclusively in the 12 to <18 years age group.

Clinical Laboratory Evaluation (REPLAY)

In both age groups, the most frequent out of normal range values following Rebif initiation pertained to ALT (15/52 [39.5%] patients <12 years of age and 59/255 [37.6%] patients 12 to <18 years of age) and AST (11/52 [28.9%] patients <12 years of age and 48/255 [30.8%] patients 12 to <18 years). Hematocrit, hemoglobin, leukocytes, lymphocytes and neutrophils were out of normal range in 4 to 8 patients <12 years of age, and in 28 to 47 patients 12 to <18 years of age. No clinically relevant differences were observed between the two age groups.

Post-marketing safety data on the use of Rebif in paediatric MS Patients

The cumulative exposure to Rebif regardless of age, gender or any other factor amounts to approximately 1,021,825 patient-years in the post-marketing setting. While it is known that Rebif and other disease modifying drugs are currently prescribed to the paediatric population, the extent of Rebif exposure in the paediatric population was not established by the MAH, because sales volume gives an estimate of the number of patients treated with Rebif as a whole without providing information on age or gender.

A total of 1238 Individual Case Safety Reports (ICSR) corresponding to the search criteria outlined above were retrieved from the Global Drug Safety Database.

Table 2: Number of ISCRs reported from the pediatric population by source, seriousness, and medical confirmation.

Source ICSR	Medically confirmed			Not medically confirmed			Grand Total
	Serious	Not serious	Total	Serious	Not serious	Total	
Spontaneous /Health Authorities	42	130	172	101	926	1027	1199
Literature	9	15	24				24
Clinical Trials / Observational studies	13	2	15				15
Total	64	147	211	101	926	1027	1238

The 1,238 ICSRs contained a total of 2,889 events. Most of the events were non-serious (90.6%), versus 9.4% serious events.

Table 3: Number of events contained in the ISCRs reported from the pediatric population by source, seriousness, and medical confirmation.

Source report	Medically confirmed			Not medically confirmed			Grand Total
	Serious	Not Serious	Total	Serious	Not Serious	Total	
Spontaneous /Health Authorities	61	387	448	180	2188	2368	2816
Literature	12	37	49				49
Clinical Trials / Observational studies	20	4	24				24
Grand Total	93	428	521	180	2188	2368	2889

The SOCs showing the greatest number of serious reactions were Nervous system disorders (99), Psychiatric disorders (25), General disorders and administration site conditions (22), Infections and infestations (18), Gastro-intestinal disorders (16), Investigations (14) and Congenital, familial and genetic conditions (12).

A total of 13 cases of convulsions were reported; the majority of convulsions were coming from adolescents (11/13).

A total of 15 cases of depression and/or suicidal ideation events were reported.

Comparison of the reporting proportion of events between pediatric patients and adult patients treated with Rebif showed a higher reporting of events describing “elevation of transaminases” in pediatric MS patients. Although most case reports contained limited information, the majority of hepatic enzymes increases reported from pediatric patients were non-serious (93%). Hepatic disorders were reported in only 6 pediatric patients (one in a neonate, all other patients were >12 years old). The events reported in adolescents included interferon-induced hepatitis, one liver disorder and one liver injury described as elevated liver enzymes, all resolving following a permanent discontinuation of Rebif (22mcg), one cholelithiasis necessitating cholecystectomy with temporary

discontinuation of Rebif due to concomitant elevated liver enzymes and one hepatitis which was ongoing at the time of Rebif (22mcg) discontinuation.

Most of the non-serious events reported in more than 10 patients are well characterized with Rebif, such as injection site reactions, flu-like symptoms, headache, myalgia, chills, pyrexia, pain and fatigue.

2.3.3. Discussion

The CHMP considered that in general, the most common adverse events identified in the paediatric MS population in the REPLAY retrospective cohort study and following review of the case in the Global Drug Safety database (injection site reactions, flu-like symptoms and liver enzyme elevations) were similar to the ones reported in adult MS population treated with Rebif.

Serious adverse events of epilepsy, convulsion and suicidal ideation reported in the REPLAY study as well as post-marketing Global Drug Safety database were previously reported also in the adult MS population.

In summary, no new safety concerns were identified in the REPLAY study or post-marketing Global Drug Safety database by the MAH, which was accepted by the CHMP. The update of sections 4.2 and 4.8 of the SmPC to reflect on the safety in paediatric patients was considered appropriate and relevant to patients and prescribers.

2.4. Changes to the Product Information

The MAH proposed the following changes to the Product Information (PI), to which the CHMP agreed:

Section 4.2 of the SmPC

Paediatric population

~~The safety and efficacy of Rebif in adolescents aged 12 to 16 years have not yet been established. Currently available safety data are described in section 4.8 but no recommendation on a posology can be made.~~

No formal clinical trials or pharmacokinetic studies have been conducted in children or adolescents. However, a paediatric retrospective cohort study collected safety data with Rebif from medical records in children (n=52) and adolescents (n=255). The results of this study suggest that the safety profile in children (2 to 11 years old) and in adolescents (12 to 17 years old) receiving Rebif 22 micrograms or 44 micrograms subcutaneous three times per week is similar to that seen in adults.

~~The safety and efficacy of Rebif in children below 12 years of age have not yet been established. Only very limited data are available. Rebif should not be used in this age group.~~

The safety and efficacy of Rebif in children below 2 years of age have not been established. Rebif should not be used in this age group.

Section 4.8 of the SmPC

Paediatric population

No formal clinical trials or pharmacokinetic studies have been conducted in children or adolescents. ~~However, limited published~~ Limited safety data suggest that the safety profile in children and adolescents ~~from 1~~2 to 17 ~~16~~ years ~~of age~~ receiving Rebif 22 micrograms or 44 micrograms ~~subcutaneously~~ three times ~~per~~ weekly is similar to that seen in adults.

Package Leaflet

Use in children and teenagers (2 to 17 years old)

No formal clinical studies have been conducted in children or teenagers. However there is some clinical data available suggesting that the safety profile in children and teenagers receiving Rebif 22 micrograms or Rebif 44 micrograms three times per week is similar to that seen in adults.

Use in children (below 2 years of age)

Rebif is not recommended for use in children below 2 years of age.

3. Overall conclusion and impact on the benefit/risk balance

The CHMP considered that the changes introduced with this type II variation are acceptable and that the overall benefit-risk balance of Rebif remains favourable.

4. Recommendations

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change(s):

Variation(s) requested		Type
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	II

Update of sections 4.2 and 4.8 of the SmPC in order to add safety information relevant to the paediatric population. The Package Leaflet was updated accordingly.

The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet.

5. EPAR changes

The EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Update of sections 4.2 and 4.8 of the SmPC in order to add safety information relevant to the paediatric population. The Package Leaflet was updated accordingly.

Summary

The MAH performed a retrospective cohort study of Rebif use in pediatric MS patients (2-17 years) and conducted a review of paediatric cases captured in the company Global Drug Safety database. Consequently, with this type II variation the Product Information was updated to add information relevant to the paediatric population. The following text has been included to the Package Leaflet:

Use in children and teenagers (2 to 17 years old)

No formal clinical studies have been conducted in children or teenagers. However there is some clinical data available suggesting that the safety profile in children and teenagers receiving Rebif 22 micrograms or Rebif 44 micrograms three times per week is similar to that seen in adults.

Use in children (below 2 years of age)

Rebif is not recommended for use in children below 2 years of age.