Rebif®

1. NAME OF THE MEDICINAL PRODUCT

Rebif 22 micrograms/0.5 ml solution for injection in cartridge

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pre-filled cartridge contains 66 micrograms (18 MIU*) of interferon beta-1a** in 1.5 ml solution, corresponding to 44 micrograms/ml.
* Million International Units, measured by cytopathic effect (CPE) bioassay against the in-house IFN beta-1a standard which is calibrated against the current international NIH standard (GB-23-902-531).
** produced in Chinese hamster ovary Cells (CHO-K1) by recombinant DNA technology.
Excipient with known effect: Contains 2.5 mg benzyl alcohol per dose of 0.5 mL.
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection in cartridge.
Clear to opalescent solution, with pH 3.7 to 4.1 and osmolarity 250 to 450 mOsm/l.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Rebif is indicated for the treatment of 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 relapse activity (see section 5.1).

4.2 Posology and method of administration

Treatment should be initiated under supervision of a physician experienced in the treatment of the disease.
The recommended posology of Rebif is 44 micrograms given three times per week by subcutaneous injection. A lower dose of 22 micrograms, also given three times per week by subcutaneous injection, is recommended for patients who cannot tolerate the higher dose in view of the treating specialist.

When first starting treatment with Rebif, the dose should be gradually escalated in order to allow tachyphylaxis to develop thus reducing adverse reactions.

Method of administration
Rebif solution for injection in cartridge is intended for multidose use and should only be used with the RebiSmart autoinjector device following adequate training of the patient and/or carer.

For administration, the instructions provided in the package leaflet and in the instruction manual provided with the RebiSmart autoinjector device should be followed.

Prior to injection and for an additional 24 hours after each injection, an antipyretic analgesic is advised to decrease flu-like symptoms associated with Rebif administration.

At the present time, it is not known for how long patients should be treated. Safety and efficacy with Rebif have not been demonstrated beyond 4 years of treatment. It is recommended that patients should be evaluated at least every second year in the 4-year period after initiation of treatment with Rebif and a decision for longer term treatment should then be made on an individual basis by the treating physician.

Paediatric use
No formal clinical trials or pharmacokinetic studies have been conducted in children or adolescents. However, limited published data suggest that the safety profile in adolescents from 12 to 16 years of age receiving Rebif 22 micrograms subcutaneously three times per week is similar to that seen in adults. There is very limited information on the use of Rebif in children under 12 years of age and therefore Rebif should not be used in this population.

4.3 Contraindications

• Hypersensitivity to natural or recombinant interferon-ß, or to any excipients.
• Current severe depression and/or suicidal ideation (see sections 4.4 and 4.8).

4.4 Special warnings and precautions for use

Patients should be informed of the most frequent adverse reactions associated with interferon beta administration, including symptoms of the flu-like syndrome (see section 4.8). These symptoms tend to be most prominent at the initiation of therapy and decrease in frequency and severity with continued treatment.

Thrombotic microangiopathy
Cases of thrombotic microangiopathy, manifested as thrombotic thrombocytopenic purpura (TTP) or haemolytic uraemic syndrome (HUS), including fatal cases, have been reported with interferon beta products. Events were reported at various time points during treatment and may occur several weeks to several years after starting treatment with interferon beta. Early clinical features include thrombocytopenia, new onset hypertension, fever, central nervous system symptoms (e.g. confusion, paresis) and impaired renal function. Laboratory findings suggestive of TMA include decreased platelet counts, increased serum lactate dehydrogenase (LDH) due to haemolysis and schistocytes (erythrocyte fragmentation) on a blood film. Therefore if clinical features of TMA are observed, further testing of blood platelet levels, serum LDH, blood films and renal function is recommended. If TMA is diagnosed, prompt treatment is required (considering plasma exchange) and immediate discontinuation of Rebif is recommended.

Depression and suicidal ideation
Rebif should be administered with caution to patients with previous or current depressive disorders in particular to those with antecedents of suicidal ideation (see section 4.3). Depression and suicidal ideation are known to occur in increased frequency in the multiple sclerosis population and in association with interferon use. Patients treated with Rebif should be advised to immediately report any symptoms of depression and/or suicidal ideation to their prescribing physician. Patients exhibiting depression should be monitored closely during therapy with Rebif and treated appropriately. Cessation of therapy with Rebif should be considered (see sections 4.3 and 4.8).

Seizure disorders
Rebif should be administered with caution to patients with a history of seizures, to those receiving treatment with anti-epileptics, particularly if their epilepsy is not adequately controlled with anti-epileptics (see sections 4.5 and 4.8).

Cardiac disease
Patients with cardiac disease, such as angina, congestive heart failure or arrhythmia, should be closely monitored for worsening of their clinical condition during initiation of therapy with interferon beta-1a. Symptoms of the flu-like syndrome associated with interferon beta-1a therapy may prove stressful to patients with cardiac conditions.

Injection site necrosis
Injection site necrosis (ISN) has been reported in patients using Rebif (see section 4.8). To minimise the risk of injection site necrosis patients should be advised to:
• use an aseptic injection technique,
• rotate the injection sites with each dose.

The procedure for the self-administration by the patient should be reviewed periodically especially if injection site reactions have occurred.

If the patient experiences any break in the skin, which may be associated with swelling or drainage of fluid from the injection site, the patient should be advised to consult with their physician before continuing injections with Rebif. If the patient has multiple lesions, Rebif should be discontinued until healing has occurred. Patients with single lesions may continue provided that the necrosis is not too extensive.

Hepatic dysfunction
In clinical trials with Rebif, asymptomatic elevations of hepatic transaminases [particularly alanine aminotransferase (ALT)] were common and 1-3% of patients developed elevations of hepatic transaminases above 5 times the upper limit of normal (ULN). In the absence of clinical symptoms, serum ALT levels should be monitored prior to the start of therapy, at months 1, 3 and 6 on therapy and periodically thereafter. Dose reduction of Rebif should be considered if ALT rises above 5 times the ULN, and gradually re-escalated when enzyme levels have normalized. Rebif should be initiated with caution in patients with a history of significant liver disease, clinical evidence of active liver disease, alcohol abuse or increased serum ALT (>2.5 times ULN). Treatment with Rebif should be stopped if icterus or other clinical symptoms of liver dysfunction appear (see section 4.8). Rebif, like other interferons beta, has a potential for causing severe liver injury (see section 4.8) including acute hepatic failure. The mechanism for the rare symptomatic hepatic dysfunction is not known. No specific risk factors have been identified.

Renal and urinary disorders
Nephrotic syndrome
Cases of nephrotic syndrome with different underlying nephropathies including collapsing focal segmental glomerulosclerosis (FSGS), minimal change disease (MCD), membranoproliferative glomerulonephritis (MPGN) and membranous glomerulopathy (MGN) have been reported during treatment with interferon-beta products. Events were reported at various time points during treatment and may occur after several years of treatment with interferon-beta. Periodic monitoring of early signs or symptoms, e.g. oedema, proteinuria and impaired renal function is recommended, especially in patients at higher risk of renal disease. Prompt treatment of nephrotic syndrome is required and discontinuation of treatment with Rebif should be considered.

Laboratory abnormalities
Laboratory abnormalities are associated with the use of interferons. Therefore, in addition to those laboratory tests normally required for monitoring patients with multiple sclerosis, liver enzyme monitoring and complete and differential blood cell counts and platelet counts are recommended at regular intervals (1, 3 and 6 months) following introduction of Rebif therapy and then periodically thereafter in the absence of clinical symptoms.

Thyroid disorder
Patients being treated with Rebif may occasionally develop new or worsening thyroid abnormalities. Thyroid function testing is recommended at baseline and if abnormal, every 6-12 months following initiation of therapy. If tests are normal at baseline, routine testing is not needed but should be performed if clinical findings of thyroid dysfunction appear (see section 4.8).

Severe renal or hepatic failure and severe myelosuppression

Caution should be used, and close monitoring considered when administering interferon beta-1a to patients with severe renal and hepatic failure and to patients with severe myelosuppression.

Neutralising antibodies
Serum neutralising antibodies against interferon beta-1a may develop. The precise incidence of antibodies is as yet uncertain. Clinical data suggest that after 24 to 48 months of treatment with Rebif 22 micrograms, approximately 24% of patients develop persistent serum antibodies to interferon beta-1a. The presence of antibodies has been shown to attenuate the pharmacodynamic response to interferon beta-1a (Beta-2 microglobulin and neopterin). Although the clinical significance of the induction of antibodies has not been fully elucidated, the development of neutralising antibodies is associated with reduced efficacy on clinical and MRI variables. If a patient responds poorly to therapy with Rebif, and has neutralising antibodies, the treating physician should reassess the benefit/risk ratio of continued Rebif therapy.

The use of various assays to detect serum antibodies and differing definitions of antibody positivity limits the ability to compare antigenicity among different products.

Other forms of multiple sclerosis
Only sparse safety and efficacy data are available from non-ambulatory patients with multiple sclerosis. Rebif has not yet been investigated in patients with primary progressive multiple sclerosis and should not be used in such patients.

Excipients

Sodium content
This medicinal product contains less than 1 mmol sodium (23 mg) per dose, i.e. it is essentially 'sodium-free'.

Benzyl alcohol
This medicinal product contains benzyl alcohol. Benzyl alcohol may cause allergic reactions. Must not be given to premature babies or neonates. May cause toxic reactions and anaphylactoid reactions in infants and children up to 3 years old.

Monitor patients less than 3 years of age for respiratory symptoms.

Advise patients who are pregnant or breastfeeding of the potential risk from excipient benzyl alcohol, which might accumulate over time and cause metabolic acidosis. Use with caution in patients with hepatic or renal impairment, because of the potential risk from excipient benzyl alcohol which might accumulate over time and cause metabolic acidosis.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed with interferon beta-1a in humans.

Interferons have been reported to reduce the activity of hepatic cytochrome P450-dependent enzymes in humans and animals. Caution should be exercised when administering Rebif in combination with medicinal products that have a narrow therapeutic index and are largely dependent on the hepatic cytochrome P450 system for clearance, e.g. antiepileptics and some classes of antidepressants.

The interaction of Rebif with corticosteroids or adrenocorticotropic hormone (ACTH) has not been studied systematically. Clinical studies indicate that multiple sclerosis patients can receive Rebif and corticosteroids or ACTH during relapses.

4.6 Pregnancy and lactation

Pregnancy
Data from registries and post-marketing experience (more than 1,000 pregnancy outcomes) indicates no increased risk of major congenital anomalies after pre-conception exposure to interferon beta or such exposure during the first trimester of pregnancy.

Based on Nordic registers, the relative risk of live births with congenital anomalies (95% confidence interval) of IFN-beta-exposed only pregnancies was 0.52 (0.27-0.99) when compared to those unexposed to any disease modifying drugs. In post-marketing experience, the prevalence of live births with congenital anomalies in IFN-beta exposed pregnancies was 1.8% in line with that in the general population (2.1-4.1%).

However, the duration of exposure during the first trimester is uncertain, because data were collected when interferon beta use was contraindicated during pregnancy, and treatment likely interrupted when the pregnancy was detected and/or confirmed. Experience with exposure during the second and third trimester is very limited.

If clinically needed, the use of IFN β-1a may be considered during pregnancy. A decision to use IFN β-1a should be made based on the benefit of therapy for the pregnant woman and any potential risk to the foetus.

Breastfeeding
Based on the current information available on the transfer of interferon beta-1a into breast milk, together with the chemical/physiological characteristics of interferon beta, it suggests that levels of interferon beta-1a excreted in human milk are negligible. The potential for harmful effect on the breastfed newborn/infant is low. Rebif can be used during breast-feeding.

4.7 Effects on ability to drive and use machines

Central nervous system-related adverse events associated with the use of interferon beta (e.g. dizziness) might influence the patient's ability to drive or use machines (see section 4.8).

4.8 Undesirable effects

The highest incidence of adverse reactions associated with Rebif therapy is related to flu-like syndrome. Flu-like symptoms tend to be most prominent at the initiation of therapy and decrease in frequency with continued treatment. Approximately 70% of patients treated with Rebif can expect to experience the typical interferon flu-like syndrome within the first six months after starting treatment. Approximately 30% of patients will also experience reactions at the injection site, predominantly mild inflammation or erythema.
Asymptomatic increases in laboratory parameters of hepatic function and decreases in white blood cells (WBC) are also common.

The majority of adverse reactions observed with IFN beta-1a are usually mild and reversible, and respond well to dose reductions. In case of severe or persistent undesirable effects, the dose of Rebif may be temporarily lowered or interrupted, at the discretion of the physician.

The adverse reactions presented have been identified from clinical studies as well as from post-marketing reports *(an asterisk [*] indicates adverse reactions identified during post-marketing surveillance)*. The adverse reactions reported below are classified according to frequency of occurrence as follows:

Very Common	≥ 1/10
Common	≥1/100 to <1/10
Uncommon	≥1/1,000 to <1/100
Rare	≥1/10,000 to <1/1,000
Very rare	<1/10,000
Frequency not known	Cannot be estimated from the available data

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

The data presented is obtained from pooled clinical studies in multiple sclerosis (placebo=824 patients; Rebif 22 micrograms three times per week (TIW)=398 patients; Rebif 44 micrograms TIW=727 patients) and shows the frequency of adverse reactions observed at six months (excess over placebo). Adverse reactions are listed below by frequency of occurrence and by MedDRA System Organ Class.

System Organ Class	Very common	Common	Uncommon	Rare	Frequency not known
Blood and the lymphatic System disorders	Neutropenia, lymphopenia, leucopenia, thrombocytopenia, anemia			Thrombotic microangiopathy including thrombotic thrombocytopenic purpura/ Haemolytic uremic syndrome* (class label for interferon beta products, see section 4.4), pancytopenia*	
Endocrine Disorders			Thyroid dysfunction most often presenting as hypothyroidism or hyperthyroidism		
Psychiatric disorders		Depression, insomnia		Suicide attempt*	
Nervous system disorders	Headache		Seizures*		Transient Neurological symptoms (i.e. hypoesthesia, muscle spasm, paraesthesia, difficulty in walking, musculoskeletal stiffness) that may mimic multiple sclerosis exacerbations*
Eye disorders			Retinal vascular disorders (e.g. retinopathy, cotton wool spots and obstruction of retinal artery or vein)*		
Gastrointestinal disorders		Diarrhoea, vomiting, nausea			
Skin and subcutaneous tissue disorders		Pruritus, rash, erythematous rash, maculopapular rash, alopecia*	Urticaria*	Quincke's oedema (angio-oedema)*, erythema multiforme*, erythema multiforme-like	

				skin reactions*, Stevens-Johnson syndrome*	
Musculoskeletal and connective disorders		Myalgia, arthralgia		Drug-induced lupus erythematosus*	
General disorders and Administration site conditions	Injection site inflammation, injection site reaction, influenza-like symptoms	Injection site pain, fatigue, rigors, fever	Injection site Necrosis*, injection site mass, injection site abscess, injection site infections*, increased sweating*	Injection site cellulitis*	
Respiratory, thoracic and Mediastinal disorders			Dyspnoea*		Pulmonary arterial hypertension*
Immune system disorders				Anaphylactic reactions*	
Vascular disorders			Thromboembolic events*		
Hepatobiliary disorders	Asymptomatic transaminase increase	Severe elevations in transaminases	Hepatitis with or without icterus*	Hepatic failure*, autoimmune hepatitis*	
Renal and urinary disorders				Nephrotic syndrome*, glomerulosclerosis* (see section 4.4)	

Interferon beta has a potential for causing severe liver injury. The mechanism for the rare symptomatic hepatic dysfunction is not known. The majority of the cases of severe liver injury occurred within the first six months of treatment. No specific risk factors have been identified. Treatment with Rebif should be stopped if icterus or other clinical symptoms of liver dysfunction appear (see section 4.4).

Cases of pulmonary arterial hypertension (PAH) have been reported with interferon beta products. Events were reported at various time points including up to several years after starting treatment with interferon beta.

Class effect

The administration of interferons has been associated with anorexia, dizziness, anxiety, arrhythmias, vasodilation and palpitation, menorrhagia and metrorrhagia.

An increased formation of auto-antibodies may occur during treatment with interferon beta.

4.9 Overdose

In case of overdose, patients should be hospitalised for observation and appropriate supportive treatment should be given.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunostimulants, Interferon, ATC code: L03AB07.

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.

Regardless of the route of dosing, pronounced pharmacodynamic changes are associated with the administration of Rebif. After a single dose, intracellular and serum activity of 2-5A synthetase and serum concentrations of beta-2 microglobulin and neopterin increase within 24 hours, and start to decline within 2 days. Intramuscular and subcutaneous administrations produce fully superimposable responses. After repeated subcutaneous administration every 48 hours for 4 doses, these biological responses remain elevated, with no signs of tolerance development.

Biological response markers (e.g., 2',5'-OAS activity, neopterin and beta 2-microglobulin) are induced by interferon beta-1a following subcutaneous doses administered to healthy volunteer subjects. Time to peak concentrations following a single subcutaneous injection were 24 to 48 hours for neopterin, beta-2-microglobulin and 2'5'OAS, 12 hours for MX1 and 24 hours for OAS1 and OAS2 gene expression. Peaks of similar height and time were observed for most of these markers after first and sixth administration.

The precise mechanism of action of Rebif in multiple sclerosis is still under investigation.

Relapsing-remitting multiple sclerosis

The safety and efficacy of Rebif has been evaluated in patients with relapsing-remitting multiple sclerosis at doses ranging from 11 to 44 micrograms (3-12 million IU), administered subcutaneously three times per week. At licensed posology, Rebif 22 micrograms has been demonstrated to decrease the incidence (approximately 30% over 2 years) and severity of clinical

relapses in patients with at least 2 exacerbations in the previous 2 years and with an EDSS of 0-5.0 at entry. The proportion of patients with disability progression, as defined by at least one point increase in EDSS confirmed three months later, was reduced from 39% (placebo) to 30% (Rebif 22 micrograms). Over 4 years, the reduction in the mean exacerbation rate was 22% in patients treated with Rebif 22 micrograms, and 29% in patients treated with Rebif 44 micrograms group compared with a group of patients treated with placebo for 2 years and then either Rebif 22 or Rebif 44 micrograms for 2 years.

Secondary progressive multiple sclerosis
In a 3-year study in patients with secondary progressive multiple sclerosis (EDSS 3-6.5) with evidence of clinical progression in the preceding two years and who had not experienced relapses in the preceding 8 weeks, Rebif had no significant effect on progression of disability, but relapse rate was reduced by approximately 30%. If the patient population was divided into 2 subgroups (those with and those without relapses in the 2-year period prior to study entry), there was no effect on disability in patients without relapses, but in patients with relapses, the proportion with progression in disability at the end of the study was reduced from 70% (placebo) to 57% (Rebif 22 micrograms and 44 micrograms combined).
These results obtained in a subgroup of patients a posteriori should be interpreted cautiously.

Primary progressive multiple sclerosis
Rebif has not yet been investigated in patients with primary progressive multiple sclerosis, and should not be used in such patients.

5.2 Pharmacokinetic properties

Absorption
In healthy volunteers after intravenous administration, interferon beta-1a exhibits a sharp multi-exponential decline, with serum levels proportional to the dose. The initial half-life is in the order of minutes and the terminal half-life is several hours.

When administered by the subcutaneous or intramuscular routes, serum levels of interferon beta remain low, but are still measurable up to 12 to 24 hours post-dose. Subcutaneous and intramuscular administrations of Rebif produce equivalent exposure to interferon beta.

Distribution
Following repeated subcutaneous injections of 22 and 44 micrograms doses of Rebif maximum concentrations were typically observed after 8 hours, but this was highly variable.

Elimination
After repeated subcutaneous doses in healthy volunteers, the main PK parameters (AUCtau and Cmax) increased proportional to the increased in dose from 22 micrograms to 44 micrograms. The estimated apparent half-life is 50 to 60 hours, which is in line with the accumulation observed after multiple dosing.

Metabolism
Interferon beta-1a is mainly metabolised and excreted by the liver and the kidneys.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated-dose toxicity, and genotoxicity.

Rebif has not been investigated for carcinogenicity.

A study on embryo/foetal toxicity in monkeys showed no evidence of reproductive disturbances.
An increased risk of abortions has been reported in animal studies of other alpha and beta interferons. No information is available on the effects of the interferon beta-1a on male fertility.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol
Poloxamer 188
L-methionine
Benzyl alcohol
Sodium acetate
Acetic acid for pH adjustment
Sodium hydroxide for pH adjustment
Water for injections

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

After first injection use within 28 days.

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C) away from the cooling element. Do not freeze. Store the cartridge in the original package in order to protect from light.

The RebiSmart autoinjector device containing a prefilled cartridge of Rebif must be stored in the device storage box in a refrigerator (2°C – 8°C).

6.5 Nature and contents of container

Cartridges (type 1 glass) with a plunger stopper (rubber) and crimp cap (aluminium and halobutyl rubber) containing 1.5 ml solution for injection.
Pack size of 4 cartridges.

6.6 Special precautions for disposal and other handling

The solution for injection in a pre-filled cartridge is ready for use with the RebiSmart autoinjector device. For storage of the autoinjector device with the cartridge, see section 6.4.

For multidose use. Only clear to opalescent solution without particles should be used and without visible signs of deterioration. Any unused product or waste material should be disposed of in accordance with local requirements.

7. MANUFACTURER

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8. DATE OF REVISION OF THE TEXT

April 2021 (Based on MDS V9.0)