

ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Rebif 22 micrograms solution for injection in pre-filled syringe

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pre-filled syringe (0.5 mL) contains 22 micrograms (6 MIU*) of interferon beta-1a**.

* Million International Units, measured by cytopathic effect (CPE) bioassay against the in-house interferon 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 the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection in pre-filled syringe.

Clear to opalescent solution, with pH 3.5 to 4.5 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.

Rebif is available in three strengths: 8.8 micrograms, 22 micrograms and 44 micrograms. For patients initiating treatment with Rebif, Rebif 8.8 micrograms and Rebif 22 micrograms are available in a pack that corresponds to the patient needs for the first month of therapy.

Posology

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. The Rebif initiation package corresponds to the patient needs for the first month of treatment.

Paediatric population

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 2 years of age have not yet been established. Rebif should not be used in this age group.

Method of administration

Rebif is administered by subcutaneous injection. 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.

4.3 Contraindications

- Hypersensitivity to natural or recombinant interferon beta or to any of the excipients listed in section 6.1.
- Current severe depression and/or suicidal ideation (see sections 4.4 and 4.8).

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

General recommendations

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 (TMA)

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 antiepileptics (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.

Rebif, like other interferons beta, has a potential for causing severe liver injury including acute hepatic failure (see section 4.8). The majority of the cases of severe liver injury occurred within the first six months of treatment. 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 disorders

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 these 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.

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 adrenocorticotrophic 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 Fertility, pregnancy and lactation

Pregnancy

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

Based on animal data (see section 5.3), there is a possibly increased risk for spontaneous abortion. The risk of spontaneous abortions in pregnant women exposed to interferon beta cannot adequately be evaluated based on the currently available data, but the data do not suggest an increased risk so far.

If clinically needed, the use of Rebif may be considered during pregnancy

Breast-feeding

Limited information available on the transfer of interferon beta-1a into breast milk, together with the chemical/physiological characteristics of interferon beta, suggests that levels of interferon beta-1a excreted in human milk are negligible. No harmful effects on the breastfed newborn/infant are anticipated.

Rebif can be used during breast-feeding.

Fertility

The effects of Rebif on fertility have not been investigated.

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

Summary of the safety profile

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 are also common.

The majority of adverse reactions observed with interferon 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.

List of adverse reactions

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 following definitions apply to the frequency terminology used hereafter: very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ to $< 1/1,000$), very rare ($< 1/10,000$), frequency not known (cannot be estimated from the available data).

Blood and the lymphatic system disorders

Very common: Neutropenia, lymphopenia, leukopenia, thrombocytopenia, anaemia
Rare: Thrombotic microangiopathy including thrombotic thrombocytopenic purpura/haemolytic uraemic syndrome* (class label for interferon beta products, see section 4.4), pancytopenia*

Endocrine disorders

Uncommon: Thyroid dysfunction, most often presenting as hypothyroidism or hyperthyroidism

Immune system disorders

Rare: Anaphylactic reactions*

Hepatobiliary disorders

Very common: Asymptomatic transaminase increase
Common: Severe elevations in transaminases
Uncommon: Hepatitis with or without icterus*
Rare: Hepatic failure* (see section 4.4), autoimmune hepatitis*

Psychiatric disorders

Common: Depression, insomnia
Rare: Suicide attempt*

Nervous system disorders

Very common:	Headache
Uncommon:	Seizures*
Frequency not known:	Transient neurological symptoms (i.e. hypoesthesia, muscle spasm, paraesthesia, difficulty in walking, musculoskeletal stiffness) that may mimic multiple sclerosis exacerbations*

Eye disorders

Uncommon:	Retinal vascular disorders (i.e. retinopathy, cotton wool spots, obstruction of retinal artery or vein)*
-----------	--

Vascular disorders

Uncommon:	Thromboembolic events*
-----------	------------------------

Respiratory, thoracic and mediastinal disorders

Uncommon:	Dyspnoea*
Frequency not known:	Pulmonary arterial hypertension* (class label for interferon products, see below Pulmonary arterial hypertension)

Gastrointestinal disorders

Common:	Diarrhoea, vomiting, nausea
---------	-----------------------------

Skin and subcutaneous tissue disorders

Common:	Pruritus, rash, erythematous rash, maculo-papular rash, alopecia*
Uncommon:	Urticaria*
Rare:	Quincke's oedema (angio-oedema)*, erythema multiforme*, erythema multiforme-like skin reactions*, Stevens Johnson syndrome*

Musculoskeletal and connective disorders

Common:	Myalgia, arthralgia
Rare:	Drug-induced lupus erythematosus*

Renal and urinary disorders

Rare:	Nephrotic syndrome*, glomerulosclerosis* (see section 4.4)
-------	--

General disorders and administration site conditions

Very common:	Injection site inflammation, injection site reaction, influenza-like symptoms
Common:	Injection site pain, fatigue, rigors, fever
Uncommon:	Injection site necrosis, injection site mass, injection site abscess, injection site infections*, increased sweating*
Rare:	Injection site cellulitis*
Frequency not known:	Panniculitis (occurred in the injection site)

Paediatric population

No formal clinical trials or pharmacokinetic studies have been conducted in children or adolescents. Limited safety data suggest that the safety profile in children and adolescents (2 to 17 years old) receiving Rebif 22 micrograms or 44 micrograms three times weekly is similar to that seen in adults.

Class effects

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.

Pulmonary arterial hypertension

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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in [Appendix V](#).

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, Interferons, ATC code: L03AB07

Interferons 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 2'5'OAS 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 these 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. 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 (AUC_{tau} and C_{max}) 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

18 months.

6.4 Special precautions for storage

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

For the purpose of ambulatory use, the patient may remove Rebif from the refrigerator and store it not above 25°C for one single period of up to 14 days. Rebif must then be returned to the refrigerator and used before the expiry date.

6.5 Nature and contents of container

One mL type 1 glass syringe, with a stainless steel needle, containing 0.5 mL solution.

Rebif 22 micrograms is available as a package of 1, 3, 12, or 36 syringes.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

The solution for injection in a pre-filled syringe is ready for use. It may also be administered with a suitable auto-injector.

For single use only. Only clear to opalescent solution without particles and without visible signs of deterioration should be used.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Merck Europe B.V.
Gustav Mahlerplein 102
1082 MA Amsterdam
The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/98/063/001
EU/1/98/063/002
EU/1/98/063/003
EU/1/98/063/020

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 04 May 1998
Date of latest renewal: 04 May 2008

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>.

1. NAME OF THE MEDICINAL PRODUCT

Rebif 44 micrograms solution for injection in pre-filled syringe

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pre-filled syringe (0.5 mL) contains 44 micrograms (12 MIU*) of interferon beta-1a**.

* Million International Units, measured by cytopathic effect (CPE) bioassay against the in-house interferon 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 the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection in pre-filled syringe.

Clear to opalescent solution, with pH 3.5 to 4.5 and osmolarity 250 to 450 mOsm/L.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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 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.

Rebif is available in three strengths: 8.8 micrograms, 22 micrograms and 44 micrograms. For patients initiating treatment with Rebif, Rebif 8.8 micrograms and Rebif 22 micrograms are available in a pack that corresponds to the patient needs for the first month of therapy.

Posology

When first starting treatment with Rebif, in order to allow tachyphylaxis to develop thus reducing adverse reactions it is recommended that patients be started at 8.8 micrograms dose subcutaneously and the dose be increased over a 4 week period to the targeted dose, according to the following schedule:

	Recommended Titration (% of final dose)	Titration dose for Rebif 44 micrograms three times per week (tiw)
Weeks 1-2	20%	8.8 micrograms tiw
Weeks 3-4	50%	22 micrograms tiw
Weeks 5+	100%	44 micrograms tiw

First demyelinating event

The posology for patients who have experienced a first demyelinating event is 44 micrograms of Rebif given three times per week by subcutaneous injection.

Relapsing multiple sclerosis

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.

Paediatric population

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 2 years of age have not yet been established. Rebif should not be used in this age group.

Method of administration

Rebif is administered by subcutaneous injection. 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.

4.3 Contraindications

- Hypersensitivity to natural or recombinant interferon beta or to any of the excipients listed in section 6.1.
- Current severe depression and/or suicidal ideation (see sections 4.4 and 4.8).

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

General recommendations

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 (TMA)

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 antiepileptics (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.

Rebif, like other interferons beta, has a potential for causing severe liver injury including acute hepatic failure (see section 4.8). The majority of the cases of severe liver injury occurred within the first six months of treatment. 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. The overall incidence of these is slightly higher with Rebif 44 than Rebif 22 micrograms. 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. These should be more frequent when initiating Rebif 44 micrograms.

Thyroid disorders

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 44 micrograms, approximately 13 to 14% 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 these 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.

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 adrenocorticotrophic 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 Fertility, pregnancy and lactation

Pregnancy

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

Based on animal data (see section 5.3), there is a possibly increased risk for spontaneous abortion. The risk of spontaneous abortions in pregnant women exposed to interferon beta cannot adequately be evaluated based on the currently available data, but the data do not suggest an increased risk so far.

If clinically needed, the use of Rebif may be considered during pregnancy

Breast-feeding

Limited information available on the transfer of interferon beta-1a into breast milk, together with the chemical/physiological characteristics of interferon beta, suggests that levels of interferon beta-1a excreted in human milk are negligible. No harmful effects on the breastfed newborn/infant are anticipated.

Rebif can be used during breast-feeding.

Fertility

The effects of Rebif on fertility have not been investigated.

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

Summary of the safety profile

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 are also common.

The majority of adverse reactions observed with interferon 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.

List of adverse reactions

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 following definitions apply to the frequency terminology used hereafter: very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ to $< 1/1,000$), very rare ($< 1/10,000$), frequency not known (cannot be estimated from the available data).

Blood and the lymphatic system disorders

Very common:	Neutropenia, lymphopenia, leukopenia, thrombocytopenia, anaemia
Rare:	Thrombotic microangiopathy including thrombotic thrombocytopenic purpura/haemolytic uraemic syndrome* (class label for interferon beta products, see section 4.4), pancytopenia*

Endocrine disorders

Uncommon:	Thyroid dysfunction, most often presenting as hypothyroidism or hyperthyroidism
-----------	---

Immune system disorders

Rare: Anaphylactic reactions*

Hepatobiliary disorders

Very common: Asymptomatic transaminase increase

Common: Severe elevations in transaminases

Uncommon: Hepatitis with or without icterus*

Rare: Hepatic failure* (see section 4.4), autoimmune hepatitis*

Psychiatric disorders

Common: Depression, insomnia

Rare: Suicide attempt*

Nervous system disorders

Very common: Headache

Uncommon: Seizures*

Frequency not known: Transient neurological symptoms (i.e. hypoesthesia, muscle spasm, paraesthesia, difficulty in walking, musculoskeletal stiffness) that may mimic multiple sclerosis exacerbations*

Eye disorders

Uncommon: Retinal vascular disorders (i.e. retinopathy, cotton wool spots, obstruction of retinal artery or vein)*

Vascular disorders

Uncommon: Thromboembolic events*

Respiratory, thoracic and mediastinal disorders

Uncommon: Dyspnoea*

Frequency not known: Pulmonary arterial hypertension* (class label for interferon products, see below Pulmonary arterial hypertension)

Gastrointestinal disorders

Common: Diarrhoea, vomiting, nausea

Skin and subcutaneous tissue disorders

Common: Pruritus, rash, erythematous rash, maculo-papular rash, alopecia*

Uncommon: Urticaria*

Rare: Quincke's oedema (angio-oedema)*, erythema multiforme*, erythema multiforme-like skin reactions*, Stevens Johnson syndrome*

Musculoskeletal and connective disorders

Common: Myalgia, arthralgia

Rare: Drug-induced lupus erythematosus*

Renal and urinary disorders

Rare: Nephrotic syndrome*, glomerulosclerosis* (see section 4.4)

General disorders and administration site conditions

Very common: Injection site inflammation, injection site reaction, influenza-like symptoms

Common: Injection site pain, fatigue, rigors, fever

Uncommon: Injection site necrosis, injection site mass, injection site abscess, injection site infections*, increased sweating*

Rare: Injection site cellulitis*

Frequency not known: Panniculitis (occurred in the injection site)

Paediatric population

No formal clinical trials or pharmacokinetic studies have been conducted in children or adolescents. Limited safety data suggest that the safety profile in children and adolescents (2 to 17 years old) receiving Rebif 22 micrograms or 44 micrograms three times weekly is similar to that seen in adults.

Class effects

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.

Pulmonary arterial hypertension

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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in [Appendix V](#).

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, Interferons, ATC code: L03AB07

Interferons 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 2'5'OAS 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.

Single clinical event suggestive of multiple sclerosis

One 2-year controlled clinical trial with Rebif was performed in patients with a single clinical event suggestive of demyelination due to multiple sclerosis. The patients enrolled into the trial had at least two clinically silent lesions on the T2-weighted MRI scan, with a size of at least 3 mm, at least one of which is ovoid or periventricular or infratentorial. Any disease other than multiple sclerosis that could better explain signs and symptoms of the patient had to be excluded.

Patients were randomised in a double-blind manner to either Rebif 44 micrograms given three times per week, Rebif 44 micrograms once weekly, or placebo. If a second clinical demyelinating event occurred confirming definite multiple sclerosis, patients switched to the recommended posology of Rebif 44 micrograms three times per week in an open label manner, while maintaining blinding as to initial randomisation.

Efficacy results of Rebif 44 micrograms given three times per week compared to placebo from this study are as follows:

Parameter Statistics	Treatment		Treatment Comparison Rebif 44 mcg tiw versus Placebo		
	Placebo (n=171)	Rebif 44 mcg tiw (n=171)	Risk Reduction	Cox's Proportional Hazard Ratio [95% CI]	Log-Rank p-value
McDonald (2005) Conversion					
Number of events	144	106	51%	0.49 [0.38;0.64]	<0.001
KM Estimate	85.8%	62.5%			
CDMS Conversion					
Number of events	60	33	52%	0.48 [0.31;0.73]	<0.001
KM Estimate	37.5%	20.6%			
Mean CUA Lesions per Subject per Scan During the Double Blind Period					
Least Square Means (SE)	2.59 (0.30)	0.50 (0.06)	81%	0.19 [0.14;0.26]*	<0.001

tiw: three times per week, CI: confidence interval, CUA: combined unique active

* Least Squared Mean Ratio [95% CI]

For the time being there is no well established definition of a high risk patient, although a more conservative approach is to accept at least nine T2 hyperintense lesions on the initial scan and at least one new T2 or one new Gd-enhancing lesion on a follow-up scan taken at least 1 month after the initial scan. In any case, treatment should only be considered for patients classified as high risk.

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 44 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 27% (Rebif 44 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 these 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. 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 (AUC_{tau} and C_{max}) 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

18 months.

6.4 Special precautions for storage

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

For the purpose of ambulatory use, the patient may remove Rebif from the refrigerator and store it not above 25°C for one single period of up to 14 days. Rebif must then be returned to the refrigerator and used before the expiry date.

6.5 Nature and contents of container

One mL type 1 glass syringe, with a stainless steel needle, containing 0.5 mL solution.

Rebif 44 micrograms is available as a package of 1, 3, 12, or 36 syringes.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

The solution for injection in a pre-filled syringe is ready for use. It may also be administered with a suitable auto-injector.

For single use only. Only clear to opalescent solution without particles and without visible signs of deterioration should be used.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Merck Europe B.V.
Gustav Mahlerplein 102
1082 MA Amsterdam
The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/98/063/004
EU/1/98/063/005
EU/1/98/063/006
EU/1/98/063/021

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 04 May 1998
Date of latest renewal: 04 May 2008

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>.

1. NAME OF THE MEDICINAL PRODUCT

Rebif 8.8 micrograms solution for injection in pre-filled syringe
Rebif 22 micrograms solution for injection in pre-filled syringe

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pre-filled syringe (0.2 mL) contains 8.8 micrograms (2.4 MIU*) of interferon beta-1a**.

* Million International Units, measured by cytopathic effect (CPE) bioassay against the in-house interferon 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 1.0 mg benzyl alcohol per dose of 0.2 mL.
For the full list of excipients, see section 6.1.

Each pre-filled syringe (0.5 mL) contains 22 micrograms (6 MIU*) of interferon beta-1a**.

* Million International Units, measured by cytopathic effect (CPE) bioassay against the in-house interferon 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 the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection in pre-filled syringe.

Clear to opalescent solution, with pH 3.5 to 4.5 and osmolarity 250 to 450 mOsm/L.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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 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.

Posology

The Rebif initiation package corresponds to the patient needs for the first month of treatment. When first starting treatment with Rebif, in order to allow tachyphylaxis to develop thus reducing adverse reactions, it is recommended that patients be started at 8.8 micrograms dose subcutaneously and the dose be increased over a 4 week period to the targeted dose, according to the following schedule:

	Recommended Titration (% of final dose)	Titration dose for Rebif 44 micrograms three times per week (tiw)
Weeks 1-2	20%	8.8 micrograms tiw
Weeks 3-4	50%	22 micrograms tiw
Weeks 5+	100%	44 micrograms tiw

Paediatric population

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 2 years of age have not yet been established. Rebif should not be used in this age group.

Method of administration

Rebif is administered by subcutaneous injection. 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.

4.3 Contraindications

- Hypersensitivity to natural or recombinant interferon beta or to any of the excipients listed in section 6.1.
- Current severe depression and/or suicidal ideation (see sections 4.4 and 4.8).

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

General recommendations

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 (TMA)

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 antiepileptics (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.

Rebif, like other interferons beta, has a potential for causing severe liver injury including acute hepatic failure (see section 4.8). The majority of the cases of severe liver injury occurred within the first six months of treatment. 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 disorders

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 these 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.

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 adrenocorticotrophic 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 Fertility, pregnancy and lactation

Pregnancy

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

Based on animal data (see section 5.3), there is a possibly increased risk for spontaneous abortion. The risk of spontaneous abortions in pregnant women exposed to interferon beta cannot adequately be evaluated based on the currently available data, but the data do not suggest an increased risk so far.

If clinically needed, the use of Rebif may be considered during pregnancy

Breast-feeding

Limited information available on the transfer of interferon beta-1a into breast milk, together with the chemical/physiological characteristics of interferon beta, suggests that levels of interferon beta-1a excreted in human milk are negligible. No harmful effects on the breastfed newborn/infant are anticipated.

Rebif can be used during breast-feeding.

Fertility

The effects of Rebif on fertility have not been investigated.

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

Summary of the safety profile

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 are also common.

The majority of adverse reactions observed with interferon 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.

List of adverse reactions

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 following definitions apply to the frequency terminology used hereafter: very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ to $< 1/1,000$), very rare ($< 1/10,000$), frequency not known (cannot be estimated from the available data).

Blood and the lymphatic system disorders

Very common:	Neutropenia, lymphopenia, leukopenia, thrombocytopenia, anaemia
Rare:	Thrombotic microangiopathy including thrombotic thrombocytopenic purpura/haemolytic uraemic syndrome* (class label for interferon beta products, see section 4.4), pancytopenia*

Endocrine disorders

Uncommon:	Thyroid dysfunction, most often presenting as hypothyroidism or hyperthyroidism
-----------	---

Immune system disorders

Rare:	Anaphylactic reactions*
-------	-------------------------

Hepatobiliary disorders

Very common:	Asymptomatic transaminase increase
Common:	Severe elevations in transaminases
Uncommon:	Hepatitis with or without icterus*
Rare:	Hepatic failure* (see section 4.4), autoimmune hepatitis*

Psychiatric disorders

Common:	Depression, insomnia
Rare:	Suicide attempt*

Nervous system disorders

Very common:	Headache
Uncommon:	Seizures*
Frequency not known:	Transient neurological symptoms (i.e. hypoesthesia, muscle spasm, paraesthesia, difficulty in walking, musculoskeletal stiffness) that may mimic multiple sclerosis exacerbations*

Eye disorders

Uncommon:	Retinal vascular disorders (i.e. retinopathy, cotton wool spots, obstruction of retinal artery or vein)*
-----------	--

Vascular disorders

Uncommon:	Thromboembolic events*
-----------	------------------------

Respiratory, thoracic and mediastinal disorders

Uncommon:	Dyspnoea*
Frequency not known:	Pulmonary arterial hypertension* (class label for interferon products, see below Pulmonary arterial hypertension)

Gastrointestinal disorders

Common:	Diarrhoea, vomiting, nausea
---------	-----------------------------

Skin and subcutaneous tissue disorders

Common:	Pruritus, rash, erythematous rash, maculo-papular rash, alopecia*
Uncommon:	Urticaria*
Rare:	Quincke's oedema (angio-oedema)*, erythema multiforme*, erythema multiforme-like skin reactions*, Stevens Johnson syndrome*

Musculoskeletal and connective disorders

Common:	Myalgia, arthralgia
Rare:	Drug-induced lupus erythematosus*

Renal and urinary disorders

Rare:	Nephrotic syndrome*, glomerulosclerosis* (see section 4.4)
-------	--

General disorders and administration site conditions

Very common:	Injection site inflammation, injection site reaction, influenza-like symptoms
Common:	Injection site pain, fatigue, rigors, fever
Uncommon:	Injection site necrosis, injection site mass, injection site abscess, injection site infections*, increased sweating*
Rare:	Injection site cellulitis*
Frequency not known:	Panniculitis (occurred in the injection site)

Paediatric population

No formal clinical trials or pharmacokinetic studies have been conducted in children or adolescents. Limited safety data suggest that the safety profile in children and adolescents (2 to 17 years old) receiving Rebif 22 micrograms or 44 micrograms three times weekly is similar to that seen in adults.

Class effects

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.

Pulmonary arterial hypertension

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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in [Appendix V](#).

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, Interferons, ATC code: L03AB07

Interferons 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 2'5'OAS 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.

Single clinical event suggestive of multiple sclerosis

One 2-year controlled clinical trial with Rebif was performed in patients with a single clinical event suggestive of demyelination due to multiple sclerosis. The patients enrolled into the trial had at least two clinically silent lesions on the T2-weighted MRI scan, with a size of at least 3 mm, at least one of which is ovoid or periventricular or infratentorial. Any disease other than multiple sclerosis that could better explain signs and symptoms of the patient had to be excluded.

Patients were randomised in a double-blind manner to either Rebif 44 micrograms given three times per week, Rebif 44 micrograms once weekly, or placebo. If a second clinical demyelinating event occurred confirming definite multiple sclerosis, patients switched to the recommended posology of Rebif 44 micrograms three times per week in an open label manner, while maintaining blinding as to initial randomisation.

Efficacy results of Rebif 44 micrograms given three times per week compared to placebo from this study are as follows:

Parameter Statistics	Treatment		Treatment Comparison Rebif 44 mcg tiw versus Placebo		
	Placebo (n=171)	Rebif 44 mcg tiw (n=171)	Risk Reduction	Cox's Proportional Hazard Ratio [95% CI]	Log-Rank p-value
McDonald (2005) Conversion					
Number of events	144	106	51%	0.49 [0.38;0.64]	<0.001
KM Estimate	85.8%	62.5%			
CDMS Conversion					
Number of events	60	33	52%	0.48 [0.31;0.73]	<0.001
KM Estimate	37.5%	20.6%			
Mean CUA Lesions per Subject per Scan During the Double Blind Period					
Least Square Means (SE)	2.59 (0.30)	0.50 (0.06)	81%	0.19 [0.14;0.26]*	<0.001

tiw: three times per week, CI: confidence interval, CUA: combined unique active

* Least Squared Mean Ratio [95% CI]

For the time being there is no well established definition of a high risk patient, although a more conservative approach is to accept at least nine T2 hyperintense lesions on the initial scan and at least one new T2 or one new Gd-enhancing lesion on a follow-up scan taken at least 1 month after the initial scan. In any case, treatment should only be considered for patients classified as high risk.

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 these 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. 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 (AUC_{tau} and C_{max}) 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

18 months.

6.4 Special precautions for storage

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

For the purpose of ambulatory use, the patient may remove Rebif from the refrigerator and store it not above 25°C for one single period of up to 14 days. Rebif must then be returned to the refrigerator and used before the expiry date.

6.5 Nature and contents of container

For patients starting treatment with Rebif, Rebif 8.8 micrograms and Rebif 22 micrograms are available in an initiation pack. The pack contains 6 individual doses of 0.2 mL of Rebif 8.8 micrograms solution for injection in a 1 mL type 1 glass syringe with a stainless steel needle and 6 individual doses of 0.5 mL of Rebif 22 micrograms solution for injection in a 1 mL type 1 glass syringe with a stainless steel needle.

This pack corresponds to the individual patient needs for the first month of therapy.

6.6 Special precautions for disposal and other handling

The solution for injection in a pre-filled syringe is ready for use. It may also be administered with a suitable auto-injector.

For single use only. Only clear to opalescent solution without particles and without visible signs of deterioration should be used.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Merck Europe B.V.
Gustav Mahlerplein 102
1082 MA Amsterdam
The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/98/063/007

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 04 May 1998

Date of latest renewal: 04 May 2008

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>.

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 interferon 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 the 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.

Posology

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. The Rebif initiation package corresponds to the patient needs for the first month of treatment.

Paediatric population

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 2 years of age have not yet been established. Rebif should not be used in this age group.

Method of administration

Rebif solution for subcutaneous injection in a cartridge is intended for multidose use with the RebiSmart electronic injection device following adequate training of the patient and/or carer.

For administration, the instructions provided in the package leaflet and in the instruction manual (Instructions for Use) provided with RebiSmart 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.

4.3 Contraindications

- Hypersensitivity to natural or recombinant interferon beta or to any of the excipients listed in section 6.1.
- Current severe depression and/or suicidal ideation (see sections 4.4 and 4.8).

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

General recommendations

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 (TMA)

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 antiepileptics (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.

Rebif, like other interferons beta, has a potential for causing severe liver injury including acute hepatic failure (see section 4.8). The majority of the cases of severe liver injury occurred within the first six months of treatment. 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 disorders

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 these 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.

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 adrenocorticotrophic 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 Fertility, pregnancy and lactation

Pregnancy

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

Based on animal data (see section 5.3), there is a possibly increased risk for spontaneous abortion. The risk of spontaneous abortions in pregnant women exposed to interferon beta cannot adequately be evaluated based on the currently available data, but the data do not suggest an increased risk so far.

If clinically needed, the use of Rebif may be considered during pregnancy

Breast-feeding

Limited information available on the transfer of interferon beta-1a into breast milk, together with the chemical/physiological characteristics of interferon beta, suggests that levels of interferon beta-1a excreted in human milk are negligible. No harmful effects on the breastfed newborn/infant are anticipated.

Rebif can be used during breast-feeding.

Fertility

The effects of Rebif on fertility have not been investigated.

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

Summary of the safety profile

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 are also common.

The majority of adverse reactions observed with interferon 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.

List of adverse reactions

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 following definitions apply to the frequency terminology used hereafter: very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ to $< 1/1,000$), very rare ($< 1/10,000$), frequency not known (cannot be estimated from the available data).

Blood and the lymphatic system disorders

Very common:	Neutropenia, lymphopenia, leukopenia, thrombocytopenia, anaemia
Rare:	Thrombotic microangiopathy including thrombotic thrombocytopenic purpura/haemolytic uraemic syndrome* (class label for interferon beta products, see section 4.4), pancytopenia*

Endocrine disorders

Uncommon:	Thyroid dysfunction, most often presenting as hypothyroidism or hyperthyroidism
-----------	---

Immune system disorders

Rare:	Anaphylactic reactions*
-------	-------------------------

Hepatobiliary disorders

Very common:	Asymptomatic transaminase increase
Common:	Severe elevations in transaminases
Uncommon:	Hepatitis with or without icterus*
Rare:	Hepatic failure* (see section 4.4), autoimmune hepatitis*

Psychiatric disorders

Common:	Depression, insomnia
Rare:	Suicide attempt*

Nervous system disorders

Very common:	Headache
Uncommon:	Seizures*
Frequency not known:	Transient neurological symptoms (i.e. hypoesthesia, muscle spasm, paraesthesia, difficulty in walking, musculoskeletal stiffness) that may mimic multiple sclerosis exacerbations*

Eye disorders

Uncommon:	Retinal vascular disorders (i.e. retinopathy, cotton wool spots, obstruction of retinal artery or vein)*
-----------	--

Vascular disorders

Uncommon:	Thromboembolic events*
-----------	------------------------

Respiratory, thoracic and mediastinal disorders

Uncommon:	Dyspnoea*
Frequency not known:	Pulmonary arterial hypertension* (class label for interferon products, see below Pulmonary arterial hypertension)

Gastrointestinal disorders

Common:	Diarrhoea, vomiting, nausea
---------	-----------------------------

Skin and subcutaneous tissue disorders

Common:	Pruritus, rash, erythematous rash, maculo-papular rash, alopecia*
Uncommon:	Urticaria*
Rare:	Quincke's oedema (angio-oedema)*, erythema multiforme*, erythema multiforme-like skin reactions*, Stevens Johnson syndrome*

Musculoskeletal and connective disorders

Common:	Myalgia, arthralgia
Rare:	Drug-induced lupus erythematosus*

Renal and urinary disorders

Rare:	Nephrotic syndrome*, glomerulosclerosis* (see section 4.4)
-------	--

General disorders and administration site conditions

Very common:	Injection site inflammation, injection site reaction, influenza-like symptoms
Common:	Injection site pain, fatigue, rigors, fever
Uncommon:	Injection site necrosis, injection site mass, injection site abscess, injection site infections*, increased sweating*
Rare:	Injection site cellulitis*
Frequency not known:	Panniculitis (occurred in the injection site)

Paediatric population

No formal clinical trials or pharmacokinetic studies have been conducted in children or adolescents. Limited safety data suggest that the safety profile in children and adolescents (2 to 17 years old) receiving Rebif 22 micrograms or 44 micrograms three times weekly is similar to that seen in adults.

Class effects

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.

Pulmonary arterial hypertension

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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in [Appendix V](#).

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, Interferons, ATC code: L03AB07

Interferons 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 2'5'OAS 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 these 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. 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 (AUC_{tau} and C_{max}) 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

18 months.
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 device (RebiSmart) containing a pre-filled cartridge of Rebif must be stored in the device storage box in a refrigerator (2°C – 8°C).

For the purpose of ambulatory use, the patient may remove Rebif from the refrigerator and store it not above 25°C for one single period of up to 14 days. Rebif must then be returned to the refrigerator and used before the expiry date.

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 or 12 cartridges.
Not all pack sizes may be marketed.

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 electronic injection device. For storage of the device with the cartridge, see section 6.4.

For multidose use. Only clear to opalescent solution without particles and without visible signs of deterioration should be used.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Merck Europe B.V.
Gustav Mahlerplein 102
1082 MA Amsterdam
The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/98/063/008
EU/1/98/063/018

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 04 May 1998
Date of latest renewal: 04 May 2008

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>.

1. NAME OF THE MEDICINAL PRODUCT

Rebif 44 micrograms/0.5 mL solution for injection in cartridge

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pre-filled cartridge contains 132 micrograms (36 MIU*) of interferon beta-1a** in 1.5 mL solution, corresponding to 88 micrograms/mL.

* Million International Units, measured by cytopathic effect (CPE) bioassay against the in-house interferon 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 the 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

- 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 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.

For patients initiating treatment with Rebif, Rebif 8.8 micrograms and Rebif 22 micrograms are available in a pack that corresponds to the patient needs for the first month of therapy.

Posology

When first starting treatment with Rebif, in order to allow tachyphylaxis to develop thus reducing adverse reactions it is recommended that patients be started at 8.8 micrograms dose subcutaneously and the dose be increased over a 4 week period to the targeted dose, according to the following schedule:

	Recommended Titration (% of final dose)	Titration dose for Rebif 44 micrograms three times per week (tiw)
Weeks 1-2	20%	8.8 micrograms tiw
Weeks 3-4	50%	22 micrograms tiw
Weeks 5+	100%	44 micrograms tiw

First demyelinating event

The posology for patients who have experienced a first demyelinating event is 44 micrograms of Rebif given three times per week by subcutaneous injection.

Relapsing multiple sclerosis

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.

Paediatric population

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 2 years of age have not yet been established. Rebif should not be used in this age group.

Method of administration

Rebif solution for subcutaneous injection in a cartridge is intended for multidose use with the RebiSmart electronic injection device following adequate training of the patient and/or carer.

For administration, the instructions provided in the package leaflet and in the instruction manual (Instructions for Use) provided with RebiSmart 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.

4.3 Contraindications

- Hypersensitivity to natural or recombinant interferon beta or to any of the excipients listed in section 6.1.
- Current severe depression and/or suicidal ideation (see sections 4.4 and 4.8).

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

General recommendations

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 (TMA)

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 antiepileptics (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.

Rebif, like other interferons beta, has a potential for causing severe liver injury including acute hepatic failure (see section 4.8). The majority of the cases of severe liver injury occurred within the first six months of treatment. 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. The overall incidence of these is slightly higher with Rebif 44 than Rebif 22 micrograms. 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. These should be more frequent when initiating Rebif 44 micrograms.

Thyroid disorders

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 44 micrograms, approximately 13 to 14% 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 these 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.

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 adrenocorticotrophic 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 Fertility, pregnancy and lactation

Pregnancy

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

Based on animal data (see section 5.3), there is a possibly increased risk for spontaneous abortion. The risk of spontaneous abortions in pregnant women exposed to interferon beta cannot adequately be evaluated based on the currently available data, but the data do not suggest an increased risk so far.

If clinically needed, the use of Rebif may be considered during pregnancy

Breast-feeding

Limited information available on the transfer of interferon beta-1a into breast milk, together with the chemical/physiological characteristics of interferon beta, suggests that levels of interferon beta-1a excreted in human milk are negligible. No harmful effects on the breastfed newborn/infant are anticipated.

Rebif can be used during breast-feeding.

Fertility

The effects of Rebif on fertility have not been investigated.

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

Summary of the safety profile

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 are also common.

The majority of adverse reactions observed with interferon 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.

List of adverse reactions

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 following definitions apply to the frequency terminology used hereafter: very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ to $< 1/1,000$), very rare ($< 1/10,000$), frequency not known (cannot be estimated from the available data).

Blood and the lymphatic system disorders

Very common: Neutropenia, lymphopenia, leukopenia, thrombocytopenia, anaemia
Rare: Thrombotic microangiopathy including thrombotic thrombocytopenic purpura/haemolytic uraemic syndrome* (class label for interferon beta products, see section 4.4), pancytopenia*

Endocrine disorders

Uncommon: Thyroid dysfunction, most often presenting as hypothyroidism or hyperthyroidism

Immune system disorders

Rare: Anaphylactic reactions*

Hepatobiliary disorders

Very common: Asymptomatic transaminase increase
Common: Severe elevations in transaminases
Uncommon: Hepatitis with or without icterus*
Rare: Hepatic failure* (see section 4.4), autoimmune hepatitis*

Psychiatric disorders

Common: Depression, insomnia
Rare: Suicide attempt*

Nervous system disorders

Very common: Headache
Uncommon: Seizures*
Frequency not known: Transient neurological symptoms (i.e. hypoesthesia, muscle spasm, paraesthesia, difficulty in walking, musculoskeletal stiffness) that may mimic multiple sclerosis exacerbations*

Eye disorders

Uncommon: Retinal vascular disorders (i.e. retinopathy, cotton wool spots, obstruction of retinal artery or vein)*

Vascular disorders

Uncommon: Thromboembolic events*

Respiratory, thoracic and mediastinal disorders

Uncommon: Dyspnoea*
Frequency not known: Pulmonary arterial hypertension* (class label for interferon products, see below Pulmonary arterial hypertension)

Gastrointestinal disorders

Common: Diarrhoea, vomiting, nausea

Skin and subcutaneous tissue disorders

Common:	Pruritus, rash, erythematous rash, maculo-papular rash, alopecia*
Uncommon:	Urticaria*
Rare:	Quincke's oedema (angio-oedema)*, erythema multiforme*, erythema multiforme-like skin reactions*, Stevens Johnson syndrome*

Musculoskeletal and connective disorders

Common:	Myalgia, arthralgia
Rare:	Drug-induced lupus erythematosus*

Renal and urinary disorders

Rare:	Nephrotic syndrome*, glomerulosclerosis* (see section 4.4)
-------	--

General disorders and administration site conditions

Very common:	Injection site inflammation, injection site reaction, influenza-like symptoms
Common:	Injection site pain, fatigue, rigors, fever
Uncommon:	Injection site necrosis, injection site mass, injection site abscess, injection site infections*, increased sweating*
Rare:	Injection site cellulitis*
Frequency not known:	Panniculitis (occurred in the injection site)

Paediatric population

No formal clinical trials or pharmacokinetic studies have been conducted in children or adolescents. Limited safety data suggest that the safety profile in children and adolescents (2 to 17 years old) receiving Rebif 22 micrograms or 44 micrograms three times weekly is similar to that seen in adults.

Class effects

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.

Pulmonary arterial hypertension

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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in [Appendix V](#).

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, Interferons, ATC code: L03AB07

Interferons 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 2'5'OAS 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.

Single clinical event suggestive of multiple sclerosis

One 2-year controlled clinical trial with Rebif was performed in patients with a single clinical event suggestive of demyelination due to multiple sclerosis. The patients enrolled into the trial had at least two clinically silent lesions on the T2-weighted MRI scan, with a size of at least 3 mm, at least one of which is ovoid or periventricular or infratentorial. Any disease other than multiple sclerosis that could better explain signs and symptoms of the patient had to be excluded.

Patients were randomised in a double-blind manner to either Rebif 44 micrograms given three times per week, Rebif 44 micrograms once weekly, or placebo. If a second clinical demyelinating event occurred confirming definite multiple sclerosis, patients switched to the recommended posology of Rebif 44 micrograms three times per week in an open label manner, while maintaining blinding as to initial randomisation.

Efficacy results of Rebif 44 micrograms given three times per week compared to placebo from this study are as follows:

Parameter Statistics	Treatment		Treatment Comparison Rebif 44 mcg tiw versus Placebo		
	Placebo (n=171)	Rebif 44 mcg tiw (n=171)	Risk Reduction	Cox's Proportional Hazard Ratio [95% CI]	Log-Rank p-value
McDonald (2005) Conversion					
Number of events	144	106	51%	0.49 [0.38;0.64]	<0.001
KM Estimate	85.8%	62.5%			
CDMS Conversion					
Number of events	60	33	52%	0.48 [0.31;0.73]	<0.001
KM Estimate	37.5%	20.6%			
Mean CUA Lesions per Subject per Scan During the Double Blind Period					
Least Square Means (SE)	2.59 (0.30)	0.50 (0.06)	81%	0.19 [0.14;0.26]*	<0.001

tiw: three times per week, CI: confidence interval, CUA: combined unique active

* Least Squared Mean Ratio [95% CI]

For the time being there is no well established definition of a high risk patient, although a more conservative approach is to accept at least nine T2 hyperintense lesions on the initial scan and at least one new T2 or one new Gd-enhancing lesion on a follow-up scan taken at least 1 month after the initial scan. In any case, treatment should only be considered for patients classified as high risk.

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 44 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 27% (Rebif 44 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 these 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. 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 (AUC_{tau} and C_{max}) 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

18 months.
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 device (RebiSmart) containing a pre-filled cartridge of Rebif must be stored in the device storage box in a refrigerator (2°C – 8°C).

For the purpose of ambulatory use, the patient may remove Rebif from the refrigerator and store it not above 25°C for one single period of up to 14 days. Rebif must then be returned to the refrigerator and used before the expiry date.

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 or 12 cartridges.

Not all pack sizes may be marketed.

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 electronic injection device. For storage of the device with the cartridge, see section 6.4.

For multidose use. Only clear to opalescent solution without particles and without visible signs of deterioration should be used.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Merck Europe B.V.
Gustav Mahlerplein 102
1082 MA Amsterdam
The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/98/063/009
EU/1/98/063/019

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 04 May 1998
Date of latest renewal: 04 May 2008

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>.

1. NAME OF THE MEDICINAL PRODUCT

Rebif 8.8 micrograms/0.1 mL solution for injection in cartridge
Rebif 22 micrograms/0.25 mL solution for injection in cartridge

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pre-filled cartridge contains 132 micrograms (36 MIU*) of interferon beta-1a** in 1.5 mL solution, corresponding to 88 micrograms/mL.

* Million International Units, measured by cytopathic effect (CPE) bioassay against the in-house interferon 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 0.5 mg benzyl alcohol per dose of 0.1 mL and 1.25 mg benzyl alcohol per dose of 0.25 mL.

For the 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

- 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 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.

Posology

The Rebif initiation package corresponds to the patient needs for the first month of treatment. When first starting treatment with Rebif, in order to allow tachyphylaxis to develop thus reducing adverse reactions, it is recommended that patients be started at 8.8 micrograms dose subcutaneously and the dose be increased over a 4 week period to the targeted dose, according to the following schedule:

	Recommended Titration (% of final dose)	Titration dose for Rebif 44 micrograms three times per week (tiw)
Weeks 1-2	20%	8.8 micrograms tiw
Weeks 3-4	50%	22 micrograms tiw
Weeks 5+	100%	44 micrograms tiw

Paediatric population

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 2 years of age have not yet been established. Rebif should not be used in this age group.

Method of administration

Rebif solution for subcutaneous injection in a cartridge is intended for multidose use with the RebiSmart electronic injection device following adequate training of the patient and/or carer.

For administration, the instructions provided in the package leaflet and in the instruction manual (Instructions for Use) provided with RebiSmart 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.

4.3 Contraindications

- Hypersensitivity to natural or recombinant interferon beta or to any of the excipients listed in section 6.1.
- Current severe depression and/or suicidal ideation (see sections 4.4 and 4.8).

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

General recommendations

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 (TMA)

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 antiepileptics (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.

Rebif, like other interferons beta, has a potential for causing severe liver injury including acute hepatic failure (see section 4.8). The majority of the cases of severe liver injury occurred within the first six months of treatment. 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 disorders

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 these 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.

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 adrenocorticotrophic 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 Fertility, pregnancy and lactation

Pregnancy

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

Based on animal data (see section 5.3), there is a possibly increased risk for spontaneous abortion. The risk of spontaneous abortions in pregnant women exposed to interferon beta cannot adequately be evaluated based on the currently available data, but the data do not suggest an increased risk so far.

If clinically needed, the use of Rebif may be considered during pregnancy

Breast-feeding

Limited information available on the transfer of interferon beta-1a into breast milk, together with the chemical/physiological characteristics of interferon beta, suggests that levels of interferon beta-1a excreted in human milk are negligible. No harmful effects on the breastfed newborn/infant are anticipated.

Rebif can be used during breast-feeding.

Fertility

The effects of Rebif on fertility have not been investigated.

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

Summary of the safety profile

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 are also common.

The majority of adverse reactions observed with interferon 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.

List of adverse reactions

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 following definitions apply to the frequency terminology used hereafter: very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ to $< 1/1,000$), very rare ($< 1/10,000$), frequency not known (cannot be estimated from the available data).

Blood and the lymphatic system disorders

Very common:	Neutropenia, lymphopenia, leukopenia, thrombocytopenia, anaemia
Rare:	Thrombotic microangiopathy including thrombotic thrombocytopenic purpura/haemolytic uraemic syndrome* (class label for interferon beta products, see section 4.4), pancytopenia*

Endocrine disorders

Uncommon:	Thyroid dysfunction, most often presenting as hypothyroidism or hyperthyroidism
-----------	---

Immune system disorders

Rare:	Anaphylactic reactions*
-------	-------------------------

Hepatobiliary disorders

Very common:	Asymptomatic transaminase increase
Common:	Severe elevations in transaminases
Uncommon:	Hepatitis with or without icterus*
Rare:	Hepatic failure* (see section 4.4), autoimmune hepatitis*

Psychiatric disorders

Common:	Depression, insomnia
Rare:	Suicide attempt*

Nervous system disorders

Very common:	Headache
Uncommon:	Seizures*
Frequency not known:	Transient neurological symptoms (i.e. hypoesthesia, muscle spasm, paraesthesia, difficulty in walking, musculoskeletal stiffness) that may mimic multiple sclerosis exacerbations*

Eye disorders

Uncommon:	Retinal vascular disorders (i.e. retinopathy, cotton wool spots, obstruction of retinal artery or vein)*
-----------	--

Vascular disorders

Uncommon:	Thromboembolic events*
-----------	------------------------

Respiratory, thoracic and mediastinal disorders

Uncommon:	Dyspnoea*
Frequency not known:	Pulmonary arterial hypertension* (class label for interferon products, see below Pulmonary arterial hypertension)

Gastrointestinal disorders

Common:	Diarrhoea, vomiting, nausea
---------	-----------------------------

Skin and subcutaneous tissue disorders

Common:	Pruritus, rash, erythematous rash, maculo-papular rash, alopecia*
Uncommon:	Urticaria*
Rare:	Quincke's oedema (angio-oedema)*, erythema multiforme*, erythema multiforme-like skin reactions*, Stevens Johnson syndrome*

Musculoskeletal and connective disorders

Common:	Myalgia, arthralgia
Rare:	Drug-induced lupus erythematosus*

Renal and urinary disorders

Rare:	Nephrotic syndrome*, glomerulosclerosis* (see section 4.4)
-------	--

General disorders and administration site conditions

Very common:	Injection site inflammation, injection site reaction, influenza-like symptoms
Common:	Injection site pain, fatigue, rigors, fever
Uncommon:	Injection site necrosis, injection site mass, injection site abscess, injection site infections*, increased sweating*
Rare:	Injection site cellulitis*
Frequency not known:	Panniculitis (occurred in the injection site)

Paediatric population

No formal clinical trials or pharmacokinetic studies have been conducted in children or adolescents. Limited safety data suggest that the safety profile in children and adolescents (2 to 17 years old) receiving Rebif 22 micrograms or 44 micrograms three times weekly is similar to that seen in adults.

Class effects

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.

Pulmonary arterial hypertension

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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in [Appendix V](#).

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, Interferons, ATC code: L03AB07

Interferons 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 2'5'OAS 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.

Single clinical event suggestive of multiple sclerosis

One 2-year controlled clinical trial with Rebif was performed in patients with a single clinical event suggestive of demyelination due to multiple sclerosis. The patients enrolled into the trial had at least two clinically silent lesions on the T2-weighted MRI scan, with a size of at least 3 mm, at least one of which is ovoid or periventricular or infratentorial. Any disease other than multiple sclerosis that could better explain signs and symptoms of the patient had to be excluded.

Patients were randomised in a double-blind manner to either Rebif 44 micrograms given three times per week, Rebif 44 micrograms once weekly, or placebo. If a second clinical demyelinating event occurred confirming definite multiple sclerosis, patients switched to the recommended posology of Rebif 44 micrograms three times per week in an open label manner, while maintaining blinding as to initial randomisation.

Efficacy results of Rebif 44 micrograms given three times per week compared to placebo from this study are as follows:

Parameter Statistics	Treatment		Treatment Comparison Rebif 44 mcg tiw versus Placebo		
	Placebo (n=171)	Rebif 44 mcg tiw (n=171)	Risk Reduction	Cox's Proportional Hazard Ratio [95% CI]	Log-Rank p-value
McDonald (2005) Conversion					
Number of events	144	106	51%	0.49 [0.38;0.64]	<0.001
KM Estimate	85.8%	62.5%			
CDMS Conversion					
Number of events	60	33	52%	0.48 [0.31;0.73]	<0.001
KM Estimate	37.5%	20.6%			
Mean CUA Lesions per Subject per Scan During the Double Blind Period					
Least Square Means (SE)	2.59 (0.30)	0.50 (0.06)	81%	0.19 [0.14;0.26]*	<0.001

tiw: three times per week, CI: confidence interval, CUA: combined unique active

* Least Squared Mean Ratio [95% CI]

For the time being there is no well established definition of a high risk patient, although a more conservative approach is to accept at least nine T2 hyperintense lesions on the initial scan and at least one new T2 or one new Gd-enhancing lesion on a follow-up scan taken at least 1 month after the initial scan. In any case, treatment should only be considered for patients classified as high risk.

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 these 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. 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 (AUC_{tau} and C_{max}) 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

18 months.
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 device (RebiSmart) containing a pre-filled cartridge of Rebif must be stored in the device storage box in a refrigerator (2°C – 8°C).

For the purpose of ambulatory use, the patient may remove Rebif from the refrigerator and store it not above 25°C for one single period of up to 14 days. Rebif must then be returned to the refrigerator and used before the expiry date.

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 2 cartridges.

This package corresponds to the patient needs for the first month of therapy.

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 electronic injection device. For storage of the device with the cartridge, see section 6.4.

For multidose use. Only clear to opalescent solution without particles and without visible signs of deterioration should be used.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Merck Europe B.V.
Gustav Mahlerplein 102
1082 MA Amsterdam
The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/98/063/010

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 04 May 1998
Date of latest renewal: 04 May 2008

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>.

1. NAME OF THE MEDICINAL PRODUCT

Rebif 22 micrograms solution for injection in pre-filled pen

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pre-filled pen contains 22 micrograms (6 MIU*) of interferon beta-1a** in 0.5 mL solution.

* Million International Units, measured by cytopathic effect (CPE) bioassay against the in-house interferon 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 the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection in pre-filled pen.

Clear to opalescent solution, with pH 3.5 to 4.5 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.

Rebif is available in three strengths: 8.8 micrograms, 22 micrograms and 44 micrograms. For patients initiating treatment with Rebif, Rebif 8.8 micrograms and Rebif 22 micrograms are available in a package that corresponds to the patient needs for the first month of therapy.

Posology

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. The Rebif initiation package corresponds to the patient needs for the first month of treatment.

Paediatric population

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 2 years of age have not yet been established. Rebif should not be used in this age group.

Method of administration

RebiDose is a ready to use pre-filled pen for subcutaneous injection. It is intended for single use and should only be used following adequate training of the patient and/or carer.

For administration of Rebif with RebiDose, the instructions provided in the package leaflet 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.

4.3 Contraindications

- Hypersensitivity to natural or recombinant interferon beta or to any of the excipients listed in section 6.1.
- Current severe depression and/or suicidal ideation (see sections 4.4 and 4.8).

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

General recommendations

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 (TMA)

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 antiepileptics (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.

Rebif, like other interferons beta, has a potential for causing severe liver injury including acute hepatic failure (see section 4.8). The majority of the cases of severe liver injury occurred within the first six months of treatment. 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 disorders

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 these 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.

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 adrenocorticotrophic 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 Fertility, pregnancy and lactation

Pregnancy

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

Based on animal data (see section 5.3), there is a possibly increased risk for spontaneous abortion. The risk of spontaneous abortions in pregnant women exposed to interferon beta cannot adequately be evaluated based on the currently available data, but the data do not suggest an increased risk so far.

If clinically needed, the use of Rebif may be considered during pregnancy

Breast-feeding

Limited information available on the transfer of interferon beta-1a into breast milk, together with the chemical/physiological characteristics of interferon beta, suggests that levels of interferon beta-1a excreted in human milk are negligible. No harmful effects on the breastfed newborn/infant are anticipated.

Rebif can be used during breast-feeding.

Fertility

The effects of Rebif on fertility have not been investigated.

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

Summary of the safety profile

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 are also common.

The majority of adverse reactions observed with interferon 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.

List of adverse reactions

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 following definitions apply to the frequency terminology used hereafter: very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ to $< 1/1,000$), very rare ($< 1/10,000$), frequency not known (cannot be estimated from the available data).

Blood and the lymphatic system disorders

Very common:	Neutropenia, lymphopenia, leukopenia, thrombocytopenia, anaemia
Rare:	Thrombotic microangiopathy including thrombotic thrombocytopenic purpura/haemolytic uraemic syndrome* (class label for interferon beta products, see section 4.4), pancytopenia*

Endocrine disorders

Uncommon:	Thyroid dysfunction, most often presenting as hypothyroidism or hyperthyroidism
-----------	---

Immune system disorders

Rare:	Anaphylactic reactions*
-------	-------------------------

Hepatobiliary disorders

Very common:	Asymptomatic transaminase increase
Common:	Severe elevations in transaminases
Uncommon:	Hepatitis with or without icterus*
Rare:	Hepatic failure* (see section 4.4), autoimmune hepatitis*

Psychiatric disorders

Common:	Depression, insomnia
Rare:	Suicide attempt*

Nervous system disorders

Very common:	Headache
Uncommon:	Seizures*
Frequency not known:	Transient neurological symptoms (i.e. hypoesthesia, muscle spasm, paraesthesia, difficulty in walking, musculoskeletal stiffness) that may mimic multiple sclerosis exacerbations*

Eye disorders

Uncommon:	Retinal vascular disorders (i.e. retinopathy, cotton wool spots, obstruction of retinal artery or vein)*
-----------	--

Vascular disorders

Uncommon:	Thromboembolic events*
-----------	------------------------

Respiratory, thoracic and mediastinal disorders

Uncommon:	Dyspnoea*
Frequency not known:	Pulmonary arterial hypertension* (class label for interferon products, see below Pulmonary arterial hypertension)

Gastrointestinal disorders

Common:	Diarrhoea, vomiting, nausea
---------	-----------------------------

Skin and subcutaneous tissue disorders

Common:	Pruritus, rash, erythematous rash, maculo-papular rash, alopecia*
Uncommon:	Urticaria*
Rare:	Quincke's oedema (angio-oedema)*, erythema multiforme*, erythema multiforme-like skin reactions*, Stevens Johnson syndrome*

Musculoskeletal and connective disorders

Common:	Myalgia, arthralgia
Rare:	Drug-induced lupus erythematosus*

Renal and urinary disorders

Rare:	Nephrotic syndrome*, glomerulosclerosis* (see section 4.4)
-------	--

General disorders and administration site conditions

Very common:	Injection site inflammation, injection site reaction, influenza-like symptoms
Common:	Injection site pain, fatigue, rigors, fever
Uncommon:	Injection site necrosis, injection site mass, injection site abscess, injection site infections*, increased sweating*
Rare:	Injection site cellulitis*
Frequency not known:	Panniculitis (occurred in the injection site)

Paediatric population

No formal clinical trials or pharmacokinetic studies have been conducted in children or adolescents. Limited safety data suggest that the safety profile in children and adolescents (2 to 17 years old) receiving Rebif 22 micrograms or 44 micrograms three times weekly is similar to that seen in adults.

Class effects

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.

Pulmonary arterial hypertension

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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in [Appendix V](#).

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, Interferons, ATC code: L03AB07

Interferons 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 2'5'OAS 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 these 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. 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 (AUC_{tau} and C_{max}) 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

18 months.

6.4 Special precautions for storage

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

For the purpose of ambulatory use, the patient may remove Rebif from the refrigerator and store it not above 25°C for one single period of up to 14 days. Rebif must then be returned to the refrigerator and used before the expiry date.

6.5 Nature and contents of container

One mL type 1 glass syringe, with a stainless steel needle, containing 0.5 mL solution.
The syringe is sealed in a disposable pen injector called RebiDose.

Pack sizes of 1, 3 or 12 pre-filled pens.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

The solution for injection in a pre-filled pen is ready for use. The carton contains a package leaflet with full instructions for use and handling.

For single use only. Only clear to opalescent solution without particles and without visible signs of deterioration should be used.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Merck Europe B.V.
Gustav Mahlerplein 102
1082 MA Amsterdam
The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/98/063/011

EU/1/98/063/012

EU/1/98/063/013

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 04 May 1998

Date of latest renewal: 04 May 2008

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>.

1. NAME OF THE MEDICINAL PRODUCT

Rebif 44 micrograms solution for injection in pre-filled pen

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pre-filled pen contains 44 micrograms (12 MIU*) of interferon beta-1a** in 0.5 mL solution.

* Million International Units, measured by cytopathic effect (CPE) bioassay against the in-house interferon 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 the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection in pre-filled pen.

Clear to opalescent solution, with pH 3.5 to 4.5 and osmolarity 250 to 450 mOsm/L.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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 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.

Rebif is available in three strengths: 8.8 micrograms, 22 micrograms and 44 micrograms. For patients initiating treatment with Rebif, Rebif 8.8 micrograms and Rebif 22 micrograms are available in a package that corresponds to the patient needs for the first month of therapy.

Posology

When first starting treatment with Rebif, in order to allow tachyphylaxis to develop thus reducing adverse reactions it is recommended that patients be started at 8.8 micrograms dose subcutaneously and the dose be increased over a 4 week period to the targeted dose, according to the following schedule:

	Recommended Titration (% of final dose)	Titration dose for Rebif 44 micrograms three times per week (tiw)
Weeks 1-2	20%	8.8 micrograms tiw
Weeks 3-4	50%	22 micrograms tiw
Weeks 5+	100%	44 micrograms tiw

First demyelinating event

The posology for patients who have experienced a first demyelinating event is 44 micrograms of Rebif given three times per week by subcutaneous injection.

Relapsing multiple sclerosis

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.

Paediatric population

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 2 years of age have not yet been established. Rebif should not be used in this age group.

Method of administration

RebiDose is a ready to use pre-filled pen for subcutaneous injection. It is intended for single use and should only be used following adequate training of the patient and/or carer.

For administration of Rebif with RebiDose, the instructions provided in the package leaflet 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.

4.3 Contraindications

- Hypersensitivity to natural or recombinant interferon beta or to any of the excipients listed in section 6.1.
- Current severe depression and/or suicidal ideation (see sections 4.4 and 4.8).

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

General recommendations

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 (TMA)

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 antiepileptics (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.

Rebif, like other interferons beta, has a potential for causing severe liver injury including acute hepatic failure (see section 4.8). The majority of the cases of severe liver injury occurred within the first six months of treatment. 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. The overall incidence of these is slightly higher with Rebif 44 than Rebif 22 micrograms. 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. These should be more frequent when initiating Rebif 44 micrograms.

Thyroid disorders

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 44 micrograms, approximately 13 to 14% 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 these 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.

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 adrenocorticotrophic 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 Fertility, pregnancy and lactation

Pregnancy

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

Based on animal data (see section 5.3), there is a possibly increased risk for spontaneous abortion. The risk of spontaneous abortions in pregnant women exposed to interferon beta cannot adequately be evaluated based on the currently available data, but the data do not suggest an increased risk so far.

If clinically needed, the use of Rebif may be considered during pregnancy

Breast-feeding

Limited information available on the transfer of interferon beta-1a into breast milk, together with the chemical/physiological characteristics of interferon beta, suggests that levels of interferon beta-1a excreted in human milk are negligible. No harmful effects on the breastfed newborn/infant are anticipated.

Rebif can be used during breast-feeding.

Fertility

The effects of Rebif on fertility have not been investigated.

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

Summary of the safety profile

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 are also common.

The majority of adverse reactions observed with interferon 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.

List of adverse reactions

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 following definitions apply to the frequency terminology used hereafter: very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ to $< 1/1,000$), very rare ($< 1/10,000$), frequency not known (cannot be estimated from the available data).

Blood and the lymphatic system disorders

Very common: Neutropenia, lymphopenia, leukopenia, thrombocytopenia, anaemia
Rare: Thrombotic microangiopathy including thrombotic thrombocytopenic purpura/haemolytic uraemic syndrome* (class label for interferon beta products, see section 4.4), pancytopenia*

Endocrine disorders

Uncommon: Thyroid dysfunction, most often presenting as hypothyroidism or hyperthyroidism

Immune system disorders

Rare: Anaphylactic reactions*

Hepatobiliary disorders

Very common: Asymptomatic transaminase increase
Common: Severe elevations in transaminases
Uncommon: Hepatitis with or without icterus*
Rare: Hepatic failure* (see section 4.4), autoimmune hepatitis*

Psychiatric disorders

Common: Depression, insomnia
Rare: Suicide attempt*

Nervous system disorders

Very common: Headache
Uncommon: Seizures*
Frequency not known: Transient neurological symptoms (i.e. hypoesthesia, muscle spasm, paraesthesia, difficulty in walking, musculoskeletal stiffness) that may mimic multiple sclerosis exacerbations*

Eye disorders

Uncommon: Retinal vascular disorders (i.e. retinopathy, cotton wool spots, obstruction of retinal artery or vein)*

Vascular disorders

Uncommon: Thromboembolic events*

Respiratory, thoracic and mediastinal disorders

Uncommon: Dyspnoea*
Frequency not known: Pulmonary arterial hypertension* (class label for interferon products, see below Pulmonary arterial hypertension)

Gastrointestinal disorders

Common: Diarrhoea, vomiting, nausea

Skin and subcutaneous tissue disorders

Common:	Pruritus, rash, erythematous rash, maculo-papular rash, alopecia*
Uncommon:	Urticaria*
Rare:	Quincke's oedema (angio-oedema)*, erythema multiforme*, erythema multiforme-like skin reactions*, Stevens Johnson syndrome*

Musculoskeletal and connective disorders

Common:	Myalgia, arthralgia
Rare:	Drug-induced lupus erythematosus*

Renal and urinary disorders

Rare:	Nephrotic syndrome*, glomerulosclerosis* (see section 4.4)
-------	--

General disorders and administration site conditions

Very common:	Injection site inflammation, injection site reaction, influenza-like symptoms
Common:	Injection site pain, fatigue, rigors, fever
Uncommon:	Injection site necrosis, injection site mass, injection site abscess, injection site infections*, increased sweating*
Rare:	Injection site cellulitis*
Frequency not known:	Panniculitis (occurred in the injection site)

Paediatric population

No formal clinical trials or pharmacokinetic studies have been conducted in children or adolescents. Limited safety data suggest that the safety profile in children and adolescents (2 to 17 years old) receiving Rebif 22 micrograms or 44 micrograms three times weekly is similar to that seen in adults.

Class effects

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.

Pulmonary arterial hypertension

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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in [Appendix V](#).

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, Interferons, ATC code: L03AB07

Interferons 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 2'5'OAS 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.

Single clinical event suggestive of multiple sclerosis

One 2-year controlled clinical trial with Rebif was performed in patients with a single clinical event suggestive of demyelination due to multiple sclerosis. The patients enrolled into the trial had at least two clinically silent lesions on the T2-weighted MRI scan, with a size of at least 3 mm, at least one of which is ovoid or periventricular or infratentorial. Any disease other than multiple sclerosis that could better explain signs and symptoms of the patient had to be excluded.

Patients were randomised in a double-blind manner to either Rebif 44 micrograms given three times per week, Rebif 44 micrograms once weekly, or placebo. If a second clinical demyelinating event occurred confirming definite multiple sclerosis, patients switched to the recommended posology of Rebif 44 micrograms three times per week in an open label manner, while maintaining blinding as to initial randomisation.

Efficacy results of Rebif 44 micrograms given three times per week compared to placebo from this study are as follows:

Parameter Statistics	Treatment		Treatment Comparison Rebif 44 mcg tiw versus Placebo		
	Placebo (n=171)	Rebif 44 mcg tiw (n=171)	Risk Reduction	Cox's Proportional Hazard Ratio [95% CI]	Log-Rank p-value
McDonald (2005) Conversion					
Number of events	144	106	51%	0.49 [0.38;0.64]	<0.001
KM Estimate	85.8%	62.5%			
CDMS Conversion					
Number of events	60	33	52%	0.48 [0.31;0.73]	<0.001
KM Estimate	37.5%	20.6%			
Mean CUA Lesions per Subject per Scan During the Double Blind Period					
Least Square Means (SE)	2.59 (0.30)	0.50 (0.06)	81%	0.19 [0.14;0.26]*	<0.001

tiw: three times per week, CI: confidence interval, CUA: combined unique active

* Least Squared Mean Ratio [95% CI]

For the time being there is no well established definition of a high risk patient, although a more conservative approach is to accept at least nine T2 hyperintense lesions on the initial scan and at least one new T2 or one new Gd-enhancing lesion on a follow-up scan taken at least 1 month after the initial scan. In any case, treatment should only be considered for patients classified as high risk.

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 44 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 27% (Rebif 44 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 these 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. 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 (AUC_{tau} and C_{max}) 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

18 months.

6.4 Special precautions for storage

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

For the purpose of ambulatory use, the patient may remove Rebif from the refrigerator and store it not above 25°C for one single period of up to 14 days. Rebif must then be returned to the refrigerator and used before the expiry date.

6.5 Nature and contents of container

One mL type 1 glass syringe, with a stainless steel needle, containing 0.5 mL solution.
The syringe is sealed in a disposable pen injector called RebiDose.

Pack sizes of 1, 3 or 12 pre-filled pens.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

The solution for injection in a pre-filled pen is ready for use. The carton contains a package leaflet with full instructions for use and handling.

For single use only. Only clear to opalescent solution without particles and without visible signs of deterioration should be used.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Merck Europe B.V.
Gustav Mahlerplein 102
1082 MA Amsterdam
The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/98/063/014
EU/1/98/063/015
EU/1/98/063/016

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 04 May 1998
Date of latest renewal: 04 May 2008

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>.

1. NAME OF THE MEDICINAL PRODUCT

Rebif 8.8 micrograms solution for injection in pre-filled pen
Rebif 22 micrograms solution for injection in pre-filled pen

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pre-filled pen contains 8.8 micrograms (2.4 MIU*) of interferon beta-1a** in 0.2 mL solution.

* Million International Units, measured by cytopathic effect (CPE) bioassay against the in-house interferon 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 1.0 mg benzyl alcohol per dose of 0.2 mL.
For the full list of excipients, see section 6.1.

Each pre-filled pen contains 22 micrograms (6 MIU*) of interferon beta-1a** in 0.5 mL solution.

* Million International Units, measured by cytopathic effect (CPE) bioassay against the in-house interferon 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 the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection in pre-filled pen.

Clear to opalescent solution, with pH 3.5 to 4.5 and osmolarity 250 to 450 mOsm/L.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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 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.

Posology

The Rebif initiation packs correspond to the patient needs for the first month of treatment. When first starting treatment with Rebif, in order to allow tachyphylaxis to develop thus reducing adverse reactions, it is recommended that patients be started at 8.8 micrograms dose subcutaneously and the dose be increased over a 4 week period to the targeted dose, according to the following schedule:

	Recommended Titration (% of final dose)	Titration dose for Rebif 44 micrograms three times per week (tiw)
Weeks 1-2	20%	8.8 micrograms tiw
Weeks 3-4	50%	22 micrograms tiw
Weeks 5+	100%	44 micrograms tiw

Paediatric population

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 2 years of age have not yet been established. Rebif should not be used in this age group.

Method of administration

RebiDose is a ready to use pre-filled pen for subcutaneous injection. It is intended for single use and should only be used following adequate training of the patient and/or carer.

For administration of Rebif with RebiDose, the instructions provided in the package leaflet 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.

4.3 Contraindications

- Hypersensitivity to natural or recombinant interferon beta or to any of the excipients listed in section 6.1.
- Current severe depression and/or suicidal ideation (see sections 4.4 and 4.8).

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

General recommendations

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 (TMA)

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 antiepileptics (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.

Rebif, like other interferons beta, has a potential for causing severe liver injury including acute hepatic failure (see section 4.8). The majority of the cases of severe liver injury occurred within the first six months of treatment. 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 disorders

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 these 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.

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 adrenocorticotrophic 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 Fertility, pregnancy and lactation

Pregnancy

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

Based on animal data (see section 5.3), there is a possibly increased risk for spontaneous abortion. The risk of spontaneous abortions in pregnant women exposed to interferon beta cannot adequately be evaluated based on the currently available data, but the data do not suggest an increased risk so far.

If clinically needed, the use of Rebif may be considered during pregnancy

Breast-feeding

Limited information available on the transfer of interferon beta-1a into breast milk, together with the chemical/physiological characteristics of interferon beta, suggests that levels of interferon beta-1a excreted in human milk are negligible. No harmful effects on the breastfed newborn/infant are anticipated.

Rebif can be used during breast-feeding.

Fertility

The effects of Rebif on fertility have not been investigated.

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

Summary of the safety profile

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 are also common.

The majority of adverse reactions observed with interferon 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.

List of adverse reactions

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 following definitions apply to the frequency terminology used hereafter: very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ to $< 1/1,000$), very rare ($< 1/10,000$), frequency not known (cannot be estimated from the available data).

Blood and the lymphatic system disorders

Very common:	Neutropenia, lymphopenia, leukopenia, thrombocytopenia, anaemia
Rare:	Thrombotic microangiopathy including thrombotic thrombocytopenic purpura/haemolytic uraemic syndrome* (class label for interferon beta products, see section 4.4), pancytopenia*

Endocrine disorders

Uncommon: Thyroid dysfunction, most often presenting as hypothyroidism or hyperthyroidism

Immune system disorders

Rare: Anaphylactic reactions*

Hepatobiliary disorders

Very common: Asymptomatic transaminase increase

Common: Severe elevations in transaminases

Uncommon: Hepatitis with or without icterus*

Rare: Hepatic failure* (see section 4.4), autoimmune hepatitis*

Psychiatric disorders

Common: Depression, insomnia

Rare: Suicide attempt*

Nervous system disorders

Very common: Headache

Uncommon: Seizures*

Frequency not known: Transient neurological symptoms (i.e. hypoesthesia, muscle spasm, paraesthesia, difficulty in walking, musculoskeletal stiffness) that may mimic multiple sclerosis exacerbations*

Eye disorders

Uncommon: Retinal vascular disorders (i.e. retinopathy, cotton wool spots, obstruction of retinal artery or vein)*

Vascular disorders

Uncommon: Thromboembolic events*

Respiratory, thoracic and mediastinal disorders

Uncommon: Dyspnoea*

Frequency not known: Pulmonary arterial hypertension* (class label for interferon products, see below Pulmonary arterial hypertension)

Gastrointestinal disorders

Common: Diarrhoea, vomiting, nausea

Skin and subcutaneous tissue disorders

Common: Pruritus, rash, erythematous rash, maculo-papular rash, alopecia*

Uncommon: Urticaria*

Rare: Quincke's oedema (angio-oedema)*, erythema multiforme*, erythema multiforme-like skin reactions*, Stevens Johnson syndrome*

Musculoskeletal and connective disorders

Common: Myalgia, arthralgia

Rare: Drug-induced lupus erythematosus*

Renal and urinary disorders

Rare: Nephrotic syndrome*, glomerulosclerosis* (see section 4.4)

General disorders and administration site conditions

Very common:	Injection site inflammation, injection site reaction, influenza-like symptoms
Common:	Injection site pain, fatigue, rigors, fever
Uncommon:	Injection site necrosis, injection site mass, injection site abscess, injection site infections*, increased sweating*
Rare:	Injection site cellulitis*
Frequency not known:	Panniculitis (occurred in the injection site)

Paediatric population

No formal clinical trials or pharmacokinetic studies have been conducted in children or adolescents. Limited safety data suggest that the safety profile in children and adolescents (2 to 17 years old) receiving Rebif 22 micrograms or 44 micrograms three times weekly is similar to that seen in adults.

Class effects

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.

Pulmonary arterial hypertension

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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in [Appendix V](#).

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, Interferons, ATC code: L03AB07

Interferons 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 2'5'OAS 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.

Single clinical event suggestive of multiple sclerosis

One 2-year controlled clinical trial with Rebif was performed in patients with a single clinical event suggestive of demyelination due to multiple sclerosis. The patients enrolled into the trial had at least two clinically silent lesions on the T2-weighted MRI scan, with a size of at least 3 mm, at least one of which is ovoid or periventricular or infratentorial. Any disease other than multiple sclerosis that could better explain signs and symptoms of the patient had to be excluded.

Patients were randomised in a double-blind manner to either Rebif 44 micrograms given three times per week, Rebif 44 micrograms once weekly, or placebo. If a second clinical demyelinating event occurred confirming definite multiple sclerosis, patients switched to the recommended posology of Rebif 44 micrograms three times per week in an open label manner, while maintaining blinding as to initial randomisation.

Efficacy results of Rebif 44 micrograms given three times per week compared to placebo from this study are as follows:

Parameter Statistics	Treatment		Treatment Comparison Rebif 44 mcg tiw versus Placebo		
	Placebo (n=171)	Rebif 44 mcg tiw (n=171)	Risk Reduction	Cox's Proportional Hazard Ratio [95% CI]	Log-Rank p-value
McDonald (2005) Conversion					
Number of events	144	106	51%	0.49 [0.38;0.64]	<0.001
KM Estimate	85.8%	62.5%			
CDMS Conversion					
Number of events	60	33	52%	0.48 [0.31;0.73]	<0.001
KM Estimate	37.5%	20.6%			
Mean CUA Lesions per Subject per Scan During the Double Blind Period					
Least Square Means (SE)	2.59 (0.30)	0.50 (0.06)	81%	0.19 [0.14;0.26]*	<0.001

tiw: three times per week, CI: confidence interval, CUA: combined unique active

* Least Squared Mean Ratio [95% CI]

For the time being there is no well established definition of a high risk patient, although a more conservative approach is to accept at least nine T2 hyperintense lesions on the initial scan and at least one new T2 or one new Gd-enhancing lesion on a follow-up scan taken at least 1 month after the initial scan. In any case, treatment should only be considered for patients classified as high risk.

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 these 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. 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 (AUC_{tau} and C_{max}) 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

18 months.

6.4 Special precautions for storage

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

For the purpose of ambulatory use, the patient may remove Rebif from the refrigerator and store it not above 25°C for one single period of up to 14 days. Rebif must then be returned to the refrigerator and used before the expiry date.

6.5 Nature and contents of container

For patients starting treatment with Rebif, Rebif 8.8 micrograms and Rebif 22 micrograms are available in an initiation pack. The pack contains 6 individual doses of 0.2 mL of Rebif 8.8 micrograms solution for injection in a 1 mL type 1 glass syringe with a stainless steel needle and 6 individual doses of 0.5 mL of Rebif 22 micrograms solution for injection in a 1 mL type 1 glass syringe with a stainless steel needle. The syringes are sealed in disposable pen injectors called RebiDose.

This package corresponds to the patient needs for the first month of therapy.

6.6 Special precautions for disposal and other handling

The solution for injection in a pre-filled pen is ready for use. The carton contains a package leaflet with full instructions for use and handling.

For single use only. Only clear to opalescent solution without particles and without visible signs of deterioration should be used.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Merck Europe B.V.
Gustav Mahlerplein 102
1082 MA Amsterdam
The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/98/063/017

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 04 May 1998
Date of latest renewal: 04 May 2008

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>.

ANNEX II

- A. MANUFACTURERS OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**
- D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

A. MANUFACTURERS OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers of the biological active substance

Merck Serono S.A. – Corsier-sur-Vevey
Route de Fenil – Z.I.B.
CH-1804 Corsier-sur-Vevey
Switzerland

Name and address of the manufacturer responsible for batch release

Merck Serono S.p.A.
Via delle Magnolie 15
I-70026 Modugno (Bari)
Italy

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

• **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

• **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING
BOX OF 1, 3, 12 AND 36 SYRINGES**

1. NAME OF THE MEDICINAL PRODUCT

Rebif 22 micrograms solution for injection in pre-filled syringe

interferon beta-1a

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Composition: Each pre-filled syringe (0.5 mL) contains 22 micrograms (6 MIU) of interferon beta-1a.

3. LIST OF EXCIPIENTS

Mannitol, poloxamer 188, L-methionine, benzyl alcohol, sodium acetate, acetic acid and sodium hydroxide for pH adjustment and water for injections.

See the package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection.

1 pre-filled syringe.

3 pre-filled syringes.

12 pre-filled syringes.

36 pre-filled syringes.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use.

Read the package leaflet before use.

For single dose only.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.

Do not freeze.

Store the syringe in the original package in order to protect from light. The patient may store Rebif at or below 25°C for a single period up to 14 days. Rebif must then be returned to the refrigerator and used before the expiry date.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Merck Europe B.V.
Gustav Mahlerplein 102
1082 MA Amsterdam
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/98/063/001 1 pre-filled syringe
EU/1/98/063/002 3 pre-filled syringes
EU/1/98/063/003 12 pre-filled syringes
EU/1/98/063/020 36 pre-filled syringes

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE**16. INFORMATION IN BRAILLE**

rebif 22

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS
PRE-FILLED SYRINGE**

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Rebif 22 mcg solution for injection

interferon beta-1a
SC use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

22 micrograms (6 million IU)/0.5 mL

6. OTHER

Merck Europe B.V.

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING
BOX OF 1, 3, 12 AND 36 SYRINGES**

1. NAME OF THE MEDICINAL PRODUCT

Rebif 44 micrograms solution for injection in pre-filled syringe

interferon beta-1a

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Composition: Each pre-filled syringe (0.5 mL) contains 44 micrograms (12 MIU) of interferon beta-1a.

3. LIST OF EXCIPIENTS

Mannitol, poloxamer 188, L-methionine, benzyl alcohol, sodium acetate, acetic acid and sodium hydroxide for pH adjustment and water for injections.

See the package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection.

1 pre-filled syringe.

3 pre-filled syringes.

12 pre-filled syringes.

36 pre-filled syringes.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use.

Read the package leaflet before use.

For single dose only.

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT
OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.

Do not freeze.

Store the syringe in the original package in order to protect from light. The patient may store Rebif at or below 25°C for a single period up to 14 days. Rebif must then be returned to the refrigerator and used before the expiry date.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Merck Europe B.V.
Gustav Mahlerplein 102
1082 MA Amsterdam
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/98/063/004 1 pre-filled syringe
EU/1/98/063/005 3 pre-filled syringes
EU/1/98/063/006 12 pre-filled syringes
EU/1/98/063/021 36 pre-filled syringes

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE**16. INFORMATION IN BRAILLE**

rebif 44

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS
PRE-FILLED SYRINGE**

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Rebif 44 mcg solution for injection

interferon beta-1a
SC use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

44 micrograms (12 million IU)/0.5 mL

6. OTHER

Merck Europe B.V.

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING
BOX OF 6 X 8.8 MICROGRAMS SYRINGES + 6 X 22 MICROGRAMS SYRINGES**

1. NAME OF THE MEDICINAL PRODUCT

Rebif 8.8 micrograms solution for injection in pre-filled syringe
Rebif 22 micrograms solution for injection in pre-filled syringe

interferon beta-1a

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Composition: Each Rebif 8.8 micrograms pre-filled syringe (0.2 mL) contains 8.8 micrograms (2.4 Million IU) of interferon beta-1a.
Each Rebif 22 micrograms pre-filled syringe (0.5 mL) contains 22 micrograms (6 Million IU) of interferon beta-1a.

3. LIST OF EXCIPIENTS

Mannitol, poloxamer 188, L-methionine, benzyl alcohol, sodium acetate, acetic acid and sodium hydroxide for pH adjustment and water for injections.
See the package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection.

Initiation pack.

6 pre-filled syringes of Rebif 8.8 micrograms and 6 pre-filled syringes of Rebif 22 micrograms.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use.

Read the package leaflet before use.

For single dose only.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.

Do not freeze.

Store the syringe in the original package in order to protect from light. The patient may store Rebif at or below 25°C for a single period up to 14 days. Rebif must then be returned to the refrigerator and used before the expiry date.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Merck Europe B.V.
Gustav Mahlerplein 102
1082 MA Amsterdam
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/98/063/007

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE**16. INFORMATION IN BRAILLE**

rebif 8.8
rebif 22

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS
PRE-FILLED SYRINGE**

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Rebif 8.8 mcg solution for injection

interferon beta-1a
SC use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

8.8 micrograms (2.4 million IU)/0.2 mL

6. OTHER

Merck Europe B.V.

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS
PRE-FILLED SYRINGE**

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Rebif 22 mcg solution for injection

interferon beta-1a
SC use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

22 micrograms (6 million IU)/0.5 mL

6. OTHER

Merck Europe B.V.

PARTICULARS TO APPEAR ON THE LAYERS SEPARATORS FOR THE STARTER PACK

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

(UPPER FLAP)

Rebif 8.8 micrograms solution for injection
interferon beta-1a
Subcutaneous use
BRAILLE: rebif 8.8

(LOWER FLAP)

Rebif 22 micrograms solution for injection
interferon beta-1a
Subcutaneous use
BRAILLE: rebif 22

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

4. BATCH NUMBER

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6. OTHER

(UPPER FLAP)

6 pre-filled syringes of Rebif 8.8 micrograms

(LOWER FLAP)

6 pre-filled syringes of Rebif 22 micrograms

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING
BOX OF 4 OR 12 CARTRIDGES**

1. NAME OF THE MEDICINAL PRODUCT

Rebif 22 micrograms/0.5 mL solution for injection in cartridge

interferon beta-1a

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Composition: Each cartridge contains 66 micrograms (18 MIU) of interferon beta-1a in 1.5 mL solution.

3. LIST OF EXCIPIENTS

Mannitol, poloxamer 188, L-methionine, benzyl alcohol, sodium acetate, acetic acid and sodium hydroxide for pH adjustment and water for injections.
See the package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection.

4 cartridges
12 cartridges

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use.
Read the package leaflet before use.

For multidose use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
After first injection use within 28 days.

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.

Do not freeze.

Store the cartridge in the original package in order to protect from light.

The device containing a cartridge of Rebif must be stored in the device storage box in a refrigerator (2°C – 8°C). The patient may store Rebif at or below 25°C for a single period up to 14 days. Rebif must then be returned to the refrigerator and used before the expiry date.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Merck Europe B.V.
Gustav Mahlerplein 102
1082 MA Amsterdam
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/98/063/008 4 cartridges

EU/1/98/063/018 12 cartridges

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE**16. INFORMATION IN BRAILLE**

rebif 22/0.5

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS
CARTRIDGE**

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Rebif 22 mcg/0.5 mL solution for injection

interferon beta-1a
SC use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

66 micrograms (18 million IU)/1.5 mL

6. OTHER

Merck Europe B.V.

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING
BOX OF 4 OR 12 CARTRIDGES**

1. NAME OF THE MEDICINAL PRODUCT

Rebif 44 micrograms/0.5 mL solution for injection in cartridge

interferon beta-1a

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Composition: Each cartridge contains 132 micrograms (36 MIU) of interferon beta-1a in 1.5 mL solution.

3. LIST OF EXCIPIENTS

Mannitol, poloxamer 188, L-methionine, benzyl alcohol, sodium acetate, acetic acid and sodium hydroxide for pH adjustment and water for injections.
See the package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection.

4 cartridges
12 cartridges

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use.
Read the package leaflet before use.

For multidose use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
After first injection use within 28 days.

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.

Do not freeze.

Store the cartridge in the original package in order to protect from light.

The device containing a cartridge of Rebif must be stored in the device storage box in a refrigerator (2°C – 8°C). The patient may store Rebif at or below 25°C for a single period up to 14 days. Rebif must then be returned to the refrigerator and used before the expiry date.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Merck Europe B.V.
Gustav Mahlerplein 102
1082 MA Amsterdam
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/98/063/009 4 cartridges

EU/1/98/063/019 12 cartridges

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE**16. INFORMATION IN BRAILLE**

rebif 44/0.5

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS
CARTRIDGE**

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Rebif 44 mcg/0.5 mL solution for injection

interferon beta-1a
SC use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

132 micrograms (36 million IU)/1.5 mL

6. OTHER

Merck Europe B.V.

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING
BOX OF 2 CARTRIDGES**

1. NAME OF THE MEDICINAL PRODUCT

Rebif 8.8 micrograms/0.1 mL solution for injection in cartridge
Rebif 22 micrograms/0.25 mL solution for injection in cartridge

interferon beta-1a

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Composition: Each cartridge contains 132 micrograms (36 MIU) of interferon beta-1a in 1.5 mL solution.

3. LIST OF EXCIPIENTS

Mannitol, poloxamer 188, L-methionine, benzyl alcohol, sodium acetate, acetic acid and sodium hydroxide for pH adjustment and water for injections.
See the package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection.

Initiation pack.
2 cartridges

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use.
Read the package leaflet before use.

For multidose use.

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT
OF THE REACH AND SIGHT OF CHILDREN**

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
After first injection use within 28 days.

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.

Do not freeze.

Store the cartridge in the original package in order to protect from light.

The device containing a cartridge of Rebif must be stored in the device storage box in a refrigerator (2°C – 8°C). The patient may store Rebif at or below 25°C for a single period up to 14 days. Rebif must then be returned to the refrigerator and used before the expiry date.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Merck Europe B.V.
Gustav Mahlerplein 102
1082 MA Amsterdam
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/98/063/010

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE**16. INFORMATION IN BRAILLE**

rebif 8.8/0.1 / 22/0.25

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS
CARTRIDGE**

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Rebif 8.8 mcg/0.1 mL
Rebif 22 mcg/0.25 mL
Solution for injection

interferon beta-1a
SC use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

132 micrograms (36 million IU)/1.5 mL

6. OTHER

Merck Europe B.V.

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING
BOX OF 1, 3 AND 12 PRE-FILLED PENS**

1. NAME OF THE MEDICINAL PRODUCT

Rebif 22 micrograms solution for injection in pre-filled pen

interferon beta-1a

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Composition: Each pre-filled pen contains 22 micrograms (6 MIU) of interferon beta-1a in 0.5 mL solution.

3. LIST OF EXCIPIENTS

Mannitol, poloxamer 188, L-methionine, benzyl alcohol, sodium acetate, acetic acid and sodium hydroxide for pH adjustment and water for injections.
See the package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection.

1 pre-filled pen. RebiDose.

3 pre-filled pens. RebiDose.

12 pre-filled pens. RebiDose.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use.

Read the package leaflet before use.

For single dose only.

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT
OF THE REACH AND SIGHT OF CHILDREN**

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.

Do not freeze.

Store the pre-filled pen in the original package in order to protect from light. The patient may store Rebif at or below 25°C for a single period up to 14 days. Rebif must then be returned to the refrigerator and used before the expiry date.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Merck Europe B.V.
Gustav Mahlerplein 102
1082 MA Amsterdam
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/98/063/011 1 pre-filled pen
EU/1/98/063/012 3 pre-filled pens
EU/1/98/063/013 12 pre-filled pens

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE**16. INFORMATION IN BRAILLE**

rebif 22

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS
PRE-FILLED PEN**

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Rebif 22 micrograms solution for injection

interferon beta-1a
SC use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

22 micrograms (6 million IU)/0.5 mL

6. OTHER

Merck Europe B.V.

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING
BOX OF 1, 3 AND 12 PRE-FILLED PENS**

1. NAME OF THE MEDICINAL PRODUCT

Rebif 44 micrograms solution for injection in pre-filled pen

interferon beta-1a

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Composition: Each pre-filled pen contains 44 micrograms (12 MIU) of interferon beta-1a in 0.5 mL solution.

3. LIST OF EXCIPIENTS

Mannitol, poloxamer 188, L-methionine, benzyl alcohol, sodium acetate, acetic acid and sodium hydroxide for pH adjustment and water for injections.
See the package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection.

1 pre-filled pen. RebiDose.

3 pre-filled pens. RebiDose.

12 pre-filled pens. RebiDose.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use.

Read the package leaflet before use.

For single dose only.

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT
OF THE REACH AND SIGHT OF CHILDREN**

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.

Do not freeze.

Store the pre-filled pen in the original package in order to protect from light. The patient may store Rebif at or below 25°C for a single period up to 14 days. Rebif must then be returned to the refrigerator and used before the expiry date.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Merck Europe B.V.
Gustav Mahlerplein 102
1082 MA Amsterdam
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/98/063/014 1 pre-filled pen
EU/1/98/063/015 3 pre-filled pens
EU/1/98/063/016 12 pre-filled pens

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE**16. INFORMATION IN BRAILLE**

rebif 44

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS
PRE-FILLED PEN**

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Rebif 44 micrograms solution for injection

interferon beta-1a
SC use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

44 micrograms (12 million IU)/0.5 mL

6. OTHER

Merck Europe B.V.

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING
BOX OF 6 X 8.8 MICROGRAMS PRE-FILLED PENS + 6 X 22 MICROGRAMS PRE-FILLED PENS**

1. NAME OF THE MEDICINAL PRODUCT

Rebif 8.8 micrograms solution for injection in pre-filled pen
Rebif 22 micrograms solution for injection in pre-filled pen

interferon beta-1a

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Composition: Each Rebif 8.8 micrograms pre-filled pen contains 8.8 micrograms (2.4 Million IU) of interferon beta-1a in 0.2 mL solution.
Each Rebif 22 micrograms pre-filled pen contains 22 micrograms (6 Million IU) of interferon beta-1a in 0.5 mL solution.

3. LIST OF EXCIPIENTS

Mannitol, poloxamer 188, L-methionine, benzyl alcohol, sodium acetate, acetic acid and sodium hydroxide for pH adjustment and water for injections.
See the package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection.

Initiation pack.
6 pre-filled pens of 8.8 micrograms and 6 pre-filled pens of 22 micrograms. RebiDose.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use.
Read the package leaflet before use.

For single dose only.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.

Do not freeze.

Store the pre-filled pen in the original package in order to protect from light. The patient may store Rebif at or below 25°C for a single period up to 14 days. Rebif must then be returned to the refrigerator and used before the expiry date.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Merck Europe B.V.
Gustav Mahlerplein 102
1082 MA Amsterdam
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/98/063/017

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE**16. INFORMATION IN BRAILLE**

rebif 8.8
rebif 22

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS
PRE-FILLED PEN**

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Rebif 8.8 micrograms solution for injection

interferon beta-1a
SC use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

8.8 micrograms (2.4 million IU)/0.2 mL

6. OTHER

Merck Europe B.V.

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS
PRE-FILLED PEN**

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Rebif 22 micrograms solution for injection

interferon beta-1a
SC use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

22 micrograms (6 million IU)/0.5 mL

6. OTHER

Merck Europe B.V.

PARTICULARS TO APPEAR ON THE LAYERS SEPARATORS FOR THE STARTER PACK

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

(UPPER FLAP)

Rebif 8.8 micrograms solution for injection in pre-filled pen
interferon beta-1a
Subcutaneous use
BRAILLE: rebif 8.8

(LOWER FLAP)

Rebif 22 micrograms solution for injection in pre-filled pen
interferon beta-1a
Subcutaneous use
BRAILLE: rebif 22

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

4. BATCH NUMBER

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6. OTHER

(UPPER FLAP)

6 pre-filled pens
RebiDose

(LOWER FLAP)

6 pre-filled pens
RebiDose

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Rebif 22 micrograms solution for injection in pre-filled syringe interferon beta-1a

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Rebif is and what it is used for
2. What you need to know before you use Rebif
3. How to use Rebif
4. Possible side effects
5. How to store Rebif
6. Contents of the pack and other information

1. What Rebif is and what it is used for

Rebif belongs to a class of medicines known as interferons. These are natural substances that transmit messages between cells. Interferons are produced by the body and play an essential role in the immune system. Through mechanisms that are not totally understood, interferons help to limit the damage of the central nervous system associated with multiple sclerosis.

Rebif is a highly purified soluble protein that is similar to the natural interferon beta that is produced in the human body.

Rebif is used for the treatment of multiple sclerosis. It has been shown to reduce the number and the severity of relapses and to slow the progression of disability.

2. What you need to know before you use Rebif

Do not use Rebif

- if you are allergic to natural or recombinant interferon beta or any of the other ingredients of this medicine (listed in section 6).
- if you are severely depressed at present.

Warnings and precautions

Talk to your doctor, pharmacist or nurse before using Rebif.

- Rebif should only be used under the supervision of your doctor.
- Before treatment with Rebif, read carefully and follow the advice given under “How to use Rebif” in order to minimise the risk of injection site necrosis (skin breakdown and tissue destruction) that has been reported in patients treated with Rebif. If you experience troubling local reactions, contact your doctor.
- Talk to your doctor or pharmacist before taking Rebif if you have an allergy (hypersensitivity) to any other medicines.

- Blood clots in the small blood vessels may occur during your treatment. These blood clots could affect your kidneys. This might happen several weeks to several years after starting Rebif. Your doctor may want to check your blood pressure, blood (platelet count) and the function of your kidney.

Inform your doctor if you have a disease of

- the bone marrow,
- kidney,
- liver,
- heart,
- thyroid,
- or if you have experienced depression,
- or if you have any history of epileptic seizures,

so that he/she can closely monitor your treatment and any worsening of these conditions.

Other medicines and Rebif

Tell your doctor or pharmacist if you are using, have recently used or might use any other medicines. In particular you should tell your doctor if you are using antiepileptics or antidepressants.

Pregnancy and breast-feeding

If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

No harmful effects on the breastfed newborn/infant are anticipated. Rebif can be used during breast-feeding.

Driving and using machines

Effects of the disease itself or of its treatment might influence your ability to drive or to use machines. You should discuss this with your doctor if you are concerned.

Rebif contains sodium and benzyl alcohol

This medicine contains less than 1 mmol sodium (23 mg) per dose, that is to say it is essentially 'sodium-free'.

This medicine contains 2.5 mg benzyl alcohol per dose. Benzyl alcohol may cause allergic reactions.

Benzyl alcohol has been linked with the risk of severe side effects including breathing problems (called "gaspings syndrome") in young children.

Do not use for more than a week in young children (less than 3 years old), unless advised by your doctor or pharmacist.

Ask your doctor or pharmacist for advice if you are pregnant or breast-feeding, or if you have a liver or kidney disease. This is because large amounts of benzyl alcohol can build-up in your body and may cause side effects (called "metabolic acidosis").

3. How to use Rebif

Always use this medicine exactly as your doctor has told you. Check with your doctor if you are not sure.

Dose

The usual dose is 44 micrograms (12 million IU) given three times per week. Your doctor has prescribed you a lower dose of 22 micrograms (6 million IU) given three times per week. This lower dose is recommended for patients who cannot tolerate the higher dose.

Rebif should be administered three times per week, and if possible:

- on the same three days every week (at least 48 hours apart, e.g. Monday, Wednesday, Friday)
- at the same time of day (preferably in the evening).

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.

Method of administration

Rebif is intended for subcutaneous (under the skin) injection.

The first injection(s) must be performed under the supervision of an appropriately qualified healthcare professional. After receiving adequate training, you, a family member, friend or carer can use Rebif syringes to administer the medicine at home. It may also be administered with a suitable auto-injector.

For administration of Rebif, please read the following instructions carefully:

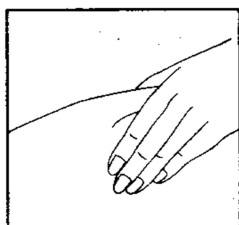
This medicine is for single use. Only clear to opalescent solution without particles and without visible signs of deterioration should be used.

How to inject Rebif

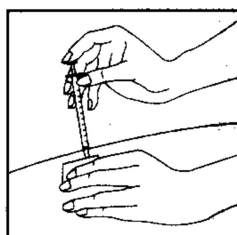


- Choose an injection site. Your doctor will advise you on the possible injection sites (good sites include the upper thighs and the lower abdomen). Hold the syringe like a pencil or dart. It is recommended that you keep track of and rotate your injection sites, so that one area is not injected too frequently in order to minimise the risk of injection site necrosis. NOTE: do not use any areas in which you feel lumps, firm knots, or pain; talk to your doctor or healthcare professional about anything you find.

- Wash your hands thoroughly with soap and water.
- Remove the Rebif syringe from the blister pack by peeling back the plastic covering.
- Before the injection, use an alcohol wipe to clean the skin at the injection site. Let the skin dry. If a bit of alcohol is left on the skin, you may get a stinging sensation.



- Gently pinch the skin together around the site (to lift it up a bit).
- Resting your wrist on the skin near the site, stick the needle at a right angle straight into the skin with a quick, firm motion.



- Inject the medicine by using a slow, steady push (push the plunger all the way in until the syringe is empty).
- Hold a swab on the injection site. Remove the needle from the skin.

- Gently massage the injection site with a dry cotton ball or gauze.
- Dispose of all used items: once you have finished your injection, immediately discard the syringe in an appropriate disposal unit.

If you use more Rebif than you should

In case of overdose, contact your doctor immediately.

If you forget to use Rebif

If you miss a dose, continue to inject from the day of the next scheduled dose. Do not use a double dose to make up for a forgotten dose.

If you stop using Rebif

The effects of Rebif may not be noticed immediately. Therefore, you should not stop using Rebif but continue to use it regularly to achieve the desired result. If you are uncertain about the benefits, please consult your doctor.

You should not discontinue the treatment without first contacting your doctor.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Tell your doctor immediately and stop using Rebif if you experience any of the following serious side effects:

- **Serious allergic (hypersensitivity) reactions.** If, immediately following Rebif administration you experience a sudden difficulty breathing, which may appear in association with swelling of face, lips, tongue or throat, nettle rash, itching all over the body, and a feeling of weakness or faintness, contact your doctor immediately or seek urgent medical attention. These reactions are *rare* (may affect up to 1 in 1,000 people).
- Inform your doctor immediately if you experience any of the following possible symptoms of a **liver problem**: jaundice (yellowing of the skin or of the whites of the eyes), widespread itching, loss of appetite accompanied by nausea and vomiting and easy bruising of the skin. Severe liver problems can be associated with additional signs, e.g. difficulty concentrating, sleepiness and confusion.
- **Depression** is *common* (may affect up to 1 in 10 people) in treated patients with multiple sclerosis. If you feel **depressed or develop thoughts of suicide**, report it immediately to your doctor.

Talk to your doctor if you experience any of the following side effects:

- **Flu-like symptoms**, such as headache, fever, chills, muscle and joint pains, fatigue and nausea are *very common* (may affect more than 1 in 10 people).
These symptoms are usually mild, are more common at the start of the treatment and decrease with continued use.
To help reduce these symptoms your doctor may advise you to take a fever reducing painkiller before a dose of Rebif and then for 24 hours after each injection.
- **Injection site reactions** including redness, swelling, discoloration, inflammation, pain and skin breakdown are *very common*.
The occurrence of injection site reactions usually decreases over time.

Tissue destruction (necrosis), abscess and mass at injection site are *uncommon* (may affect up to 1 in 100 people).

See recommendations in section “Warnings and precautions” to minimise the risk of injection site reactions.

The injection site can become infected (*uncommon*); the skin may become swollen tender and hard and the whole area could be very painful. If you experience any of these symptoms, contact your doctor for advice.

- Certain **laboratory tests** may change. These changes are generally not noticed by the patient (no symptoms), are usually reversible and mild, and most often do not require particular treatment.
The number of red blood cells, white blood cells or platelets may decrease either individually (*very common*) or all at one time (*rare*). Possible symptoms resulting from these changes could include tiredness, reduced ability to fight infection, bruising or unexplained bleeding.
Liver function tests may be disturbed (*very common*). Inflammation of the liver has also been reported (*uncommon*). If you experience symptoms suggesting a liver disorder, such as loss of appetite accompanied by other symptoms such as nausea, vomiting, jaundice, please contact your doctor immediately (see above “Tell your doctor immediately...”).
- **Thyroid dysfunction** is *uncommon*. The thyroid gland may function either excessively, or insufficiently. These changes in the thyroid activity are almost always not felt by the patient as symptoms; however your doctor may recommend testing as appropriate.
- **MS pseudo-relapse** (*frequency not known*): There is a possibility that at the beginning of your treatment with Rebif you may experience symptoms that resemble those of a multiple sclerosis relapse. For example, your muscles may feel very tense or very weak, preventing you from moving as you want. In some cases such symptoms are associated with fever or flu-like symptoms described above. If you notice any of these side effects talk to your doctor.

Other possible side effects include:

Very common (may affect more than 1 in 10 people):

- Headache

Common (may affect up to 1 in 10 people):

- Insomnia (sleeping difficulty)
- Diarrhoea, nausea, vomiting
- Itching, rash (skin eruptions)
- Muscle and joints pain
- Fatigue, fever, chills
- Hair loss

Uncommon (may affect up to 1 in 100 people):

- Hives
- Epileptic seizures
- Liver inflammation (hepatitis)
- Breathing difficulties
- Blood clots such as deep venous thrombosis
- Disorders of the retina (back of the eye) such as inflammation or blood clots with consequent vision disorders (vision disturbances, loss of vision)
- Increased sweating

Rare (may affect up to 1 in 1,000 people):

- Suicide attempt
- Serious skin reactions - some with mucosal lesions

- Blood clots in the small blood vessels that can affect your kidneys (thrombotic thrombocytopenic purpura or haemolytic uremic syndrome). Symptoms may include increased bruising, bleeding, fever, extreme weakness, headache, dizziness or light-headedness. Your doctor may find changes in your blood and the function of your kidneys.
- Drug-induced lupus erythematosus: a side-effect of long-term use of Rebif. Symptoms may include muscle pain, joint pain and swelling, and rash. You may also experience other signs such as fever, weight loss, and fatigue. Usually symptoms disappear within one or two weeks after treatment is stopped.
- Kidney problems including scarring that may reduce your kidney function.
If you get some or all of these symptoms:
 - foamy urine
 - fatigue
 - swelling, particularly in the ankles and eyelids, and weight gain.
 Tell your doctor as they may be signs of a possible kidney problem.

The following side effects were reported for interferon beta (frequency not known)

- Dizziness
- Nervousness
- Loss of appetite
- Dilatation of the blood vessels and palpitation
- Irregularities and/or changes in menstrual flow.
- Pulmonary arterial hypertension - a disease of severe narrowing of the blood vessels in the lungs resulting in high blood pressure in the blood vessels that carry blood from the heart to the lungs. Pulmonary arterial hypertension has been seen at various time points during treatment, including several years after starting treatment with Rebif.
- Inflammation of the fatty tissue under the skin (panniculitis), which can make the skin feel hard and possibly develop painful red lumps or patches.

You should not stop or alter the medication without your doctor's advice.

Children and teenagers

Side effects in children and teenagers are similar to those observed in adults.

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly [via the national reporting system listed in Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Rebif

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the label after EXP.

Store in a refrigerator (2°C – 8°C).

Do not freeze. (To prevent accidental freezing, avoid placing near the freezer compartment).

For the purpose of ambulatory use, you may remove Rebif from the refrigerator and store it not above 25°C for one single period of up to 14 days. Rebif must then be returned to the refrigerator and used before the expiry date.

Store in the original package in order to protect from light.

Do not use this medicine if you notice any visible signs of deterioration such as if the solution is no longer clear or if it contains particles.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away of medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Rebif contains

- The active substance is interferon beta-1a. Each syringe contains 22 micrograms, corresponding to 6 million International Units (IU) of interferon beta-1a.
- The other ingredients are mannitol, poloxamer 188, L-methionine, benzyl alcohol, sodium acetate, acetic acid, sodium hydroxide and water for injections.

What Rebif looks like and contents of the pack

Rebif is available as a solution for injection in a pre-filled syringe with a fixed needle for self-administration. Rebif solution is clear to opalescent. The pre-filled syringe is ready for use and contains 0.5 mL of solution.

Rebif is available in packs of 1, 3, 12 and 36 pre-filled syringes. Not all pack sizes may be marketed.

Marketing Authorisation Holder

Merck Europe B.V.
Gustav Mahlerplein 102
1082 MA Amsterdam
The Netherlands

Manufacturer

Merck Serono S.p.A.
Via delle Magnolie 15
I-70026 Modugno (Bari)
Italy

This leaflet was last revised in

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency website:

<http://www.ema.europa.eu>.

Package leaflet: Information for the user

Rebif 44 micrograms solution for injection in pre-filled syringe interferon beta-1a

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Rebif is and what it is used for
2. What you need to know before you use Rebif
3. How to use Rebif
4. Possible side effects
5. How to store Rebif
6. Contents of the pack and other information

1. What Rebif is and what it is used for

Rebif belongs to a class of medicines known as interferons. These are natural substances that transmit messages between cells. Interferons are produced by the body and play an essential role in the immune system. Through mechanisms that are not totally understood, interferons help to limit the damage of the central nervous system associated with multiple sclerosis.

Rebif is a highly purified soluble protein that is similar to the natural interferon beta that is produced in the human body.

Rebif is used for the treatment of multiple sclerosis. It has been shown to reduce the number and the severity of relapses and to slow the progression of disability. It is also approved for use in patients who have experienced a single clinical event likely to be a first sign of multiple sclerosis.

2. What you need to know before you use Rebif

Do not use Rebif

- if you are allergic to natural or recombinant interferon beta or any of the other ingredients of this medicine (listed in section 6).
- if you are severely depressed at present.

Warnings and precautions

Talk to your doctor, pharmacist or nurse before using Rebif.

- Rebif should only be used under the supervision of your doctor.
- Before treatment with Rebif, read carefully and follow the advice given under “How to use Rebif” in order to minimise the risk of injection site necrosis (skin breakdown and tissue destruction) that has been reported in patients treated with Rebif. If you experience troubling local reactions, contact your doctor.
- Talk to your doctor or pharmacist before taking Rebif if you have an allergy (hypersensitivity) to any other medicines.

- Blood clots in the small blood vessels may occur during your treatment. These blood clots could affect your kidneys. This might happen several weeks to several years after starting Rebif. Your doctor may want to check your blood pressure, blood (platelet count) and the function of your kidney.

Inform your doctor if you have a disease of

- the bone marrow,
- kidney,
- liver,
- heart,
- thyroid,
- or if you have experienced depression,
- or if you have any history of epileptic seizures,

so that he/she can closely monitor your treatment and any worsening of these conditions.

Other medicines and Rebif

Tell your doctor or pharmacist if you are using, have recently used or might use any other medicines. In particular you should tell your doctor if you are using antiepileptics or antidepressants.

Pregnancy and breast-feeding

If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

No harmful effects on the breastfed newborn/infant are anticipated. Rebif can be used during breast-feeding.

Driving and using machines

Effects of the disease itself or of its treatment might influence your ability to drive or to use machines. You should discuss this with your doctor if you are concerned.

Rebif contains sodium and benzyl alcohol

This medicine contains less than 1 mmol sodium (23 mg) per dose, that is to say it is essentially 'sodium-free'.

This medicine contains 2.5 mg benzyl alcohol per dose. Benzyl alcohol may cause allergic reactions.

Benzyl alcohol has been linked with the risk of severe side effects including breathing problems (called "gaspings syndrome") in young children.

Do not use for more than a week in young children (less than 3 years old), unless advised by your doctor or pharmacist.

Ask your doctor or pharmacist for advice if you are pregnant or breast-feeding, or if you have a liver or kidney disease. This is because large amounts of benzyl alcohol can build-up in your body and may cause side effects (called "metabolic acidosis").

3. How to use Rebif

Always use this medicine exactly as your doctor has told you. Check with your doctor if you are not sure.

Dose

Patients who have experienced a single clinical event

The usual dose is 44 micrograms (12 million IU) given three times per week.

Patients with multiple sclerosis

The usual dose is 44 micrograms (12 million IU) given three times per week.

A lower dose of 22 micrograms (6 million IU) given three times per week is recommended for patients who cannot tolerate the higher dose.

Rebif should be administered three times per week, and if possible:

- on the same three days every week (at least 48 hours apart, e.g. Monday, Wednesday, Friday)
- at the same time of day (preferably in the evening).

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.

Method of administration

Rebif is intended for subcutaneous (under the skin) injection.

The first injection(s) must be performed under the supervision of an appropriately qualified healthcare professional. After receiving adequate training, you, a family member, friend or carer can use Rebif syringes to administer the medicine at home. It may also be administered with a suitable auto-injector.

For administration of Rebif, please read the following instructions carefully:

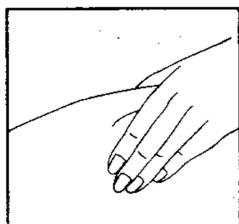
This medicine is for single use. Only clear to opalescent solution without particles and without visible signs of deterioration should be used.

How to inject Rebif

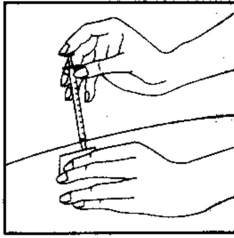


- Choose an injection site. Your doctor will advise you on the possible injection sites (good sites include the upper thighs and the lower abdomen). Hold the syringe like a pencil or dart. It is recommended that you keep track of and rotate your injection sites, so that one area is not injected too frequently in order to minimise the risk of injection site necrosis. NOTE: do not use any areas in which you feel lumps, firm knots, or pain; talk to your doctor or healthcare professional about anything you find.

- Wash your hands thoroughly with soap and water.
- Remove the Rebif syringe from the blister pack by peeling back the plastic covering.
- Before the injection, use an alcohol wipe to clean the skin at the injection site. Let the skin dry. If a bit of alcohol is left on the skin, you may get a stinging sensation.



- Gently pinch the skin together around the site (to lift it up a bit).
- Resting your wrist on the skin near the site, stick the needle at a right angle straight into the skin with a quick, firm motion.



- Inject the medicine by using a slow, steady push (push the plunger all the way in until the syringe is empty).
- Hold a swab on the injection site. Remove the needle from the skin.

- Gently massage the injection site with a dry cotton ball or gauze.
- Dispose of all used items: once you have finished your injection, immediately discard the syringe in an appropriate disposal unit.

If you use more Rebif than you should

In case of overdose, contact your doctor immediately.

If you forget to use Rebif

If you miss a dose, continue to inject from the day of the next scheduled dose. Do not use a double dose to make up for a forgotten dose.

If you stop using Rebif

The effects of Rebif may not be noticed immediately. Therefore, you should not stop using Rebif but continue to use it regularly to achieve the desired result. If you are uncertain about the benefits, please consult your doctor.

You should not discontinue the treatment without first contacting your doctor.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Tell your doctor immediately and stop using Rebif if you experience any of the following serious side effects:

- **Serious allergic (hypersensitivity) reactions.** If, immediately following Rebif administration you experience a sudden difficulty breathing, which may appear in association with swelling of face, lips, tongue or throat, nettle rash, itching all over the body, and a feeling of weakness or faintness, contact your doctor immediately or seek urgent medical attention. These reactions are *rare* (may affect up to 1 in 1,000 people).
- Inform your doctor immediately if you experience any of the following possible symptoms of a **liver problem**: jaundice (yellowing of the skin or of the whites of the eyes), widespread itching, loss of appetite accompanied by nausea and vomiting and easy bruising of the skin. Severe liver problems can be associated with additional signs, e.g. difficulty concentrating, sleepiness and confusion.
- **Depression** is *common* (may affect up to 1 in 10 people) in treated patients with multiple sclerosis. If you feel **depressed or develop thoughts of suicide**, report it immediately to your doctor.

Talk to your doctor if you experience any of the following side effects:

- **Flu-like symptoms**, such as headache, fever, chills, muscle and joint pains, fatigue and nausea are *very common* (may affect more than 1 in 10 people).
These symptoms are usually mild, are more common at the start of the treatment and decrease with continued use.
To help reduce these symptoms your doctor may advise you to take a fever reducing painkiller before a dose of Rebif and then for 24 hours after each injection.
- **Injection site reactions** including redness, swelling, discoloration, inflammation, pain and skin breakdown are *very common*.
The occurrence of injection site reactions usually decreases over time.
Tissue destruction (necrosis), abscess and mass at injection site are *uncommon* (may affect up to 1 in 100 people).
See recommendations in section “Warnings and precautions” to minimise the risk of injection site reactions.
The injection site can become infected (*uncommon*); the skin may become swollen tender and hard and the whole area could be very painful. If you experience any of these symptoms, contact your doctor for advice.
- Certain **laboratory tests** may change. These changes are generally not noticed by the patient (no symptoms), are usually reversible and mild, and most often do not require particular treatment.
The number of red blood cells, white blood cells or platelets may decrease either individually (*very common*) or all at one time (*rare*). Possible symptoms resulting from these changes could include tiredness, reduced ability to fight infection, bruising or unexplained bleeding.
Liver function tests may be disturbed (*very common*). Inflammation of the liver has also been reported (*uncommon*). If you experience symptoms suggesting a liver disorder, such as loss of appetite accompanied by other symptoms such as nausea, vomiting, jaundice, please contact your doctor immediately (see above “Tell your doctor immediately...”).
- **Thyroid dysfunction** is *uncommon*. The thyroid gland may function either excessively, or insufficiently. These changes in the thyroid activity are almost always not felt by the patient as symptoms; however your doctor may recommend testing as appropriate.
- **MS pseudo-relapse** (*frequency not known*): There is a possibility that at the beginning of your treatment with Rebif you may experience symptoms that resemble those of a multiple sclerosis relapse. For example, your muscles may feel very tense or very weak, preventing you from moving as you want. In some cases such symptoms are associated with fever or flu-like symptoms described above. If you notice any of these side effects talk to your doctor.

Other possible side effects include:

Very common (may affect more than 1 in 10 people):

- Headache

Common (may affect up to 1 in 10 people):

- Insomnia (sleeping difficulty)
- Diarrhoea, nausea, vomiting
- Itching, rash (skin eruptions)
- Muscle and joints pain
- Fatigue, fever, chills
- Hair loss

Uncommon (may affect up to 1 in 100 people):

- Hives
- Epileptic seizures
- Liver inflammation (hepatitis)
- Breathing difficulties
- Blood clots such as deep venous thrombosis
- Disorders of the retina (back of the eye) such as inflammation or blood clots with consequent vision disorders (vision disturbances, loss of vision)
- Increased sweating

Rare (may affect up to 1 in 1,000 people):

- Suicide attempt
- Serious skin reactions - some with mucosal lesions
- Blood clots in the small blood vessels that can affect your kidneys (thrombotic thrombocytopenic purpura or haemolytic uremic syndrome). Symptoms may include increased bruising, bleeding, fever, extreme weakness, headache, dizziness or light-headedness. Your doctor may find changes in your blood and the function of your kidneys.
- Drug-induced lupus erythematosus: a side-effect of long-term use of Rebif. Symptoms may include muscle pain, joint pain and swelling, and rash. You may also experience other signs such as fever, weight loss, and fatigue. Usually symptoms disappear within one or two weeks after treatment is stopped.
- Kidney problems including scarring that may reduce your kidney function.
If you get some or all of these symptoms:
 - foamy urine
 - fatigue
 - swelling, particularly in the ankles and eyelids, and weight gain.Tell your doctor as they may be signs of a possible kidney problem.

The following side effects were reported for interferon beta (frequency not known)

- Dizziness
- Nervousness
- Loss of appetite
- Dilatation of the blood vessels and palpitation
- Irregularities and/or changes in menstrual flow.
- Pulmonary arterial hypertension - a disease of severe narrowing of the blood vessels in the lungs resulting in high blood pressure in the blood vessels that carry blood from the heart to the lungs. Pulmonary arterial hypertension has been seen at various time points during treatment, including several years after starting treatment with Rebif.
- Inflammation of the fatty tissue under the skin (panniculitis), which can make the skin feel hard and possibly develop painful red lumps or patches.

You should not stop or alter the medication without your doctor's advice.

Children and teenagers

Side effects in children and teenagers are similar to those observed in adults.

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in [Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Rebif

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the label after EXP.

Store in a refrigerator (2°C – 8°C).

Do not freeze. (To prevent accidental freezing, avoid placing near the freezer compartment).

For the purpose of ambulatory use, you may remove Rebif from the refrigerator and store it not above 25°C for one single period of up to 14 days. Rebif must then be returned to the refrigerator and used before the expiry date.

Store in the original package in order to protect from light.

Do not use this medicine if you notice any visible signs of deterioration such as if the solution is no longer clear or if it contains particles.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away of medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Rebif contains

- The active substance is interferon beta-1a. Each syringe contains 44 micrograms, corresponding to 12 million International Units (IU) of interferon beta-1a.
- The other ingredients are mannitol, poloxamer 188, L-methionine, benzyl alcohol, sodium acetate, acetic acid, sodium hydroxide and water for injections.

What Rebif looks like and contents of the pack

Rebif is available as a solution for injection in a pre-filled syringe with a fixed needle for self-administration. Rebif solution is clear to opalescent. The pre-filled syringe is ready for use and contains 0.5 mL of solution.

Rebif is available in packs of 1, 3, 12 and 36 pre-filled syringes. Not all pack sizes may be marketed.

Marketing Authorisation Holder

Merck Europe B.V.
Gustav Mahlerplein 102
1082 MA Amsterdam
The Netherlands

Manufacturer

Merck Serono S.p.A.
Via delle Magnolie 15
I-70026 Modugno (Bari)
Italy

This leaflet was last revised in

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency website:
<http://www.ema.europa.eu>.

Package leaflet: Information for the user

Rebif 8.8 micrograms solution for injection in pre-filled syringe **Rebif 22 micrograms solution for injection in pre-filled syringe** interferon beta-1a Initiation pack

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Rebif is and what it is used for
2. What you need to know before you use Rebif
3. How to use Rebif
4. Possible side effects
5. How to store Rebif
6. Contents of the pack and other information

1. What Rebif is and what it is used for

Rebif belongs to a class of medicines known as interferons. These are natural substances that transmit messages between cells. Interferons are produced by the body and play an essential role in the immune system. Through mechanisms that are not totally understood, interferons help to limit the damage of the central nervous system associated with multiple sclerosis.

Rebif is a highly purified soluble protein that is similar to the natural interferon beta that is produced in the human body.

Rebif is used for the treatment of multiple sclerosis. It has been shown to reduce the number and the severity of relapses and to slow the progression of disability. It is also approved for use in patients who have experienced a single clinical event likely to be a first sign of multiple sclerosis.

2. What you need to know before you use Rebif

Do not use Rebif

- if you are allergic to natural or recombinant interferon beta or any of the other ingredients of this medicine (listed in section 6).
- if you are severely depressed at present.

Warnings and precautions

Talk to your doctor, pharmacist or nurse before using Rebif.

- Rebif should only be used under the supervision of your doctor.
- Before treatment with Rebif, read carefully and follow the advice given under “How to use Rebif” in order to minimise the risk of injection site necrosis (skin breakdown and tissue destruction) that has been reported in patients treated with Rebif. If you experience troubling local reactions, contact your doctor.

- Talk to your doctor or pharmacist before taking Rebif if you have an allergy (hypersensitivity) to any other medicines.
- Blood clots in the small blood vessels may occur during your treatment. These blood clots could affect your kidneys. This might happen several weeks to several years after starting Rebif. Your doctor may want to check your blood pressure, blood (platelet count) and the function of your kidney.

Inform your doctor if you have a disease of

- the bone marrow,
- kidney,
- liver,
- heart,
- thyroid,
- or if you have experienced depression,
- or if you have any history of epileptic seizures,

so that he/she can closely monitor your treatment and any worsening of these conditions.

Other medicines and Rebif

Tell your doctor or pharmacist if you are using, have recently used or might use any other medicines. In particular you should tell your doctor if you are using antiepileptics or antidepressants.

Pregnancy and breast-feeding

If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

No harmful effects on the breastfed newborn/infant are anticipated. Rebif can be used during breast-feeding.

Driving and using machines

Effects of the disease itself or of its treatment might influence your ability to drive or to use machines. You should discuss this with your doctor if you are concerned.

Rebif contains sodium and benzyl alcohol

This medicine contains less than 1 mmol sodium (23 mg) per dose, that is to say it is essentially 'sodium-free'.

This medicine contains 1.0 mg benzyl alcohol per dose of 0.2 mL and 2.5 mg benzyl alcohol per dose of 0.5 mL. Benzyl alcohol may cause allergic reactions.

Benzyl alcohol has been linked with the risk of severe side effects including breathing problems (called "gasping syndrome") in young children.

Do not use for more than a week in young children (less than 3 years old), unless advised by your doctor or pharmacist.

Ask your doctor or pharmacist for advice if you are pregnant or breast-feeding, or if you have a liver or kidney disease. This is because large amounts of benzyl alcohol can build-up in your body and may cause side effects (called "metabolic acidosis").

3. How to use Rebif

Always use this medicine exactly as your doctor has told you. Check with your doctor if you are not sure.

Initiating treatment

Treatment is initiated by gradual increase of the dose (a so-called ‘dose titration’) over a period of 4 weeks in order to reduce some of the side effects it is recommended that:

- During weeks one and two, Rebif 8.8 micrograms should be injected three times per week.
- During weeks three and four, Rebif 22 micrograms should be injected three times per week.

From the fifth week onwards, after you have completed your initiation period, you will follow the usual dose regimen prescribed by your doctor.

Dose

The usual dose is 44 micrograms (12 million IU) given three times per week.

A lower dose of 22 micrograms (6 million IU) given three times per week is recommended for patients with multiple sclerosis who cannot tolerate the higher dose

Rebif should be administered three times per week, and if possible:

- on the same three days every week (at least 48 hours apart, e.g. Monday, Wednesday, Friday)
- at the same time of day (preferably in the evening).

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.

Method of administration

Rebif is intended for subcutaneous (under the skin) injection.

The first injection(s) must be performed under the supervision of an appropriately qualified healthcare professional. After receiving adequate training, you, a family member, friend or carer can use Rebif syringes to administer the medicine at home. It may also be administered with a suitable auto-injector.

For administration of Rebif, please read the following instructions carefully:

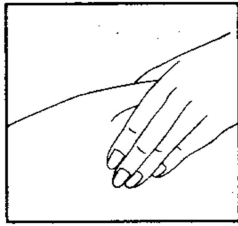
This medicine is for single use. Only clear to opalescent solution without particles and without visible signs of deterioration should be used.

How to inject Rebif

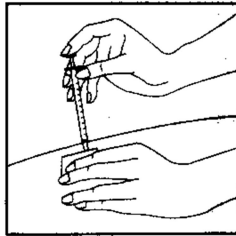


- Choose an injection site. Your doctor will advise you on the possible injection sites (good sites include the upper thighs and the lower abdomen). Hold the syringe like a pencil or dart. It is recommended that you keep track of and rotate your injection sites, so that one area is not injected too frequently in order to minimise the risk of injection site necrosis.
NOTE: do not use any areas in which you feel lumps, firm knots, or pain; talk to your doctor or healthcare professional about anything you find.

- Wash your hands thoroughly with soap and water.
- Remove the Rebif syringe from the blister pack by peeling back the plastic covering.
- Before the injection, use an alcohol wipe to clean the skin at the injection site. Let the skin dry. If a bit of alcohol is left on the skin, you may get a stinging sensation.



- Gently pinch the skin together around the site (to lift it up a bit).
- Resting your wrist on the skin near the site, stick the needle at a right angle straight into the skin with a quick, firm motion.



- Inject the medicine by using a slow, steady push (push the plunger all the way in until the syringe is empty).
- Hold a swab on the injection site. Remove the needle from the skin.

- Gently massage the injection site with a dry cotton ball or gauze.
- Dispose of all used items: once you have finished your injection, immediately discard the syringe in an appropriate disposal unit.

If you use more Rebif than you should

In case of overdose, contact your doctor immediately.

If you forget to use Rebif

If you miss a dose, continue to inject from the day of the next scheduled dose. Do not use a double dose to make up for a forgotten dose.

If you stop using Rebif

The effects of Rebif may not be noticed immediately. Therefore, you should not stop using Rebif but continue to use it regularly to achieve the desired result. If you are uncertain about the benefits, please consult your doctor.

You should not discontinue the treatment without first contacting your doctor.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Tell your doctor immediately and stop using Rebif if you experience any of the following serious side effects:

- **Serious allergic (hypersensitivity) reactions.** If, immediately following Rebif administration you experience a sudden difficulty breathing, which may appear in association with swelling of face, lips, tongue or throat, nettle rash, itching all over the body, and a feeling of weakness or faintness, contact your doctor immediately or seek urgent medical attention. These reactions are *rare* (may affect up to 1 in 1,000 people).
- Inform your doctor immediately if you experience any of the following possible symptoms of a **liver problem**: jaundice (yellowing of the skin or of the whites of the eyes), widespread itching, loss of appetite accompanied by nausea and vomiting and easy bruising of the skin. Severe liver problems can be associated with additional signs, e.g. difficulty concentrating, sleepiness and confusion.

- **Depression** is *common* (may affect up to 1 in 10 people) in treated patients with multiple sclerosis. If you feel **depressed or develop thoughts of suicide**, report it immediately to your doctor.

Talk to your doctor if you experience any of the following side effects:

- **Flu-like symptoms**, such as headache, fever, chills, muscle and joint pains, fatigue and nausea are *very common* (may affect more than 1 in 10 people). These symptoms are usually mild, are more common at the start of the treatment and decrease with continued use. To help reduce these symptoms your doctor may advise you to take a fever reducing painkiller before a dose of Rebif and then for 24 hours after each injection.
- **Injection site reactions** including redness, swelling, discoloration, inflammation, pain and skin breakdown are *very common*. The occurrence of injection site reactions usually decreases over time. Tissue destruction (necrosis), abscess and mass at injection site are *uncommon* (may affect up to 1 in 100 people). See recommendations in section “Warnings and precautions” to minimise the risk of injection site reactions. The injection site can become infected (*uncommon*); the skin may become swollen tender and hard and the whole area could be very painful. If you experience any of these symptoms, contact your doctor for advice.
- Certain **laboratory tests** may change. These changes are generally not noticed by the patient (no symptoms), are usually reversible and mild, and most often do not require particular treatment. The number of red blood cells, white blood cells or platelets may decrease either individually (*very common*) or all at one time (*rare*). Possible symptoms resulting from these changes could include tiredness, reduced ability to fight infection, bruising or unexplained bleeding. Liver function tests may be disturbed (*very common*). Inflammation of the liver has also been reported (*uncommon*). If you experience symptoms suggesting a liver disorder, such as loss of appetite accompanied by other symptoms such as nausea, vomiting, jaundice, please contact your doctor immediately (see above “Tell your doctor immediately...”).
- **Thyroid dysfunction** is *uncommon*. The thyroid gland may function either excessively, or insufficiently. These changes in the thyroid activity are almost always not felt by the patient as symptoms; however your doctor may recommend testing as appropriate.
- **MS pseudo-relapse** (*frequency not known*): There is a possibility that at the beginning of your treatment with Rebif you may experience symptoms that resemble those of a multiple sclerosis relapse. For example, your muscles may feel very tense or very weak, preventing you from moving as you want. In some cases such symptoms are associated with fever or flu-like symptoms described above. If you notice any of these side effects talk to your doctor.

Other possible side effects include:

Very common (may affect more than 1 in 10 people):

- Headache

Common (may affect up to 1 in 10 people):

- Insomnia (sleeping difficulty)
- Diarrhoea, nausea, vomiting
- Itching, rash (skin eruptions)
- Muscle and joints pain

- Fatigue, fever, chills
- Hair loss

Uncommon (may affect up to 1 in 100 people):

- Hives
- Epileptic seizures
- Liver inflammation (hepatitis)
- Breathing difficulties
- Blood clots such as deep venous thrombosis
- Disorders of the retina (back of the eye) such as inflammation or blood clots with consequent vision disorders (vision disturbances, loss of vision)
- Increased sweating

Rare (may affect up to 1 in 1,000 people):

- Suicide attempt
- Serious skin reactions - some with mucosal lesions
- Blood clots in the small blood vessels that can affect your kidneys (thrombotic thrombocytopenic purpura or haemolytic uremic syndrome). Symptoms may include increased bruising, bleeding, fever, extreme weakness, headache, dizziness or light-headedness. Your doctor may find changes in your blood and the function of your kidneys.
- Drug-induced lupus erythematosus: a side-effect of long-term use of Rebif. Symptoms may include muscle pain, joint pain and swelling, and rash. You may also experience other signs such as fever, weight loss, and fatigue. Usually symptoms disappear within one or two weeks after treatment is stopped.
- Kidney problems including scarring that may reduce your kidney function.
If you get some or all of these symptoms:
 - foamy urine
 - fatigue
 - swelling, particularly in the ankles and eyelids, and weight gain.
 Tell your doctor as they may be signs of a possible kidney problem.

The following side effects were reported for interferon beta (frequency not known)

- Dizziness
- Nervousness
- Loss of appetite
- Dilatation of the blood vessels and palpitation
- Irregularities and/or changes in menstrual flow.
- Pulmonary arterial hypertension - a disease of severe narrowing of the blood vessels in the lungs resulting in high blood pressure in the blood vessels that carry blood from the heart to the lungs. Pulmonary arterial hypertension has been seen at various time points during treatment, including several years after starting treatment with Rebif.
- Inflammation of the fatty tissue under the skin (panniculitis), which can make the skin feel hard and possibly develop painful red lumps or patches.

You should not stop or alter the medication without your doctor's advice.

Children and teenagers

Side effects in children and teenagers are similar to those observed in adults.

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in [Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Rebif

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the label after EXP.

Store in a refrigerator (2°C – 8°C).

Do not freeze. (To prevent accidental freezing, avoid placing near the freezer compartment).

For the purpose of ambulatory use, you may remove Rebif from the refrigerator and store it not above 25°C for one single period of up to 14 days. Rebif must then be returned to the refrigerator and used before the expiry date.

Store in the original package in order to protect from light.

Do not use this medicine if you notice any visible signs of deterioration such as if the solution is no longer clear or if it contains particles.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away of medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Rebif contains

- The active substance is interferon beta-1a.
 - Each 8.8 micrograms syringe contains 8.8 micrograms of interferon beta-1a (2.4 million IU).
 - Each 22 micrograms syringe contains 22 micrograms of interferon beta-1a (6 million IU).
- The other ingredients are mannitol, poloxamer 188, L-methionine, benzyl alcohol, sodium acetate, acetic acid, sodium hydroxide and water for injections.

What Rebif looks like and contents of the pack

Rebif 8.8 micrograms is a solution for injection in a pre-filled syringe with a fixed needle for self-administration. The pre-filled syringe is ready for use and contains 0.2 mL of solution.

Rebif 22 micrograms is a solution for injection in a pre-filled syringe with a fixed needle for self-administration. The pre-filled syringe is ready for use and contains 0.5 mL of solution.

Rebif solution is clear to opalescent.

Rebif 8.8 micrograms and Rebif 22 micrograms are supplied in an initiation pack that is intended for use during the initial 4 weeks of treatment, during which a gradual increase in Rebif dose is recommended.

One-month initiation pack contains six Rebif 8.8 micrograms pre-filled syringes and six Rebif 22 micrograms pre-filled syringes.

Marketing Authorisation Holder

Merck Europe B.V.
Gustav Mahlerplein 102
1082 MA Amsterdam
The Netherlands

Manufacturer

Merck Serono S.p.A.
Via delle Magnolie 15
I-70026 Modugno (Bari)
Italy

This leaflet was last revised in

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency website:
<http://www.ema.europa.eu>.

Package leaflet: Information for the user

Rebif 22 micrograms/0.5 mL solution for injection in cartridge interferon beta-1a

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Rebif is and what it is used for
2. What you need to know before you use Rebif
3. How to use Rebif
4. Possible side effects
5. How to store Rebif
6. Contents of the pack and other information

1. What Rebif is and what it is used for

Rebif belongs to a class of medicines known as interferons. These are natural substances that transmit messages between cells. Interferons are produced by the body and play an essential role in the immune system. Through mechanisms that are not totally understood, interferons help to limit the damage of the central nervous system associated with multiple sclerosis.

Rebif is a highly purified soluble protein that is similar to the natural interferon beta that is produced in the human body.

Rebif is used for the treatment of multiple sclerosis. It has been shown to reduce the number and the severity of relapses and to slow the progression of disability.

2. What you need to know before you use Rebif

Do not use Rebif

- if you are allergic to natural or recombinant interferon beta or any of the other ingredients of this medicine (listed in section 6).
- if you are severely depressed at present.

Warnings and precautions

Talk to your doctor, pharmacist or nurse before using Rebif.

- Rebif should only be used under the supervision of your doctor.
- Before treatment with Rebif, read carefully and follow the advice given under “How to use Rebif” in order to minimise the risk of injection site necrosis (skin breakdown and tissue destruction) that has been reported in patients treated with Rebif. If you experience troubling local reactions, contact your doctor.
- Talk to your doctor or pharmacist before taking Rebif if you have an allergy (hypersensitivity) to any other medicines.

- Blood clots in the small blood vessels may occur during your treatment. These blood clots could affect your kidneys. This might happen several weeks to several years after starting Rebif. Your doctor may want to check your blood pressure, blood (platelet count) and the function of your kidney.

Inform your doctor if you have a disease of

- the bone marrow,
- kidney,
- liver,
- heart,
- thyroid,
- or if you have experienced depression,
- or if you have any history of epileptic seizures,

so that he/she can closely monitor your treatment and any worsening of these conditions.

Other medicines and Rebif

Tell your doctor or pharmacist if you are using, have recently used or might use any other medicines. In particular you should tell your doctor if you are using antiepileptics or antidepressants.

Pregnancy and breast-feeding

If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

No harmful effects on the breastfed newborn/infant are anticipated. Rebif can be used during breast-feeding.

Driving and using machines

Effects of the disease itself or of its treatment might influence your ability to drive or to use machines. You should discuss this with your doctor if you are concerned.

Rebif contains sodium and benzyl alcohol

This medicine contains less than 1 mmol sodium (23 mg) per dose, that is to say it is essentially 'sodium-free'.

This medicine contains 2.5 mg benzyl alcohol per dose. Benzyl alcohol may cause allergic reactions.

Benzyl alcohol has been linked with the risk of severe side effects including breathing problems (called "gaspings syndrome") in young children.

Do not use for more than a week in young children (less than 3 years old), unless advised by your doctor or pharmacist.

Ask your doctor or pharmacist for advice if you are pregnant or breast-feeding, or if you have a liver or kidney disease. This is because large amounts of benzyl alcohol can build-up in your body and may cause side effects (called "metabolic acidosis").

3. How to use Rebif

This medicine is for multidose use.

Always use this medicine exactly as your doctor has told you. Check with your doctor if you are not sure.

Dose

The usual dose is 44 micrograms (12 million IU) given three times per week. Your doctor has prescribed you a lower dose of 22 micrograms (6 million IU) given three times per week. This lower dose is recommended for patients who cannot tolerate the higher dose

Rebif should be administered three times per week, and if possible:

- on the same three days every week (at least 48 hours apart, e.g., Monday, Wednesday, Friday)
- at the same time of day (preferably in the evening).

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.

Method of administration

- Rebif is intended for subcutaneous (under the skin) injection.
- The first injection(s) must be performed under the supervision of an appropriately qualified healthcare professional. After receiving adequate training, you, a family member, friend or carer can use Rebif cartridges with your device to administer the medicine at home.
- The cartridge is to be used with the RebiSmart electronic injection device.
- Full instructions for use are provided with your device. Please follow these carefully.
- Short instructions on how to use Rebif cartridges are given below.

Before you start

- Wash your hands thoroughly with soap and water.
- Remove the Rebif cartridge from the blister pack by peeling back the plastic covering.
- Check (just after removing from the refrigerator) that the cartridge is not accidentally frozen in the pack or inside the device. Only clear to opalescent solution without particles and without visible signs of deterioration should be used.
- To place the cartridge in the device and perform the injection follow the instruction manual (Instructions for Use) provided with your device.

Where to inject Rebif



- Choose an injection site. Your doctor will advise you on the possible injection sites (good sites include the upper thighs and the lower abdomen). It is recommended that you keep track of and rotate your injection sites, so that one area is not injected too frequently in order to minimise the risk of injection site necrosis.
NOTE: do not use any areas in which you feel lumps, firm knots, or pain; talk to your doctor or healthcare professional about anything you find.
- Before the injection, use an alcohol wipe to clean the skin at the injection site. Let the skin dry. If a bit of alcohol is left on the skin, you may get a stinging sensation.

How to inject Rebif

- Your doctor will tell you how to choose the correct dose of 22 micrograms. Please read also the instructions in the manual provided with your device (RebiSmart).

<i>RebiSmart</i>	<ul style="list-style-type: none"> • Please ensure that the dose displayed on the screen of the device corresponds to the prescribed dose of 22 micrograms before the injection. • Place RebiSmart at a right angle (90°) to the skin. • Press the injection button. During the injection, the button will flash. • Wait until the light switches off. This tells you that the injection is completed. • Remove RebiSmart from the injection site.
------------------	---

After the injection of Rebif with RebiSmart

- Remove and discard the needle according to the instruction manual provided with your device.
- Gently massage the injection site with a dry cotton ball or gauze.
- Store your device containing a cartridge of Rebif as instructed in section 5 “How to store Rebif”.

If you have any further questions, please ask your doctor, nurse or pharmacist.

If you use more Rebif than you should

In case of overdose, contact your doctor immediately.

If you forget to use Rebif

If you miss a dose, continue to inject from the day of the next scheduled dose. Do not use a double dose to make up for a forgotten dose.

If you stop using Rebif

The effects of Rebif may not be noticed immediately. Therefore you should not stop using Rebif but continue to use it regularly to achieve the desired result. If you are uncertain about the benefits, please consult your doctor.

You should not discontinue the treatment without first contacting your doctor.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Tell your doctor immediately and stop using Rebif if you experience any of the following serious side effects:

- **Serious allergic (hypersensitivity) reactions.** If, immediately following Rebif administration you experience a sudden difficulty breathing, which may appear in association with swelling of face, lips, tongue or throat, nettle rash, itching all over the body, and a feeling of weakness or faintness, contact your doctor immediately or seek urgent medical attention. These reactions are *rare* (may affect up to 1 in 1,000 people).
- Inform your doctor immediately if you experience any of the following possible symptoms of a **liver problem**: jaundice (yellowing of the skin or of the whites of the eyes), widespread itching, loss of appetite accompanied by nausea and vomiting and easy bruising of the skin. Severe liver problems can be associated with additional signs, e.g. difficulty concentrating, sleepiness and confusion.
- **Depression** is *common* (may affect up to 1 in 10 people) in treated patients with multiple sclerosis. If you feel **depressed or develop thoughts of suicide**, report it immediately to your doctor.

Talk to your doctor if you experience any of the following side effects:

- **Flu-like symptoms**, such as headache, fever, chills, muscle and joint pains, fatigue and nausea are *very common* (may affect more than 1 in 10 people).
These symptoms are usually mild, are more common at the start of the treatment and decrease with continued use.
To help reduce these symptoms your doctor may advise you to take a fever reducing painkiller before a dose of Rebif and then for 24 hours after each injection.
- **Injection site reactions** including redness, swelling, discoloration, inflammation, pain and skin breakdown are *very common*.
The occurrence of injection site reactions usually decreases over time.
Tissue destruction (necrosis), abscess and mass at injection site are *uncommon* (may affect up to 1 in 100 people).
See recommendations in section “Warnings and precautions” to minimise the risk of injection site reactions.
The injection site can become infected (*uncommon*); the skin may become swollen tender and hard and the whole area could be very painful. If you experience any of these symptoms, contact your doctor for advice.
- Certain **laboratory tests** may change. These changes are generally not noticed by the patient (no symptoms), are usually reversible and mild, and most often do not require particular treatment.
The number of red blood cells, white blood cells or platelets may decrease either individually (*very common*) or all at one time (*rare*). Possible symptoms resulting from these changes could include tiredness, reduced ability to fight infection, bruising or unexplained bleeding.
Liver function tests may be disturbed (*very common*). Inflammation of the liver has also been reported (*uncommon*). If you experience symptoms suggesting a liver disorder, such as loss of appetite accompanied by other symptoms such as nausea, vomiting, jaundice, please contact your doctor immediately (see above “Tell your doctor immediately...”).
- **Thyroid dysfunction** is *uncommon*. The thyroid gland may function either excessively, or insufficiently. These changes in the thyroid activity are almost always not felt by the patient as symptoms; however your doctor may recommend testing as appropriate.
- **MS pseudo-relapse** (*frequency not known*): There is a possibility that at the beginning of your treatment with Rebif you may experience symptoms that resemble those of a multiple sclerosis relapse. For example, your muscles may feel very tense or very weak, preventing you from moving as you want. In some cases such symptoms are associated with fever or flu-like symptoms described above. If you notice any of these side effects talk to your doctor.

Other possible side effects include:

Very common (may affect more than 1 in 10 people):

- Headache

Common (may affect up to 1 in 10 people):

- Insomnia (sleeping difficulty)
- Diarrhoea, nausea, vomiting
- Itching, rash (skin eruptions)
- Muscle and joints pain
- Fatigue, fever, chills
- Hair loss

Uncommon (may affect up to 1 in 100 people):

- Hives
- Epileptic seizures
- Liver inflammation (hepatitis)
- Breathing difficulties
- Blood clots such as deep venous thrombosis
- Disorders of the retina (back of the eye) such as inflammation or blood clots with consequent vision disorders (vision disturbances, loss of vision)
- Increased sweating

Rare (may affect up to 1 in 1,000 people):

- Suicide attempt
- Serious skin reactions - some with mucosal lesions
- Blood clots in the small blood vessels that can affect your kidneys (thrombotic thrombocytopenic purpura or haemolytic uremic syndrome). Symptoms may include increased bruising, bleeding, fever, extreme weakness, headache, dizziness or light-headedness. Your doctor may find changes in your blood and the function of your kidneys.
- Drug-induced lupus erythematosus: a side-effect of long-term use of Rebif. Symptoms may include muscle pain, joint pain and swelling, and rash. You may also experience other signs such as fever, weight loss, and fatigue. Usually symptoms disappear within one or two weeks after treatment is stopped.
- Kidney problems including scarring that may reduce your kidney function.
If you get some or all of these symptoms:
 - foamy urine
 - fatigue
 - swelling, particularly in the ankles and eyelids, and weight gain.Tell your doctor as they may be signs of a possible kidney problem.

The following side effects were reported for interferon beta (frequency not known)

- Dizziness
- Nervousness
- Loss of appetite
- Dilatation of the blood vessels and palpitation
- Irregularities and/or changes in menstrual flow
- Pulmonary arterial hypertension - a disease of severe narrowing of the blood vessels in the lungs resulting in high blood pressure in the blood vessels that carry blood from the heart to the lungs. Pulmonary arterial hypertension has been seen at various time points during treatment, including several years after starting treatment with Rebif.
- Inflammation of the fatty tissue under the skin (panniculitis), which can make the skin feel hard and possibly develop painful red lumps or patches.

You should not stop or alter the medication without your doctor's advice.

Children and teenagers

Side effects in children and teenagers are similar to those observed in adults.

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in [Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Rebif

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the label after EXP.

Store in a refrigerator (2°C – 8°C).

Do not freeze. (To prevent accidental freezing, avoid placing near the freezer compartment).

After first injection use within 28 days.

The device (RebiSmart) containing a pre-filled cartridge of Rebif must be stored in the device storage box in a refrigerator (2°C – 8°C). For the purpose of ambulatory use, you may remove Rebif from the refrigerator and store it not above 25°C for one single period of up to 14 days. Rebif must then be returned to the refrigerator and used before the expiry date.

Store in the original package in order to protect from light.

Do not use this medicine if you notice any visible signs of deterioration such as if the solution is no longer clear or if it contains particles.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away of medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Rebif contains

- The active substance is interferon beta-1a. Each cartridge contains 66 micrograms corresponding to 18 million International Units (IU) of interferon beta-1a.
- The other ingredients are mannitol, poloxamer 188, L-methionine, benzyl alcohol, sodium acetate, acetic acid, sodium hydroxide and water for injections.

What Rebif looks like and contents of the pack

Pre-filled cartridge (type 1 glass) with a plunger stopper (rubber) and a crimp cap (aluminium and halobutyl rubber), containing 1.5 mL solution for injection. Pack size of 4 or 12 cartridges. Not all pack sizes may be marketed.

The cartridge is to be used with the RebiSmart electronic injection device. The device is provided separately.

Marketing Authorisation Holder

Merck Europe B.V.
Gustav Mahlerplein 102
1082 MA Amsterdam
The Netherlands

Manufacturer

Merck Serono S.p.A.
Via delle Magnolie 15
I-70026 Modugno (Bari)
Italy

This leaflet was last revised in

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency website:
<http://www.ema.europa.eu>.

Package leaflet: Information for the user

Rebif 44 micrograms/0.5 mL solution for injection in cartridge interferon beta-1a

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Rebif is and what it is used for
2. What you need to know before you use Rebif
3. How to use Rebif
4. Possible side effects
5. How to store Rebif
6. Contents of the pack and other information

1. What Rebif is and what it is used for

Rebif belongs to a class of medicines known as interferons. These are natural substances that transmit messages between cells. Interferons are produced by the body and play an essential role in the immune system. Through mechanisms that are not totally understood, interferons help to limit the damage of the central nervous system associated with multiple sclerosis.

Rebif is a highly purified soluble protein that is similar to the natural interferon beta that is produced in the human body.

Rebif is used for the treatment of multiple sclerosis. It has been shown to reduce the number and the severity of relapses and to slow the progression of disability. It is also approved for use in patients who have experienced a single clinical event likely to be a first sign of multiple sclerosis.

2. What you need to know before you use Rebif

Do not use Rebif

- if you are allergic to natural or recombinant interferon beta or any of the other ingredients of this medicine (listed in section 6).
- if you are severely depressed at present.

Warnings and precautions

Talk to your doctor, pharmacist or nurse before using Rebif.

- Rebif should only be used under the supervision of your doctor.
- Before treatment with Rebif, read carefully and follow the advice given under “How to use Rebif” in order to minimise the risk of injection site necrosis (skin breakdown and tissue destruction) that has been reported in patients treated with Rebif. If you experience troubling local reactions, contact your doctor.
- Talk to your doctor or pharmacist before taking Rebif if you have an allergy (hypersensitivity) to any other medicines.

- Blood clots in the small blood vessels may occur during your treatment. These blood clots could affect your kidneys. This might happen several weeks to several years after starting Rebif. Your doctor may want to check your blood pressure, blood (platelet count) and the function of your kidney.

Inform your doctor if you have a disease of

- the bone marrow,
- kidney,
- liver,
- heart,
- thyroid,
- or if you have experienced depression,
- or if you have any history of epileptic seizures,

so that he/she can closely monitor your treatment and any worsening of these conditions.

Other medicines and Rebif

Tell your doctor or pharmacist if you are using, have recently used or might use any other medicines. In particular you should tell your doctor if you are using antiepileptics or antidepressants.

Pregnancy and breast-feeding

If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

No harmful effects on the breastfed newborn/infant are anticipated. Rebif can be used during breast-feeding.

Driving and using machines

Effects of the disease itself or of its treatment might influence your ability to drive or to use machines. You should discuss this with your doctor if you are concerned.

Rebif contains sodium and benzyl alcohol

This medicine contains less than 1 mmol sodium (23 mg) per dose, that is to say it is essentially 'sodium-free'.

This medicine contains 2.5 mg benzyl alcohol per dose. Benzyl alcohol may cause allergic reactions.

Benzyl alcohol has been linked with the risk of severe side effects including breathing problems (called "gaspingsyndrome") in young children.

Do not use for more than a week in young children (less than 3 years old), unless advised by your doctor or pharmacist.

Ask your doctor or pharmacist for advice if you are pregnant or breast-feeding, or if you have a liver or kidney disease. This is because large amounts of benzyl alcohol can build-up in your body and may cause side effects (called "metabolic acidosis").

3. How to use Rebif

This medicine is for multidose use.

Always use this medicine exactly as your doctor has told you. Check with your doctor if you are not sure.

Dose

Patients who have experienced a single clinical event

The usual dose is 44 micrograms (12 million IU) given three times per week.

Patients with multiple sclerosis

The usual dose is 44 micrograms (12 million IU) given three times per week.

A lower dose of 22 micrograms (6 million IU) given three times per week is recommended for patients who cannot tolerate the higher dose.

Rebif should be administered three times per week, and if possible:

- on the same three days every week (at least 48 hours apart, e.g., Monday, Wednesday, Friday)
- at the same time of day (preferably in the evening).

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.

Method of administration

- Rebif is intended for subcutaneous (under the skin) injection.
- The first injection(s) must be performed under the supervision of an appropriately qualified healthcare professional. After receiving adequate training, you, a family member, friend or carer can use Rebif cartridges with your device to administer the medicine at home.
- The cartridge is to be used with the RebiSmart electronic injection device.
- Full instructions for use are provided with your device. Please follow these carefully.
- Short instructions on how to use Rebif cartridges are given below.

Before you start

- Wash your hands thoroughly with soap and water.
- Remove the Rebif cartridge from the blister pack by peeling back the plastic covering.
- Check (just after removing from the refrigerator) that the cartridge is not accidentally frozen in the pack or inside the device. Only clear to opalescent solution without particles and without visible signs of deterioration should be used.
- To place the cartridge in the device and perform the injection follow the instruction manual (Instructions for Use) provided with your device.

Where to inject Rebif



- Choose an injection site. Your doctor will advise you on the possible injection sites (good sites include the upper thighs and the lower abdomen). It is recommended that you keep track of and rotate your injection sites, so that one area is not injected too frequently in order to minimise the risk of injection site necrosis.
NOTE: do not use any areas in which you feel lumps, firm knots, or pain; talk to your doctor or healthcare professional about anything you find.
- Before the injection, use an alcohol wipe to clean the skin at the injection site. Let the skin dry. If a bit of alcohol is left on the skin, you may get a stinging sensation.

How to inject Rebif

- Your doctor will tell you how to choose the correct dose of 44 micrograms. Please read also the instructions in the manual provided with your device (RebiSmart).

<i>RebiSmart</i>	<ul style="list-style-type: none"> • Please ensure that the dose displayed on the screen of the device corresponds to the prescribed dose of 44 micrograms before the injection. • Place RebiSmart at a right angle (90°) to the skin. • Press the injection button. During the injection, the button will flash. • Wait until the light switches off. This tells you that the injection is completed. • Remove RebiSmart from the injection site.
------------------	---

After the injection of Rebif with RebiSmart

- Remove and discard the needle according to the instruction manual provided with your device.
- Gently massage the injection site with a dry cotton ball or gauze.
- Store your device containing a cartridge of Rebif as instructed in section 5 “How to store Rebif”.

If you have any further questions, please ask your doctor, nurse or pharmacist.

If you use more Rebif than you should

In case of overdose, contact your doctor immediately.

If you forget to use Rebif

If you miss a dose, continue to inject from the day of the next scheduled dose. Do not use a double dose to make up for a forgotten dose.

If you stop using Rebif

The effects of Rebif may not be noticed immediately. Therefore you should not stop using Rebif but continue to use it regularly to achieve the desired result. If you are uncertain about the benefits, please consult your doctor.

You should not discontinue the treatment without first contacting your doctor.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Tell your doctor immediately and stop using Rebif if you experience any of the following serious side effects:

- **Serious allergic (hypersensitivity) reactions.** If, immediately following Rebif administration you experience a sudden difficulty breathing, which may appear in association with swelling of face, lips, tongue or throat, nettle rash, itching all over the body, and a feeling of weakness or faintness, contact your doctor immediately or seek urgent medical attention. These reactions are *rare* (may affect up to 1 in 1,000 people).
- Inform your doctor immediately if you experience any of the following possible symptoms of a **liver problem**: jaundice (yellowing of the skin or of the whites of the eyes), widespread itching, loss of appetite accompanied by nausea and vomiting and easy bruising of the skin. Severe liver problems can be associated with additional signs, e.g. difficulty concentrating, sleepiness and confusion.
- **Depression** is *common* (may affect up to 1 in 10 people) in treated patients with multiple sclerosis. If you feel **depressed or develop thoughts of suicide**, report it immediately to your doctor.

Talk to your doctor if you experience any of the following side effects:

- **Flu-like symptoms**, such as headache, fever, chills, muscle and joint pains, fatigue and nausea are *very common* (may affect more than 1 in 10 people).
These symptoms are usually mild, are more common at the start of the treatment and decrease with continued use.
To help reduce these symptoms your doctor may advise you to take a fever reducing painkiller before a dose of Rebif and then for 24 hours after each injection.
- **Injection site reactions** including redness, swelling, discoloration, inflammation, pain and skin breakdown are *very common*.
The occurrence of injection site reactions usually decreases over time.
Tissue destruction (necrosis), abscess and mass at injection site are *uncommon* (may affect up to 1 in 100 people).
See recommendations in section “Warnings and precautions” to minimise the risk of injection site reactions.
The injection site can become infected (*uncommon*); the skin may become swollen tender and hard and the whole area could be very painful. If you experience any of these symptoms, contact your doctor for advice.
- Certain **laboratory tests** may change. These changes are generally not noticed by the patient (no symptoms), are usually reversible and mild, and most often do not require particular treatment.
The number of red blood cells, white blood cells or platelets may decrease either individually (*very common*) or all at one time (*rare*). Possible symptoms resulting from these changes could include tiredness, reduced ability to fight infection, bruising or unexplained bleeding.
Liver function tests may be disturbed (*very common*). Inflammation of the liver has also been reported (*uncommon*). If you experience symptoms suggesting a liver disorder, such as loss of appetite accompanied by other symptoms such as nausea, vomiting, jaundice, please contact your doctor immediately (see above “Tell your doctor immediately...”).
- **Thyroid dysfunction** is *uncommon*. The thyroid gland may function either excessively, or insufficiently. These changes in the thyroid activity are almost always not felt by the patient as symptoms; however your doctor may recommend testing as appropriate.
- **MS pseudo-relapse** (*frequency not known*): There is a possibility that at the beginning of your treatment with Rebif you may experience symptoms that resemble those of a multiple sclerosis relapse. For example, your muscles may feel very tense or very weak, preventing you from moving as you want. In some cases such symptoms are associated with fever or flu-like symptoms described above. If you notice any of these side effects talk to your doctor.

Other possible side effects include:

Very common (may affect more than 1 in 10 people):

- Headache

Common (may affect up to 1 in 10 people):

- Insomnia (sleeping difficulty)
- Diarrhoea, nausea, vomiting
- Itching, rash (skin eruptions)
- Muscle and joints pain
- Fatigue, fever, chills
- Hair loss

Uncommon (may affect up to 1 in 100 people):

- Hives
- Epileptic seizures
- Liver inflammation (hepatitis)
- Breathing difficulties
- Blood clots such as deep venous thrombosis
- Disorders of the retina (back of the eye) such as inflammation or blood clots with consequent vision disorders (vision disturbances, loss of vision)
- Increased sweating

Rare (may affect up to 1 in 1,000 people):

- Suicide attempt
- Serious skin reactions - some with mucosal lesions
- Blood clots in the small blood vessels that can affect your kidneys (thrombotic thrombocytopenic purpura or haemolytic uremic syndrome). Symptoms may include increased bruising, bleeding, fever, extreme weakness, headache, dizziness or light-headedness. Your doctor may find changes in your blood and the function of your kidneys.
- Drug-induced lupus erythematosus: a side-effect of long-term use of Rebif. Symptoms may include muscle pain, joint pain and swelling, and rash. You may also experience other signs such as fever, weight loss, and fatigue. Usually symptoms disappear within one or two weeks after treatment is stopped.
- Kidney problems including scarring that may reduce your kidney function.
If you get some or all of these symptoms:
 - foamy urine
 - fatigue
 - swelling, particularly in the ankles and eyelids, and weight gain.Tell your doctor as they may be signs of a possible kidney problem.

The following side effects were reported for interferon beta (frequency not known)

- Dizziness
- Nervousness
- Loss of appetite
- Dilatation of the blood vessels and palpitation
- Irregularities and/or changes in menstrual flow
- Pulmonary arterial hypertension - a disease of severe narrowing of the blood vessels in the lungs resulting in high blood pressure in the blood vessels that carry blood from the heart to the lungs. Pulmonary arterial hypertension has been seen at various time points during treatment, including several years after starting treatment with Rebif.
- Inflammation of the fatty tissue under the skin (panniculitis), which can make the skin feel hard and possibly develop painful red lumps or patches.

You should not stop or alter the medication without your doctor's advice.

Children and teenagers

Side effects in children and teenagers are similar to those observed in adults.

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in [Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Rebif

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the label after EXP.

Store in a refrigerator (2°C – 8°C).

Do not freeze. (To prevent accidental freezing, avoid placing near the freezer compartment).

After first injection use within 28 days.

The device (RebiSmart) containing a pre-filled cartridge of Rebif must be stored in the device storage box in a refrigerator (2°C – 8°C). For the purpose of ambulatory use, you may remove Rebif from the refrigerator and store it not above 25°C for one single period of up to 14 days. Rebif must then be returned to the refrigerator and used before the expiry date.

Store in the original package in order to protect from light.

Do not use this medicine if you notice any visible signs of deterioration such as if the solution is no longer clear or if it contains particles.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away of medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Rebif contains

- The active substance is interferon beta-1a. Each cartridge contains 132 micrograms corresponding to 36 million International Units (IU) of interferon beta-1a.
- The other ingredients are mannitol, poloxamer 188, L-methionine, benzyl alcohol, sodium acetate, acetic acid, sodium hydroxide and water for injections.

What Rebif looks like and contents of the pack

Pre-filled cartridge (type 1 glass) with a plunger stopper (rubber) and a crimp cap (aluminium and halobutyl rubber), containing 1.5 mL solution for injection. Pack size of 4 or 12 cartridges. Not all pack sizes may be marketed.

The cartridge is to be used with the RebiSmart electronic injection device. The device is provided separately.

Marketing Authorisation Holder

Merck Europe B.V.
Gustav Mahlerplein 102
1082 MA Amsterdam
The Netherlands

Manufacturer

Merck Serono S.p.A.
Via delle Magnolie 15
I-70026 Modugno (Bari)
Italy

This leaflet was last revised in

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency website:
<http://www.ema.europa.eu>.

Package leaflet: Information for the user

Rebif 8.8 micrograms/0.1 mL solution for injection in cartridge **Rebif 22 micrograms/0.25 mL solution for injection in cartridge** interferon beta-1a Initiation pack

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Rebif is and what it is used for
2. What you need to know before you use Rebif
3. How to use Rebif
4. Possible side effects
5. How to store Rebif
6. Contents of the pack and other information

1. What Rebif is and what it is used for

Rebif belongs to a class of medicines known as interferons. These are natural substances that transmit messages between cells. Interferons are produced by the body and play an essential role in the immune system. Through mechanisms that are not totally understood, interferons help to limit the damage of the central nervous system associated with multiple sclerosis.

Rebif is a highly purified soluble protein that is similar to the natural interferon beta that is produced in the human body.

Rebif is used for the treatment of multiple sclerosis. It has been shown to reduce the number and the severity of relapses and to slow the progression of disability. It is also approved for use in patients who have experienced a single clinical event likely to be a first sign of multiple sclerosis.

2. What you need to know before you use Rebif

Do not use Rebif

- if you are allergic to natural or recombinant interferon beta or any of the other ingredients of this medicine (listed in section 6).
- if you are severely depressed at present.

Warnings and precautions

Talk to your doctor, pharmacist or nurse before using Rebif.

- Rebif should only be used under the supervision of your doctor.
- Before treatment with Rebif, read carefully and follow the advice given under “How to use Rebif” in order to minimise the risk of injection site necrosis (skin breakdown and tissue destruction) that has been reported in patients treated with Rebif. If you experience troubling local reactions, contact your doctor.

- Talk to your doctor or pharmacist before taking Rebif if you have an allergy (hypersensitivity) to any other medicines.
- Blood clots in the small blood vessels may occur during your treatment. These blood clots could affect your kidneys. This might happen several weeks to several years after starting Rebif. Your doctor may want to check your blood pressure, blood (platelet count) and the function of your kidney.

Inform your doctor if you have a disease of

- the bone marrow,
- kidney,
- liver,
- heart,
- thyroid,
- or if you have experienced depression,
- or if you have any history of epileptic seizures,

so that he/she can closely monitor your treatment and any worsening of these conditions.

Other medicines and Rebif

Tell your doctor or pharmacist if you are using, have recently used or might use any other medicines. In particular you should tell your doctor if you are using antiepileptics or antidepressants.

Pregnancy and breast-feeding

If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

No harmful effects on the breastfed newborn/infant are anticipated. Rebif can be used during breast-feeding.

Driving and using machines

Effects of the disease itself or of its treatment might influence your ability to drive or to use machines. You should discuss this with your doctor if you are concerned.

Rebif contains sodium and benzyl alcohol

This medicine contains less than 1 mmol sodium (23 mg) per dose, that is to say it is essentially 'sodium-free'.

This medicine contains 0.5 mg benzyl alcohol per dose of 0.1 mL and 1.25 mg benzyl alcohol per dose of 0.25 mL. Benzyl alcohol may cause allergic reactions.

Benzyl alcohol has been linked with the risk of severe side effects including breathing problems (called "gasping syndrome") in young children.

Do not use for more than a week in young children (less than 3 years old), unless advised by your doctor or pharmacist.

Ask your doctor or pharmacist for advice if you are pregnant or breast-feeding, or if you have a liver or kidney disease. This is because large amounts of benzyl alcohol can build-up in your body and may cause side effects (called "metabolic acidosis").

3. How to use Rebif

This medicine is for multidose use.

Always use this medicine exactly as your doctor has told you. Check with your doctor if you are not sure.

Initiating treatment

Treatment is initiated by a gradual increase of the dose (a so-called ‘dose titration’) over a period of 4 weeks in order to reduce some of the side effects, it is recommended that:

- During weeks one and two, Rebif 8.8 micrograms should be injected three times per week.
- During weeks three and four, Rebif 22 micrograms should be injected three times per week.

From the fifth week onwards, after you have completed your initiation period, you will follow the usual dose regimen prescribed by your doctor.

Dose

The usual dose is 44 micrograms (12 million IU) given three times per week.

A lower dose of 22 micrograms (6 million IU) given three times per week is recommended for patients with multiple sclerosis who cannot tolerate the higher dose.

Rebif should be administered three times per week, and if possible:

- on the same three days every week (at least 48 hours apart, e.g., Monday, Wednesday, Friday)
- at the same time of day (preferably in the evening).

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.

Method of administration

- Rebif is intended for subcutaneous (under the skin) injection.
- The first injection(s) must be performed under the supervision of an appropriately qualified healthcare professional. After receiving adequate training, you, a family member, friend or carer can use Rebif cartridges with your device to administer the medicine at home.
- The initiation pack contains two identical cartridges of Rebif and you may initiate treatment with either cartridge.
- The cartridge is to be used with the RebiSmart electronic injection device.
- Full instructions for use are provided with your device. Please follow these carefully.
- Short instructions on how to use Rebif cartridges are given below.

Before you start

- Wash your hands thoroughly with soap and water.
- Remove the Rebif cartridge from the blister pack by peeling back the plastic covering.
- Check (just after removing from the refrigerator) that the cartridge is not accidentally frozen in the pack or inside the device. Only clear to opalescent solution without particles and without visible signs of deterioration should be used.
- To place the cartridge in the device and perform the injection follow the instruction manual (Instructions for Use) provided with your device.

Where to inject Rebif



- Choose an injection site. Your doctor will advise you on the possible injection sites (good sites include the upper thighs and the lower abdomen). It is recommended that you keep track of and rotate your injection sites, so that one area is not injected too frequently in order to minimise the risk of injection site necrosis.
NOTE: do not use any areas in which you feel lumps, firm knots, or pain; talk to your doctor or healthcare professional about anything you find.
- Before the injection, use an alcohol wipe to clean the skin at the injection site. Let the skin dry. If a bit of alcohol is left on the skin, you may get a stinging sensation.

How to inject Rebif

- Your doctor will tell you how to choose the correct dose. Please read also the instructions in the manual provided with your device (RebiSmart).

<i>RebiSmart</i>	<ul style="list-style-type: none">• RebiSmart is programmed to guide you through the entire initiation process and automatically increases the dose during the initiation period. It will also instruct you when you need to change the cartridge.• You or your doctor will need to select the dose prescribed via the RebiSmart menu to ensure the correct recording of your dose.• To activate the “initiation/titration” menu you or your doctor need to first select 44 micrograms, then ‘initiation/titration’, select ‘on’ and confirm ‘initiation/titration on’ by pressing ‘ok’.
	<ul style="list-style-type: none">• The device will ensure that:<ul style="list-style-type: none">– During weeks one and two, Rebif 8.8 micrograms are injected three times per week.– During weeks three and four, Rebif 22 micrograms are injected three times per week.– From the fifth week onwards, RebiSmart will automatically switch to the usual dose regimen.• Place RebiSmart at a right angle (90°) to the skin.• Press the injection button. During the injection, the button will flash.• Wait until the light switches off. This tells you that the injection is completed.• Remove RebiSmart from the injection site.

After the injection of Rebif with RebiSmart

- Remove and discard the needle according to the instruction manual provided with your device.
- Gently massage the injection site with a dry cotton ball or gauze.
- Store your device containing a cartridge of Rebif as instructed in section 5 “How to store Rebif”.

If you have any further questions, please ask your doctor, nurse or pharmacist.

If you use more Rebif than you should

In case of overdose, contact your doctor immediately.

If you forget to use Rebif

If you miss a dose, continue to inject from the day of the next scheduled dose. Do not use a double dose to make up for a forgotten dose.

If you stop using Rebif

The effects of Rebif may not be noticed immediately. Therefore you should not stop using Rebif but continue to use it regularly to achieve the desired result. If you are uncertain about the benefits, please consult your doctor.

You should not discontinue the treatment without first contacting your doctor.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Tell your doctor immediately and stop using Rebif if you experience any of the following serious side effects:

- **Serious allergic (hypersensitivity) reactions.** If, immediately following Rebif administration you experience a sudden difficulty breathing, which may appear in association with swelling of face, lips, tongue or throat, nettle rash, itching all over the body, and a feeling of weakness or faintness, contact your doctor immediately or seek urgent medical attention. These reactions are *rare* (may affect up to 1 in 1,000 people).
- Inform your doctor immediately if you experience any of the following possible symptoms of a **liver problem**: jaundice (yellowing of the skin or of the whites of the eyes), widespread itching, loss of appetite accompanied by nausea and vomiting and easy bruising of the skin. Severe liver problems can be associated with additional signs, e.g. difficulty concentrating, sleepiness and confusion.
- **Depression** is *common* (may affect up to 1 in 10 people) in treated patients with multiple sclerosis. If you feel **depressed or develop thoughts of suicide**, report it immediately to your doctor.

Talk to your doctor if you experience any of the following side effects:

- **Flu-like symptoms**, such as headache, fever, chills, muscle and joint pains, fatigue and nausea are *very common* (may affect more than 1 in 10 people).
These symptoms are usually mild, are more common at the start of the treatment and decrease with continued use.
To help reduce these symptoms your doctor may advise you to take a fever reducing painkiller before a dose of Rebif and then for 24 hours after each injection.
- **Injection site reactions** including redness, swelling, discoloration, inflammation, pain and skin breakdown are *very common*.
The occurrence of injection site reactions usually decreases over time.
Tissue destruction (necrosis), abscess and mass at injection site are *uncommon* (may affect up to 1 in 100 people).
See recommendations in section “Warnings and precautions” to minimise the risk of injection site reactions.
The injection site can become infected (*uncommon*); the skin may become swollen tender and hard and the whole area could be very painful. If you experience any of these symptoms, contact your doctor for advice.
- Certain **laboratory tests** may change. These changes are generally not noticed by the patient (no symptoms), are usually reversible and mild, and most often do not require particular treatment.

The number of red blood cells, white blood cells or platelets may decrease either individually (*very common*) or all at one time (*rare*). Possible symptoms resulting from these changes could include tiredness, reduced ability to fight infection, bruising or unexplained bleeding. Liver function tests may be disturbed (*very common*). Inflammation of the liver has also been reported (*uncommon*). If you experience symptoms suggesting a liver disorder, such as loss of appetite accompanied by other symptoms such as nausea, vomiting, jaundice, please contact your doctor immediately (see above “Tell your doctor immediately...”).

- **Thyroid dysfunction** is *uncommon*. The thyroid gland may function either excessively, or insufficiently. These changes in the thyroid activity are almost always not felt by the patient as symptoms; however your doctor may recommend testing as appropriate.
- **MS pseudo-relapse** (*frequency not known*): There is a possibility that at the beginning of your treatment with Rebif you may experience symptoms that resemble those of a multiple sclerosis relapse. For example, your muscles may feel very tense or very weak, preventing you from moving as you want. In some cases such symptoms are associated with fever or flu-like symptoms described above. If you notice any of these side effects talk to your doctor.

Other possible side effects include:

Very common (may affect more than 1 in 10 people):

- Headache

Common (may affect up to 1 in 10 people):

- Insomnia (sleeping difficulty)
- Diarrhoea, nausea, vomiting
- Itching, rash (skin eruptions)
- Muscle and joints pain
- Fatigue, fever, chills
- Hair loss

Uncommon (may affect up to 1 in 100 people):

- Hives
- Epileptic seizures
- Liver inflammation (hepatitis)
- Breathing difficulties
- Blood clots such as deep venous thrombosis
- Disorders of the retina (back of the eye) such as inflammation or blood clots with consequent vision disorders (vision disturbances, loss of vision)
- Increased sweating

Rare (may affect up to 1 in 1,000 people):

- Suicide attempt
- Serious skin reactions - some with mucosal lesions
- Blood clots in the small blood vessels that can affect your kidneys (thrombotic thrombocytopenic purpura or haemolytic uremic syndrome). Symptoms may include increased bruising, bleeding, fever, extreme weakness, headache, dizziness or light-headedness. Your doctor may find changes in your blood and the function of your kidneys.
- Drug-induced lupus erythematosus: a side-effect of long-term use of Rebif. Symptoms may include muscle pain, joint pain and swelling, and rash. You may also experience other signs such as fever, weight loss, and fatigue. Usually symptoms disappear within one or two weeks after treatment is stopped.

- Kidney problems including scarring that may reduce your kidney function.
If you get some or all of these symptoms:
 - foamy urine
 - fatigue
 - swelling, particularly in the ankles and eyelids, and weight gain.
 Tell your doctor as they may be signs of a possible kidney problem.

The following side effects were reported for interferon beta (frequency not known)

- Dizziness
- Nervousness
- Loss of appetite
- Dilatation of the blood vessels and palpitation
- Irregularities and/or changes in menstrual flow
- Pulmonary arterial hypertension - a disease of severe narrowing of the blood vessels in the lungs resulting in high blood pressure in the blood vessels that carry blood from the heart to the lungs. Pulmonary arterial hypertension has been seen at various time points during treatment, including several years after starting treatment with Rebif.
- Inflammation of the fatty tissue under the skin (panniculitis), which can make the skin feel hard and possibly develop painful red lumps or patches.

You should not stop or alter the medication without your doctor's advice.

Children and teenagers

Side effects in children and teenagers are similar to those observed in adults.

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly [via the national reporting system listed in Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Rebif

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the label after EXP.

Store in a refrigerator (2°C – 8°C).

Do not freeze. (To prevent accidental freezing, avoid placing near the freezer compartment).

After first injection use within 28 days.

The device (RebiSmart) containing a pre-filled cartridge of Rebif must be stored in the device storage box in a refrigerator (2°C – 8°C). For the purpose of ambulatory use, you may remove Rebif from the refrigerator and store it not above 25°C for one single period of up to 14 days. Rebif must then be returned to the refrigerator and used before the expiry date.

Store in the original package in order to protect from light.

Do not use this medicine if you notice any visible signs of deterioration such as if the solution is no longer clear or if it contains particles.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away of medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Rebif contains

- The active substance is interferon beta-1a. Each cartridge contains 132 micrograms corresponding to 36 million International Units (IU) of interferon beta-1a.
- The other ingredients are mannitol, poloxamer 188, L-methionine, benzyl alcohol, sodium acetate, acetic acid, sodium hydroxide and water for injections.

What Rebif looks like and contents of the pack

Pre-filled cartridge (type 1 glass) with a plunger stopper (rubber) and a crimp cap (aluminium and halobutyl rubber), containing 1.5 mL solution for injection. Pack size of 2 cartridges.

The cartridge is to be used with the RebiSmart electronic injection device. The device is provided separately.

Marketing Authorisation Holder

Merck Europe B.V.
Gustav Mahlerplein 102
1082 MA Amsterdam
The Netherlands

Manufacturer

Merck Serono S.p.A.
Via delle Magnolie 15
I-70026 Modugno (Bari)
Italy

This leaflet was last revised in

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency website:
<http://www.ema.europa.eu>.

Package leaflet: Information for the user

Rebif 22 micrograms solution for injection in pre-filled pen interferon beta-1a

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Rebif is and what it is used for
2. What you need to know before you use Rebif
3. How to use Rebif
4. Possible side effects
5. How to store Rebif
6. Contents of the pack and other information

1. What Rebif is and what it is used for

Rebif belongs to a class of medicines known as interferons. These are natural substances that transmit messages between cells. Interferons are produced by the body and play an essential role in the immune system. Through mechanisms that are not totally understood, interferons help to limit the damage of the central nervous system associated with multiple sclerosis.

Rebif is a highly purified soluble protein that is similar to the natural interferon beta that is produced in the human body.

Rebif is used for the treatment of multiple sclerosis. It has been shown to reduce the number and the severity of relapses and to slow the progression of disability.

2. What you need to know before you use Rebif

Do not use Rebif

- if you are allergic to natural or recombinant interferon beta or any of the other ingredients of this medicine (listed in section 6).
- if you are severely depressed at present.

Warnings and precautions

Talk to your doctor, pharmacist or nurse before using Rebif.

- Rebif should only be used under the supervision of your doctor.
- Before treatment with Rebif, read carefully and follow the “RebiDose Instructions for Use” provided in a separate booklet, in order to minimise the risk of injection site necrosis (skin breakdown and tissue destruction) that has been reported in patients treated with Rebif. If you experience troubling local reactions, contact your doctor.
- Talk to your doctor or pharmacist before taking Rebif if you have an allergy (hypersensitivity) to any other medicines.

- Blood clots in the small blood vessels may occur during your treatment. These blood clots could affect your kidneys. This might happen several weeks to several years after starting Rebif. Your doctor may want to check your blood pressure, blood (platelet count) and the function of your kidney.

Inform your doctor if you have a disease of

- the bone marrow,
- kidney,
- liver,
- heart,
- thyroid,
- or if you have experienced depression,
- or if you have any history of epileptic seizures,

so that he/she can closely monitor your treatment and any worsening of these conditions.

Other medicines and Rebif

Tell your doctor or pharmacist if you are using, have recently used or might use any other medicines. In particular you should tell your doctor if you are using antiepileptics or antidepressants.

Pregnancy and breast-feeding

If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

No harmful effects on the breastfed newborn/infant are anticipated. Rebif can be used during breast-feeding.

Driving and using machines

Effects of the disease itself or of its treatment might influence your ability to drive or to use machines. You should discuss this with your doctor if you are concerned.

Rebif contains sodium and benzyl alcohol

This medicine contains less than 1 mmol sodium (23 mg) per dose, that is to say it is essentially 'sodium-free'.

This medicine contains 2.5 mg benzyl alcohol per dose. Benzyl alcohol may cause allergic reactions.

Benzyl alcohol has been linked with the risk of severe side effects including breathing problems (called "gaspingsyndrome") in young children.

Do not use for more than a week in young children (less than 3 years old), unless advised by your doctor or pharmacist.

Ask your doctor or pharmacist for advice if you are pregnant or breast-feeding, or if you have a liver or kidney disease. This is because large amounts of benzyl alcohol can build-up in your body and may cause side effects (called "metabolic acidosis").

3. How to use Rebif

Always use this medicine exactly as your doctor has told you. Check with your doctor if you are not sure.

Dose

The usual dose is 44 micrograms (12 million IU) given three times per week. Your doctor has prescribed you a lower dose of 22 micrograms (6 million IU) given three times per week. This lower dose is recommended for patients who cannot tolerate the higher dose.

Rebif should be administered three times per week, and if possible:

- on the same three days every week (at least 48 hours apart, e.g., Monday, Wednesday, Friday)
- at the same time of day (preferably in the evening).

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.

Method of administration

- Rebif is given by injection under the skin (subcutaneously) using a pre-filled pen called “RebiDose”.
- Use each RebiDose only once.
- The first injection(s) must be performed under the supervision of an appropriately qualified healthcare professional. After receiving adequate training, you, a family member, friend or carer can use Rebif pre-filled pen to administer the medicine at home.
- When you do this please read carefully and follow the “*RebiDose Instructions for Use*” provided separately in the booklet.

Only clear to opalescent solution without particles and without visible signs of deterioration should be used.

If you use more Rebif than you should

In case of overdose, contact your doctor immediately.

If you forget to use Rebif

If you miss a dose, continue to inject from the day of the next scheduled dose. Do not use a double dose to make up for a forgotten dose.

If you stop using Rebif

The effects of Rebif may not be noticed immediately. Therefore, you should not stop using Rebif but continue to use it regularly to achieve the desired result. If you are uncertain about the benefits, please consult your doctor.

You should not discontinue the treatment without first contacting your doctor.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Tell your doctor immediately and stop using Rebif if you experience any of the following serious side effects:

- **Serious allergic (hypersensitivity) reactions.** If, immediately following Rebif administration you experience a sudden difficulty breathing, which may appear in association with swelling of face, lips, tongue or throat, nettle rash, itching all over the body, and a feeling of weakness or faintness, contact your doctor immediately or seek urgent medical attention. These reactions are *rare* (may affect up to 1 in 1,000 people).

- Inform your doctor immediately if you experience any of the following possible symptoms of a **liver problem**: jaundice (yellowing of the skin or of the whites of the eyes), widespread itching, loss of appetite accompanied by nausea and vomiting and easy bruising of the skin. Severe liver problems can be associated with additional signs, e.g. difficulty concentrating, sleepiness and confusion.
- **Depression** is *common* (may affect up to 1 in 10 people) in treated patients with multiple sclerosis. If you feel **depressed or develop thoughts of suicide**, report it immediately to your doctor.

Talk to your doctor if you experience any of the following side effects:

- **Flu-like symptoms**, such as headache, fever, chills, muscle and joint pains, fatigue and nausea are very common (may affect more than 1 in 10 people).
These symptoms are usually mild, are more common at the start of the treatment and decrease with continued use.
To help reduce these symptoms your doctor may advise you to take a fever reducing painkiller before a dose of Rebif and then for 24 hours after each injection.
- **Injection site reactions** including redness, swelling, discoloration, inflammation, pain and skin breakdown are *very common*.
The occurrence of injection site reactions usually decreases over time.
Tissue destruction (necrosis), abscess and mass at injection site are *uncommon* (may affect up to 1 in 100 people).
See recommendations in section “Warnings and precautions” to minimise the risk of injection site reactions.
The injection site can become infected (*uncommon*); the skin may become swollen tender and hard and the whole area could be very painful. If you experience any of these symptoms, contact your doctor for advice.
- Certain **laboratory tests** may change. These changes are generally not noticed by the patient (no symptoms), are usually reversible and mild, and most often do not require particular treatment.
The number of red blood cells, white blood cells or platelets may decrease either individually (*very common*) or all at one time (*rare*). Possible symptoms resulting from these changes could include tiredness, reduced ability to fight infection, bruising or unexplained bleeding.
Liver function tests may be disturbed (*very common*). Inflammation of the liver has also been reported (*uncommon*). If you experience symptoms suggesting a liver disorder, such as loss of appetite accompanied by other symptoms such as nausea, vomiting, jaundice, please contact your doctor immediately (see above “Tell your doctor immediately...”).
- **Thyroid dysfunction** is *uncommon*. The thyroid gland may function either excessively, or insufficiently. These changes in the thyroid activity are almost always not felt by the patient as symptoms; however your doctor may recommend testing as appropriate.
- **MS pseudo-relapse** (*frequency not known*): There is a possibility that at the beginning of your treatment with Rebif you may experience symptoms that resemble those of a multiple sclerosis relapse. For example, your muscles may feel very tense or very weak, preventing you from moving as you want. In some cases such symptoms are associated with fever or flu-like symptoms described above. If you notice any of these side effects talk to your doctor.

Other possible side effects include:

Very common (may affect more than 1 in 10 people):

- Headache

Common (may affect up to 1 in 10 people):

- Insomnia (sleeping difficulty)
- Diarrhoea, nausea, vomiting
- Itching, rash (skin eruptions)
- Muscle and joints pain
- Fatigue, fever, chills
- Hair loss

Uncommon (may affect up to 1 in 100 people):

- Hives
- Epileptic seizures
- Liver inflammation (hepatitis)
- Breathing difficulties
- Blood clots such as deep venous thrombosis
- Disorders of the retina (back of the eye) such as inflammation or blood clots with consequent vision disorders (vision disturbances, loss of vision)
- Increased sweating

Rare (may affect up to 1 in 1,000 people):

- Suicide attempt
- Serious skin reactions - some with mucosal lesions
- Blood clots in the small blood vessels that can affect your kidneys (thrombotic thrombocytopenic purpura or haemolytic uremic syndrome). Symptoms may include increased bruising, bleeding, fever, extreme weakness, headache, dizziness or light-headedness. Your doctor may find changes in your blood and the function of your kidneys.
- Drug-induced lupus erythematosus: a side-effect of long-term use of Rebif. Symptoms may include muscle pain, joint pain and swelling, and rash. You may also experience other signs such as fever, weight loss, and fatigue. Usually symptoms disappear within one or two weeks after treatment is stopped.
- Kidney problems including scarring that may reduce your kidney function.
If you get some or all of these symptoms:
 - foamy urine
 - fatigue
 - swelling, particularly in the ankles and eyelids, and weight gain.Tell your doctor as they may be signs of a possible kidney problem.

The following side effects were reported for interferon beta (frequency not known)

- Dizziness
- Nervousness
- Loss of appetite
- Dilatation of the blood vessels and palpitation
- Irregularities and/or changes in menstrual flow.
- Pulmonary arterial hypertension - a disease of severe narrowing of the blood vessels in the lungs resulting in high blood pressure in the blood vessels that carry blood from the heart to the lungs. Pulmonary arterial hypertension has been seen at various time points during treatment, including several years after starting treatment with Rebif.
- Inflammation of the fatty tissue under the skin (panniculitis), which can make the skin feel hard and possibly develop painful red lumps or patches.

You should not stop or alter the medication without your doctor's advice.

Children and teenagers

Side effects in children and teenagers are similar to those observed in adults.

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in [Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Rebif

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the label after EXP.

Store in a refrigerator (2°C – 8°C).

Do not freeze. (To prevent accidental freezing, avoid placing near the freezer compartment).

For the purpose of ambulatory use, you may remove Rebif from the refrigerator and store it not above 25°C for one single period of up to 14 days. Rebif must then be returned to the refrigerator and used before the expiry date.

Store in the original package in order to protect from light.

Do not use this medicine if you notice any visible signs of deterioration such as if the solution is no longer clear or if it contains particles.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away of medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Rebif contains

- The active substance is interferon beta-1a. Each pre-filled pen contains 22 micrograms, corresponding to 6 million International Units (IU) of interferon beta-1a.
- The other ingredients are mannitol, poloxamer 188, L-methionine, benzyl alcohol, sodium acetate, acetic acid, sodium hydroxide and water for injections.

What Rebif looks like and contents of the pack

Rebif is available as a solution for injection in a pre-filled pen for self-administration. Rebif solution is clear to opalescent. The pre-filled pen is ready for use and contains 0.5 mL of solution. Rebif is available in packs of 1, 3 and 12 pre-filled pens (RebiDose). Not all pack sizes may be marketed.

Marketing Authorisation Holder

Merck Europe B.V.
Gustav Mahlerplein 102
1082 MA Amsterdam
The Netherlands

Manufacturer

Merck Serono S.p.A.
Via delle Magnolie 15
I-70026 Modugno (Bari)
Italy

This leaflet was last revised in

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency website:
<http://www.ema.europa.eu>.

RebiDose Instructions for use

HOW TO USE REBIF PRE-FILLED PEN (RebiDose)

- This section tells you how to use RebiDose.
- Rebif is given by injection under the skin (subcutaneously).
- Use each RebiDose only once.
- The first injection(s) must be performed under the supervision of an appropriately qualified healthcare professional. After receiving adequate training, you, a family member, friend or carer can use RebiDose to administer the medicine at home. If you have questions about how to inject, please ask your doctor, nurse or pharmacist for assistance.
- **Read all the following instructions carefully before using RebiDose.**

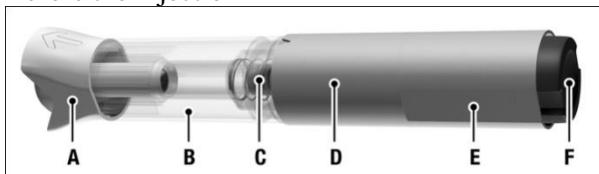
Equipment

To give yourself an injection you will need:

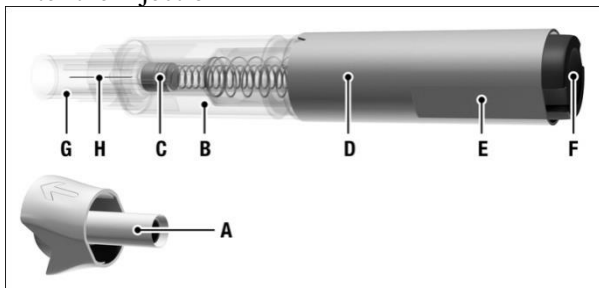
- A new RebiDose and
- Alcohol wipes or similar.
- a dry cotton ball or gauze

Below is a picture showing what RebiDose looks like.

Before the injection



After the injection



- A. Cap
- B. Transparent window
- C. Plunger
- D. Label
- E. Main body
- F. Button
- G. Safety guard
- H. Needle

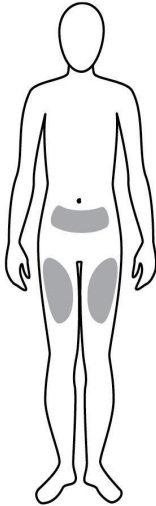
Before you start

- Wash your hands thoroughly with soap and water.
- Remove RebiDose from the blister pack by peeling back the plastic covering.
- Check the appearance of Rebif through the transparent window. It must be clear to opalescent, without particles and without any visible signs of deterioration. If there are particles or other

visible signs of deteriorations, do not use it and contact your doctor, nurse or pharmacist for assistance.

- Check the expiry date on the RebiDose label or on the outer box (as indicated as “EXP”). Do not use RebiDose if the expiry date has passed.

Where to inject with RebiDose



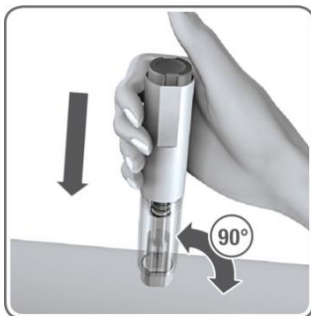
- Choose an injection site. Your doctor will advise you on the possible injection sites (good sites include the upper thighs and the lower abdomen.)
- Keep track of and rotate your injection sites, so that one area is not injected too often. This is to minimise the risk of skin damage (necrosis).
- NOTE: do not use any areas in which you feel lumps, firm knots, or pain; talk to your doctor or healthcare professional about anything you find.

How to inject with RebiDose

- **Do not** remove the cap until you are ready to administer the injection.
- Before the injection, use an alcohol wipe to clean the skin at the injection site. Let the skin dry. If a bit of alcohol is left on the skin, you may get a stinging sensation.



- Hold RebiDose by the main body and use your other hand to remove the cap.



- Hold RebiDose at a right angle (90 degrees) to the injection site. Push the pen against your skin until you feel resistance. This action unlocks the button.



- Keep enough pressure on the skin and press the button with your thumb. You will hear a click which indicates the start of the injection and the plunger will start moving. Keep RebiDose pressed against the skin for at least 10 seconds in order to inject all of the medicine. It is not necessary to keep the button pressed down with your thumb after the injection has begun.



- Remove RebiDose from the injection site. The safety guard automatically surrounds the needle and locks into place to protect you from the needle.

After the injection



- Look through the transparent window to make sure that the plunger has moved to the bottom as indicated in the figure.
- Visually check that there is no liquid left. If there is liquid left, not all of the medicine has been injected and you should consult your doctor or nurse for assistance.

- Gently massage the injection site with a dry cotton ball or gauze.
- **Do not** put the needle cap back on the used RebiDose. This is because the needle is now covered by the safety guard. **Do not put your fingers in the safety guard.**
- RebiDose is for single use only and should **never** be reused.
- Once you have finished your injection, immediately discard RebiDose. Ask your pharmacist how to safely dispose of RebiDose.

If you have any further questions, please ask your doctor, nurse or pharmacist.

This “Instructions for use” was last revised in

Package leaflet: Information for the user

Rebif 44 micrograms solution for injection in pre-filled pen interferon beta-1a

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Rebif is and what it is used for
2. What you need to know before you use Rebif
3. How to use Rebif
4. Possible side effects
5. How to store Rebif
6. Contents of the pack and other information

1. What Rebif is and what it is used for

Rebif belongs to a class of medicines known as interferons. These are natural substances that transmit messages between cells. Interferons are produced by the body and play an essential role in the immune system. Through mechanisms that are not totally understood, interferons help to limit the damage of the central nervous system associated with multiple sclerosis.

Rebif is a highly purified soluble protein that is similar to the natural interferon beta that is produced in the human body.

Rebif is used for the treatment of multiple sclerosis. It has been shown to reduce the number and the severity of relapses and to slow the progression of disability. It is also approved for use in patients who have experienced a single clinical event likely to be a first sign of multiple sclerosis.

2. What you need to know before you use Rebif

Do not use Rebif

- if you are allergic to natural or recombinant interferon beta or any of the other ingredients of this medicine (listed in section 6).
- if you are severely depressed at present.

Warnings and precautions

Talk to your doctor, pharmacist or nurse before using Rebif.

- Rebif should only be used under the supervision of your doctor.
- Before treatment with Rebif, read carefully and follow the “RebiDose Instructions for Use” provided in a separate booklet, in order to minimise the risk of injection site necrosis (skin breakdown and tissue destruction) that has been reported in patients treated with Rebif. If you experience troubling local reactions, contact your doctor.
- Talk to your doctor or pharmacist before taking Rebif if you have an allergy (hypersensitivity) to any other medicines.

- Blood clots in the small blood vessels may occur during your treatment. These blood clots could affect your kidneys. This might happen several weeks to several years after starting Rebif. Your doctor may want to check your blood pressure, blood (platelet count) and the function of your kidney.

Inform your doctor if you have a disease of

- the bone marrow,
- kidney,
- liver,
- heart,
- thyroid,
- or if you have experienced depression,
- or if you have any history of epileptic seizures,

so that he/she can closely monitor your treatment and any worsening of these conditions.

Other medicines and Rebif

Tell your doctor or pharmacist if you are using, have recently used or might use any other medicines. In particular you should tell your doctor if you are using antiepileptics or antidepressants.

Pregnancy and breast-feeding

If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

No harmful effects on the breastfed newborn/infant are anticipated. Rebif can be used during breast-feeding.

Driving and using machines

Effects of the disease itself or of its treatment might influence your ability to drive or to use machines. You should discuss this with your doctor if you are concerned.

Rebif contains sodium and benzyl alcohol

This medicine contains less than 1 mmol sodium (23 mg) per dose, that is to say it is essentially 'sodium-free'.

This medicine contains 2.5 mg benzyl alcohol per dose. Benzyl alcohol may cause allergic reactions.

Benzyl alcohol has been linked with the risk of severe side effects including breathing problems (called "gaspings syndrome") in young children.

Do not use for more than a week in young children (less than 3 years old), unless advised by your doctor or pharmacist.

Ask your doctor or pharmacist for advice if you are pregnant or breast-feeding, or if you have a liver or kidney disease. This is because large amounts of benzyl alcohol can build-up in your body and may cause side effects (called "metabolic acidosis").

3. How to use Rebif

Always use this medicine exactly as your doctor has told you. Check with your doctor if you are not sure.

Dose

Patients who have experienced a single clinical event

The usual dose is 44 micrograms (12 million IU) given three times per week.

Patients with multiple sclerosis

The usual dose is 44 micrograms (12 million IU) given three times per week.

A lower dose of 22 micrograms (6 million IU) given three times per week is recommended for patients who cannot tolerate the higher dose

Rebif should be administered three times per week, and if possible:

- on the same three days every week (at least 48 hours apart, e.g., Monday, Wednesday, Friday)
- at the same time of day (preferably in the evening).

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.

Method of administration

- Rebif is given by injection under the skin (subcutaneously) using a pre-filled pen called “RebiDose”.
- Use each RebiDose only once.
- The first injection(s) must be performed under the supervision of an appropriately qualified healthcare professional. After receiving adequate training, you, a family member, friend or carer can use Rebif pre-filled pen to administer the medicine at home.
- When you do this please read carefully and follow the “*RebiDose Instructions for Use*” provided separately in the booklet.

Only clear to opalescent solution without particles and without visible signs of deterioration should be used.

If you use more Rebif than you should

In case of overdose, contact your doctor immediately.

If you forget to use Rebif

If you miss a dose, continue to inject from the day of the next scheduled dose. Do not use a double dose to make up for a forgotten dose.

If you stop using Rebif

The effects of Rebif may not be noticed immediately. Therefore, you should not stop using Rebif but continue to use it regularly to achieve the desired result. If you are uncertain about the benefits, please consult your doctor.

You should not discontinue the treatment without first contacting your doctor.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Tell your doctor immediately and stop using Rebif if you experience any of the following serious side effects:

- **Serious allergic (hypersensitivity) reactions.** If, immediately following Rebif administration you experience a sudden difficulty breathing, which may appear in association with swelling of face, lips, tongue or throat, nettle rash, itching all over the body, and a feeling of weakness or

faintness, contact your doctor immediately or seek urgent medical attention. These reactions are *rare* (may affect up to 1 in 1,000 people).

- Inform your doctor immediately if you experience any of the following possible symptoms of a **liver problem**: jaundice (yellowing of the skin or of the whites of the eyes), widespread itching, loss of appetite accompanied by nausea and vomiting and easy bruising of the skin. Severe liver problems can be associated with additional signs, e.g. difficulty concentrating, sleepiness and confusion.
- **Depression** is *common* (may affect up to 1 in 10 people) in treated patients with multiple sclerosis. If you feel **depressed or develop thoughts of suicide**, report it immediately to your doctor.

Talk to your doctor if you experience any of the following side effects:

- **Flu-like symptoms**, such as headache, fever, chills, muscle and joint pains, fatigue and nausea are very common (may affect more than 1 in 10 people).
These symptoms are usually mild, are more common at the start of the treatment and decrease with continued use.
To help reduce these symptoms your doctor may advise you to take a fever reducing painkiller before a dose of Rebif and then for 24 hours after each injection.
- **Injection site reactions** including redness, swelling, discoloration, inflammation, pain and skin breakdown are *very common*.
The occurrence of injection site reactions usually decreases over time.
Tissue destruction (necrosis), abscess and mass at injection site are *uncommon* (may affect up to 1 in 100 people).
See recommendations in section “Warnings and precautions” to minimise the risk of injection site reactions.
The injection site can become infected (*uncommon*); the skin may become swollen tender and hard and the whole area could be very painful. If you experience any of these symptoms, contact your doctor for advice.
- Certain **laboratory tests** may change. These changes are generally not noticed by the patient (no symptoms), are usually reversible and mild, and most often do not require particular treatment.
The number of red blood cells, white blood cells or platelets may decrease either individually (*very common*) or all at one time (*rare*). Possible symptoms resulting from these changes could include tiredness, reduced ability to fight infection, bruising or unexplained bleeding.
Liver function tests may be disturbed (*very common*). Inflammation of the liver has also been reported (*uncommon*). If you experience symptoms suggesting a liver disorder, such as loss of appetite accompanied by other symptoms such as nausea, vomiting, jaundice, please contact your doctor immediately (see above “Tell your doctor immediately...”).
- **Thyroid dysfunction** is *uncommon*. The thyroid gland may function either excessively, or insufficiently. These changes in the thyroid activity are almost always not felt by the patient as symptoms; however your doctor may recommend testing as appropriate.
- **MS pseudo-relapse** (*frequency not known*): There is a possibility that at the beginning of your treatment with Rebif you may experience symptoms that resemble those of a multiple sclerosis relapse. For example, your muscles may feel very tense or very weak, preventing you from moving as you want. In some cases such symptoms are associated with fever or flu-like symptoms described above. If you notice any of these side effects talk to your doctor.

Other possible side effects include:

Very common (may affect more than 1 in 10 people):

- Headache

Common (may affect up to 1 in 10 people):

- Insomnia (sleeping difficulty)
- Diarrhoea, nausea, vomiting
- Itching, rash (skin eruptions)
- Muscle and joints pain
- Fatigue, fever, chills
- Hair loss

Uncommon (may affect up to 1 in 100 people):

- Hives
- Epileptic seizures
- Liver inflammation (hepatitis)
- Breathing difficulties
- Blood clots such as deep venous thrombosis
- Disorders of the retina (back of the eye) such as inflammation or blood clots with consequent vision disorders (vision disturbances, loss of vision)
- Increased sweating

Rare (may affect up to 1 in 1,000 people):

- Suicide attempt
- Serious skin reactions - some with mucosal lesions
- Blood clots in the small blood vessels that can affect your kidneys (thrombotic thrombocytopenic purpura or haemolytic uremic syndrome). Symptoms may include increased bruising, bleeding, fever, extreme weakness, headache, dizziness or light-headedness. Your doctor may find changes in your blood and the function of your kidneys.
- Drug-induced lupus erythematosus: a side-effect of long-term use of Rebif. Symptoms may include muscle pain, joint pain and swelling, and rash. You may also experience other signs such as fever, weight loss, and fatigue. Usually symptoms disappear within one or two weeks after treatment is stopped.
- Kidney problems including scarring that may reduce your kidney function.
If you get some or all of these symptoms:
 - foamy urine
 - fatigue
 - swelling, particularly in the ankles and eyelids, and weight gain.Tell your doctor as they may be signs of a possible kidney problem.

The following side effects were reported for interferon beta (frequency not known)

- Dizziness
- Nervousness
- Loss of appetite
- Dilatation of the blood vessels and palpitation
- Irregularities and/or changes in menstrual flow.
- Pulmonary arterial hypertension - a disease of severe narrowing of the blood vessels in the lungs resulting in high blood pressure in the blood vessels that carry blood from the heart to the lungs. Pulmonary arterial hypertension has been seen at various time points during treatment, including several years after starting treatment with Rebif.
- Inflammation of the fatty tissue under the skin (panniculitis), which can make the skin feel hard and possibly develop painful red lumps or patches.

You should not stop or alter the medication without your doctor's advice.

Children and teenagers

Side effects in children and teenagers are similar to those observed in adults.

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in [Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Rebif

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the label after EXP.

Store in a refrigerator (2°C – 8°C).

Do not freeze. (To prevent accidental freezing, avoid placing near the freezer compartment).

For the purpose of ambulatory use, you may remove Rebif from the refrigerator and store it not above 25°C for one single period of up to 14 days. Rebif must then be returned to the refrigerator and used before the expiry date.

Store in the original package in order to protect from light.

Do not use this medicine if you notice any visible signs of deterioration such as if the solution is no longer clear or if it contains particles.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away of medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Rebif contains

- The active substance is interferon beta-1a. Each pre-filled pen contains 44 micrograms, corresponding to 12 million International Units (IU) of interferon beta-1a.
- The other ingredients are mannitol, poloxamer 188, L-methionine, benzyl alcohol, sodium acetate, acetic acid, sodium hydroxide and water for injections.

What Rebif looks like and contents of the pack

Rebif is available as a solution for injection in a pre-filled pen for self-administration. Rebif solution is clear to opalescent. The pre-filled pen is ready for use and contains 0.5 mL of solution. Rebif is available in packs of 1, 3 and 12 pre-filled pens (RebiDose). Not all pack sizes may be marketed.

Marketing Authorisation Holder

Merck Europe B.V.
Gustav Mahlerplein 102
1082 MA Amsterdam
The Netherlands

Manufacturer

Merck Serono S.p.A.
Via delle Magnolie 15
I-70026 Modugno (Bari)
Italy

This leaflet was last revised in

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency website:
<http://www.ema.europa.eu>.

RebiDose Instructions for use

HOW TO USE REBIF PRE-FILLED PEN (RebiDose)

- This section tells you how to use RebiDose.
- Rebif is given by injection under the skin (subcutaneously).
- Use each RebiDose only once.
- The first injection(s) must be performed under the supervision of an appropriately qualified healthcare professional. After receiving adequate training, you, a family member, friend or carer can use RebiDose to administer the medicine at home. If you have questions about how to inject, please ask your doctor, nurse or pharmacist for assistance.
- **Read all the following instructions carefully before using RebiDose.**

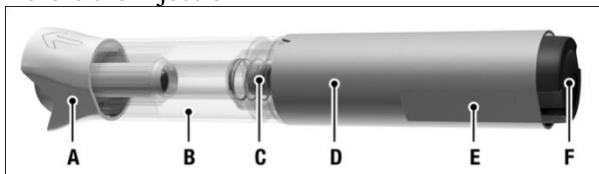
Equipment

To give yourself an injection you will need:

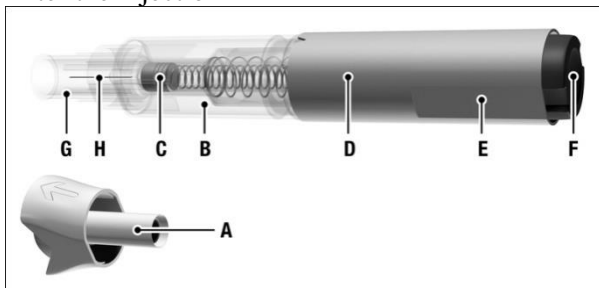
- A new RebiDose and
- Alcohol wipes or similar.
- a dry cotton ball or gauze

Below is a picture showing what RebiDose looks like.

Before the injection



After the injection



- A. Cap
- B. Transparent window
- C. Plunger
- D. Label
- E. Main body
- F. Button
- G. Safety guard
- H. Needle

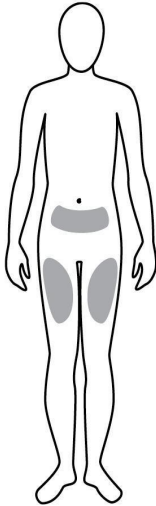
Before you start

- Wash your hands thoroughly with soap and water.
- Remove RebiDose from the blister pack by peeling back the plastic covering.
- Check the appearance of Rebif through the transparent window. It must be clear to opalescent, without particles and without any visible signs of deterioration. If there are particles or other

visible signs of deteriorations, do not use it and contact your doctor, nurse or pharmacist for assistance.

- Check the expiry date on the RebiDose label or on the outer box (as indicated as “EXP”). Do not use RebiDose if the expiry date has passed.

Where to inject with RebiDose



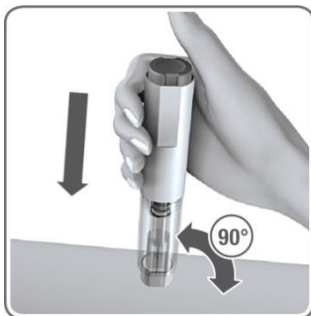
- Choose an injection site. Your doctor will advise you on the possible injection sites (good sites include the upper thighs and the lower abdomen.)
- Keep track of and rotate your injection sites, so that one area is not injected too often. This is to minimise the risk of skin damage (necrosis).
- NOTE: do not use any areas in which you feel lumps, firm knots, or pain; talk to your doctor or healthcare professional about anything you find.

How to inject with RebiDose

- **Do not** remove the cap until you are ready to administer the injection.
- Before the injection, use an alcohol wipe to clean the skin at the injection site. Let the skin dry. If a bit of alcohol is left on the skin, you may get a stinging sensation.



- Hold RebiDose by the main body and use your other hand to remove the cap.



- Hold RebiDose at a right angle (90 degrees) to the injection site. Push the pen against your skin until you feel resistance. This action unlocks the button.



- Keep enough pressure on the skin and press the button with your thumb. You will hear a click which indicates the start of the injection and the plunger will start moving. Keep RebiDose pressed against the skin for at least 10 seconds in order to inject all of the medicine. It is not necessary to keep the button pressed down with your thumb after the injection has begun.



- Remove RebiDose from the injection site. The safety guard automatically surrounds the needle and locks into place to protect you from the needle.

After the injection



- Look through the transparent window to make sure that the plunger has moved to the bottom as indicated in the figure.
- Visually check that there is no liquid left. If there is liquid left, not all of the medicine has been injected and you should consult your doctor or nurse for assistance.

- Gently massage the injection site with a dry cotton ball or gauze.
- **Do not** put the needle cap back on the used RebiDose. This is because the needle is now covered by the safety guard. **Do not put your fingers in the safety guard.**
- RebiDose is for single use only and should **never** be reused.
- Once you have finished your injection, immediately discard RebiDose. Ask your pharmacist how to safely dispose of RebiDose.

If you have any further questions, please ask your doctor, nurse or pharmacist.

This “Instructions for use” was last revised in

Package leaflet: Information for the user

Rebif 8.8 micrograms solution for injection in pre-filled pen **Rebif 22 micrograms solution for injection in pre-filled pen** interferon beta-1a Initiation pack

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Rebif is and what it is used for
2. What you need to know before you use Rebif
3. How to use Rebif
4. Possible side effects
5. How to store Rebif
6. Contents of the pack and other information

1. What Rebif is and what it is used for

Rebif belongs to a class of medicines known as interferons. These are natural substances that transmit messages between cells. Interferons are produced by the body and play an essential role in the immune system. Through mechanisms that are not totally understood, interferons help to limit the damage of the central nervous system associated with multiple sclerosis.

Rebif is a highly purified soluble protein that is similar to the natural interferon beta that is produced in the human body.

Rebif is used for the treatment of multiple sclerosis. It has been shown to reduce the number and the severity of relapses and to slow the progression of disability. It is also approved for use in patients who have experienced a single clinical event likely to be a first sign of multiple sclerosis.

2. What you need to know before you use Rebif

Do not use Rebif

- if you are allergic to natural or recombinant interferon beta or any of the other ingredients of this medicine (listed in section 6).
- if you are severely depressed at present.

Warnings and precautions

Talk to your doctor, pharmacist or nurse before using Rebif.

- Rebif should only be used under the supervision of your doctor.
- Before treatment with Rebif, read carefully and follow the “RebiDose Instructions for Use” provided in a separate booklet, in order to minimise the risk of injection site necrosis (skin breakdown and tissue destruction) that has been reported in patients treated with Rebif. If you experience troubling local reactions, contact your doctor.

- Talk to your doctor or pharmacist before taking Rebif if you have an allergy (hypersensitivity) to any other medicines.
- Blood clots in the small blood vessels may occur during your treatment. These blood clots could affect your kidneys. This might happen several weeks to several years after starting Rebif. Your doctor may want to check your blood pressure, blood (platelet count) and the function of your kidney.

Inform your doctor if you have a disease of

- the bone marrow,
- kidney,
- liver,
- heart,
- thyroid,
- or if you have experienced depression,
- or if you have any history of epileptic seizures,

so that he/she can closely monitor your treatment and any worsening of these conditions.

Other medicines and Rebif

Tell your doctor or pharmacist if you are using, have recently used or might use any other medicines. In particular you should tell your doctor if you are using antiepileptics or antidepressants.

Pregnancy and breast-feeding

If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

No harmful effects on the breastfed newborn/infant are anticipated. Rebif can be used during breast-feeding.

Driving and using machines

Effects of the disease itself or of its treatment might influence your ability to drive or to use machines. You should discuss this with your doctor if you are concerned.

Rebif contains sodium and benzyl alcohol

This medicine contains less than 1 mmol sodium (23 mg) per dose, that is to say it is essentially 'sodium-free'.

This medicine contains 1.0 mg benzyl alcohol per dose of 0.2 mL and 2.5 mg benzyl alcohol per dose of 0.5 mL. Benzyl alcohol may cause allergic reactions.

Benzyl alcohol has been linked with the risk of severe side effects including breathing problems (called "gasping syndrome") in young children.

Do not use for more than a week in young children (less than 3 years old), unless advised by your doctor or pharmacist.

Ask your doctor or pharmacist for advice if you are pregnant or breast-feeding, or if you have a liver or kidney disease. This is because large amounts of benzyl alcohol can build-up in your body and may cause side effects (called "metabolic acidosis").

3. How to use Rebif

Always use this medicine exactly as your doctor has told you. Check with your doctor if you are not sure.

Initiating treatment

Treatment is initiated by a gradual increase of the dose (a so-called “dose titration”) over a period of 4 weeks, in order to reduce some of the side effects, it is recommended that:

- During weeks one and two, Rebif 8.8 micrograms should be injected three times per week.
- During weeks three and four, Rebif 22 micrograms should be injected three times per week.

From the fifth week onwards, after you have completed your initiation period, you will follow the usual dose regimen.

Dose

The usual dose is 44 micrograms (12 million IU) given three times per week.

A lower dose of 22 micrograms (6 million IU) given three times per week is recommended for patients with multiple sclerosis who cannot tolerate the higher dose.

Rebif should be administered three times per week, and if possible:

- on the same three days every week (at least 48 hours apart, e.g., Monday, Wednesday, Friday)
- at the same time of day (preferably in the evening).

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.

Method of administration

- Rebif is given by injection under the skin (subcutaneously) using a pre-filled pen called “RebiDose”.
- Use each RebiDose only once.
- The first injection(s) must be performed under the supervision of an appropriately qualified healthcare professional. After receiving adequate training, you, a family member, friend or carer can use Rebif pre-filled pen to administer the medicine at home.
- When you do this please read carefully and follow the “*RebiDose Instructions for Use*” provided separately in the booklet.

Only clear to opalescent solution without particles and without visible signs of deterioration should be used.

If you use more Rebif than you should

In case of overdose, contact your doctor immediately.

If you forget to use Rebif

If you miss a dose, continue to inject from the day of the next scheduled dose. Do not use a double dose to make up for a forgotten dose.

If you stop using Rebif

The effects of Rebif may not be noticed immediately. Therefore, you should not stop using Rebif but continue to use it regularly to achieve the desired result. If you are uncertain about the benefits, please consult your doctor.

You should not discontinue the treatment without first contacting your doctor.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Tell your doctor immediately and stop using Rebif if you experience any of the following serious side effects:

- **Serious allergic (hypersensitivity) reactions.** If, immediately following Rebif administration you experience a sudden difficulty breathing, which may appear in association with swelling of face, lips, tongue or throat, nettle rash, itching all over the body, and a feeling of weakness or faintness, contact your doctor immediately or seek urgent medical attention. These reactions are *rare* (may affect up to 1 in 1,000 people).
- Inform your doctor immediately if you experience any of the following possible symptoms of a **liver problem**: jaundice (yellowing of the skin or of the whites of the eyes), widespread itching, loss of appetite accompanied by nausea and vomiting and easy bruising of the skin. Severe liver problems can be associated with additional signs, e.g. difficulty concentrating, sleepiness and confusion.
- **Depression** is *common* (may affect up to 1 in 10 people) in treated patients with multiple sclerosis. If you feel **depressed or develop thoughts of suicide**, report it immediately to your doctor.

Talk to your doctor if you experience any of the following side effects:

- **Flu-like symptoms**, such as headache, fever, chills, muscle and joint pains, fatigue and nausea are very common (may affect more than 1 in 10 people).
These symptoms are usually mild, are more common at the start of the treatment and decrease with continued use.
To help reduce these symptoms your doctor may advise you to take a fever reducing painkiller before a dose of Rebif and then for 24 hours after each injection.
- **Injection site reactions** including redness, swelling, discoloration, inflammation, pain and skin breakdown are *very common*.
The occurrence of injection site reactions usually decreases over time.
Tissue destruction (necrosis), abscess and mass at injection site are *uncommon* (may affect up to 1 in 100 people).
See recommendations in section “Warnings and precautions” to minimise the risk of injection site reactions.
The injection site can become infected (*uncommon*); the skin may become swollen tender and hard and the whole area could be very painful. If you experience any of these symptoms, contact your doctor for advice.
- Certain **laboratory tests** may change. These changes are generally not noticed by the patient (no symptoms), are usually reversible and mild, and most often do not require particular treatment.
The number of red blood cells, white blood cells or platelets may decrease either individually (*very common*) or all at one time (*rare*). Possible symptoms resulting from these changes could include tiredness, reduced ability to fight infection, bruising or unexplained bleeding.
Liver function tests may be disturbed (*very common*). Inflammation of the liver has also been reported (*uncommon*). If you experience symptoms suggesting a liver disorder, such as loss of appetite accompanied by other symptoms such as nausea, vomiting, jaundice, please contact your doctor immediately (see above “Tell your doctor immediately...”).
- **Thyroid dysfunction** is *uncommon*. The thyroid gland may function either excessively, or insufficiently. These changes in the thyroid activity are almost always not felt by the patient as symptoms; however your doctor may recommend testing as appropriate.

- **MS pseudo-relapse** (*frequency not known*): There is a possibility that at the beginning of your treatment with Rebif you may experience symptoms that resemble those of a multiple sclerosis relapse. For example, your muscles may feel very tense or very weak, preventing you from moving as you want. In some cases such symptoms are associated with fever or flu-like symptoms described above. If you notice any of these side effects talk to your doctor.

Other possible side effects include:

Very common (may affect more than 1 in 10 people):

- Headache

Common (may affect up to 1 in 10 people):

- Insomnia (sleeping difficulty)
- Diarrhoea, nausea, vomiting
- Itching, rash (skin eruptions)
- Muscle and joints pain
- Fatigue, fever, chills
- Hair loss

Uncommon (may affect up to 1 in 100 people):

- Hives
- Epileptic seizures
- Liver inflammation (hepatitis)
- Breathing difficulties
- Blood clots such as deep venous thrombosis
- Disorders of the retina (back of the eye) such as inflammation or blood clots with consequent vision disorders (vision disturbances, loss of vision)
- Increased sweating

Rare (may affect up to 1 in 1,000 people):

- Suicide attempt
- Serious skin reactions - some with mucosal lesions
- Blood clots in the small blood vessels that can affect your kidneys (thrombotic thrombocytopenic purpura or haemolytic uremic syndrome). Symptoms may include increased bruising, bleeding, fever, extreme weakness, headache, dizziness or light-headedness. Your doctor may find changes in your blood and the function of your kidneys.
- Drug-induced lupus erythematosus: a side-effect of long-term use of Rebif. Symptoms may include muscle pain, joint pain and swelling, and rash. You may also experience other signs such as fever, weight loss, and fatigue. Usually symptoms disappear within one or two weeks after treatment is stopped.
- Kidney problems including scarring that may reduce your kidney function.
If you get some or all of these symptoms:
 - foamy urine
 - fatigue
 - swelling, particularly in the ankles and eyelids, and weight gain.
 Tell your doctor as they may be signs of a possible kidney problem.

The following side effects were reported for interferon beta (frequency not known)

- Dizziness
- Nervousness
- Loss of appetite
- Dilatation of the blood vessels and palpitation
- Irregularities and/or changes in menstrual flow.

- Pulmonary arterial hypertension - a disease of severe narrowing of the blood vessels in the lungs resulting in high blood pressure in the blood vessels that carry blood from the heart to the lungs. Pulmonary arterial hypertension has been seen at various time points during treatment, including several years after starting treatment with Rebif.
- Inflammation of the fatty tissue under the skin (panniculitis), which can make the skin feel hard and possibly develop painful red lumps or patches.

You should not stop or alter the medication without your doctor's advice.

Children and teenagers

Side effects in children and teenagers are similar to those observed in adults.

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in [Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Rebif

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the label after EXP.

Store in a refrigerator (2°C – 8°C).

Do not freeze. (To prevent accidental freezing, avoid placing near the freezer compartment).

For the purpose of ambulatory use, you may remove Rebif from the refrigerator and store it not above 25°C for one single period of up to 14 days. Rebif must then be returned to the refrigerator and used before the expiry date.

Store in the original package in order to protect from light.

Do not use this medicine if you notice any visible signs of deterioration such as if the solution is no longer clear or if it contains particles.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away of medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Rebif contains

- The active substance is interferon beta-1a.
 - Each 8.8 micrograms pre-filled pen contains 8.8 micrograms of interferon beta-1a (2.4 million IU).
 - Each 22 micrograms pre-filled pen contains 22 micrograms of interferon beta-1a (6 million IU).
- The other ingredients are mannitol, poloxamer 188, L-methionine, benzyl alcohol, sodium acetate, acetic acid, sodium hydroxide and water for injections.

What Rebif looks like and contents of the pack

Rebif 8.8 micrograms is a solution for injection in a pre-filled pen for self-administration. The pre-filled pen is ready for use and contains 0.2 mL of solution.

Rebif 22 micrograms is a solution for injection in a pre-filled pen for self-administration. The pre-filled pen is ready for use and contains 0.5 mL of solution.

Rebif solution is clear to opalescent.

Rebif 8.8 micrograms and Rebif 22 micrograms are supplied in an initiation pack that is intended for use during the initial 4 weeks of treatment, during which a gradual increase in Rebif dose is recommended.

One-month initiation pack contains six Rebif 8.8 micrograms pre-filled pens and six Rebif 22 micrograms pre-filled pens.

Marketing Authorisation Holder

Merck Europe B.V.
Gustav Mahlerplein 102
1082 MA Amsterdam
The Netherlands

Manufacturer

Merck Serono S.p.A.
Via delle Magnolie 15
I-70026 Modugno (Bari)
Italy

This leaflet was last revised in

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency website:
<http://www.ema.europa.eu>.

RebiDose Instructions for use

HOW TO USE REBIF PRE-FILLED PEN (RebiDose)

- This section tells you how to use RebiDose.
- Rebif is given by injection under the skin (subcutaneously).
- Use each RebiDose only once.
- The first injection(s) must be performed under the supervision of an appropriately qualified healthcare professional. After receiving adequate training, you, a family member, friend or carer can use RebiDose to administer the medicine at home. If you have questions about how to inject, please ask your doctor, nurse or pharmacist for assistance.
- **Read all the following instructions carefully before using RebiDose.**

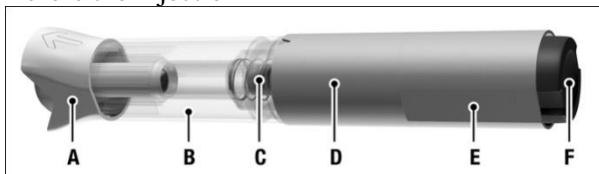
Equipment

To give yourself an injection you will need:

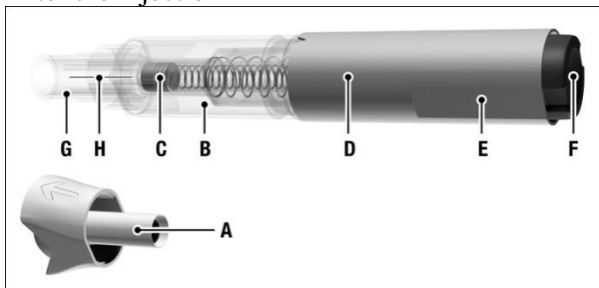
- A new RebiDose and
- Alcohol wipes or similar.
- a dry cotton ball or gauze

Below is a picture showing what RebiDose looks like.

Before the injection



After the injection



- A. Cap
- B. Transparent window
- C. Plunger
- D. Label
- E. Main body
- F. Button
- G. Safety guard
- H. Needle

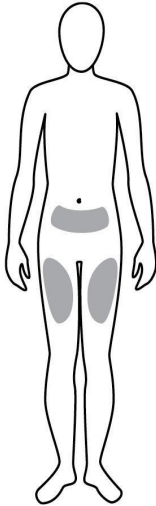
Before you start

- Wash your hands thoroughly with soap and water.
- Remove RebiDose from the blister pack by peeling back the plastic covering.
- Check the appearance of Rebif through the transparent window. It must be clear to opalescent, without particles and without any visible signs of deterioration. If there are particles or other

visible signs of deteriorations, do not use it and contact your doctor, nurse or pharmacist for assistance.

- Check the expiry date on the RebiDose label or on the outer box (as indicated as “EXP”). Do not use RebiDose if the expiry date has passed.

Where to inject with RebiDose



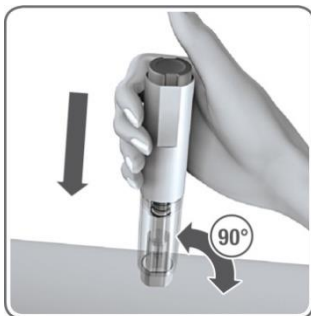
- Choose an injection site. Your doctor will advise you on the possible injection sites (good sites include the upper thighs and the lower abdomen.)
- Keep track of and rotate your injection sites, so that one area is not injected too often. This is to minimise the risk of skin damage (necrosis).
- NOTE: do not use any areas in which you feel lumps, firm knots, or pain; talk to your doctor or healthcare professional about anything you find.

How to inject with RebiDose

- **Do not** remove the cap until you are ready to administer the injection.
- Before the injection, use an alcohol wipe to clean the skin at the injection site. Let the skin dry. If a bit of alcohol is left on the skin, you may get a stinging sensation.



- Hold RebiDose by the main body and use your other hand to remove the cap.



- Hold RebiDose at a right angle (90 degrees) to the injection site. Push the pen against your skin until you feel resistance. This action unlocks the button.



- Keep enough pressure on the skin and press the button with your thumb. You will hear a click which indicates the start of the injection and the plunger will start moving. Keep RebiDose pressed against the skin for at least 10 seconds in order to inject all of the medicine. It is not necessary to keep the button pressed down with your thumb after the injection has begun.



- Remove RebiDose from the injection site. The safety guard automatically surrounds the needle and locks into place to protect you from the needle.

After the injection



- Look through the transparent window to make sure that the plunger has moved to the bottom as indicated in the figure.
- Visually check that there is no liquid left. If there is liquid left, not all of the medicine has been injected and you should consult your doctor or nurse for assistance.

- Gently massage the injection site with a dry cotton ball or gauze.
- **Do not** put the needle cap back on the used RebiDose. This is because the needle is now covered by the safety guard. **Do not put your fingers in the safety guard.**
- RebiDose is for single use only and should **never** be reused.
- Once you have finished your injection, immediately discard RebiDose. Ask your pharmacist how to safely dispose of RebiDose.

If you have any further questions, please ask your doctor, nurse or pharmacist.

This “Instructions for use” was last revised in