SUMMARY OF PRODUCT CHARACTERISTICS

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

4.6 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

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 (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), frequency not known (cannot be estimated from the available data).

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

Yellow Card Scheme
Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

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			
KM Estimate	85.8%	62.5%	51%	0.49 [0.38;0.64]	<0.001
CDMS Conversion					
Number of events	60	33			
KM Estimate	37.5%	20.6%	52%	0.48 [0.31;0.73]	<0.001
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

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 Serono Limited

5 New Square

Bedfont Lakes Business Park

Feltham

Middlesex

TW14 8HA

UK

8 MARKETING AUTHORISATION NUMBER(S)

PLGB 11648/0283

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

01/01/2021

10 DATE OF REVISION OF THE TEXT

01/01/2021