PRODUCT MONOGRAPH

PrREBIF®

(Interferon beta-1a)

8.8 µg/0.2 mL, 22 µg/0.5 mL and 44 µg/0.5 mL
Solution for Injection in Pre-filled Syringes

Multidose 22 µg × 3 (66 µg/1.5 mL)
Multidose 44 µg × 3 (132 µg/1.5 mL)
Solution for Injection in Pre-filled Cartridges

PrREBIF® RebiDose™
8.8 µg/0.2 mL, 22 µg/0.5 mL and 44 µg/0.5 mL
Solution for Injection in Pre-filled Pens

Immunomodulator

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REBIF®

(Interferon beta-1a)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Subcutaneous	Interferon beta-1a Solution for Injection in Pre-filled Syringe/ 8.8 µg/0.2 mL 22 µg/0.5 mL 44 µg/0.5 mL	Mannitol, benzyl alcohol, poloxamer-188, methionine, 0.01 M sodium acetate pH 4.2 buffer *For a complete listing see DOSAGE FORMS, COMPOSITION and PACKAGING section.*
	Interferon beta-1a Solution for Injection in a Pre-filled Cartridge/ 22 µg × 3 (66 µg/1.5 mL) 44 µg × 3 (132 µg/1.5 mL)	Mannitol, benzyl alcohol, poloxamer-188, methionine, 0.01 M sodium acetate pH 3.9 buffer *For a complete listing see DOSAGE FORMS, COMPOSITION and PACKAGING section.*
	Interferon beta-1a Solution for Injection in Pre-filled Pens/ 8.8 µg/0.2 mL, 22 µg/0.5 mL and 44 µg/0.5 mL	Mannitol, benzyl alcohol, poloxamer-188, methionine, 0.01 M sodium acetate pH 4.2 buffer *For a complete listing see DOSAGE FORMS, COMPOSITION and PACKAGING section.*

DESCRIPTION

REBIF (Interferon beta-1a) is a purified, sterile glycoprotein product produced by recombinant DNA techniques and formulated for use by injection. The active ingredient of REBIF is produced by genetically engineered Chinese Hamster Ovary (CHO) cells. Interferon beta-1a is a highly purified glycoprotein that has 166 amino acids and an approximate molecular weight of 22,500 daltons. It contains a single N-linked carbohydrate moiety attached to Asn-80 similar to that of natural human Interferon beta.

INDICATIONS AND CLINICAL USE

REBIF is indicated for the treatment of relapsing forms of multiple sclerosis (MS), to

- reduce the number and severity of clinical exacerbations,
- slow the progression of physical disability,

- reduce the requirement for steroids,
- reduce the number of hospitalizations for treatment of multiple sclerosis, and
- reduce T1-Gd enhanced and T2 (burden of disease) lesions as seen on MRI.

Relapsing forms of multiple sclerosis include the subgroups of MS in which patients still experience recurrent attacks of neurological dysfunction including traditional RRMS but also SPMS patients still experiencing relapses.

Although REBIF did not affect progression of disability in SPMS, the clinical trial has shown that secondary progressive MS patients who still experience relapses, had a statistically significant improvement on relapse rate and on MRI measures of disease activity as compared to patients on placebo.

REBIF has not yet been investigated in patients with primary progressive multiple sclerosis and should not be administered to such patients.

CONTRAINDICATIONS

REBIF (Interferon beta-1a) is contraindicated in patients with a known hypersensitivity to natural or recombinant interferon beta, or any other component of the formulation (see COMPOSITION).

REBIF is contraindicated in pregnant patients (see WARNINGS AND PRECAUTIONS).

WARNINGS AND PRECAUTIONS

REBIF (Interferon beta-1a) should be used under the supervision of a physician. The first injection should be performed under the supervision of an appropriately qualified health care professional.

Fertile women receiving REBIF should be advised to take adequate contraceptive measures. It is not known if interferon alters the efficacy of oral contraceptives. Patients planning for pregnancy and those becoming pregnant should be informed of the potential hazards of interferons to the fetus including an increased risk of early miscarriage. In theses patients discontinuation of therapy should be considered (see CONTRAINDICATIONS and also WARNINGS AND PRECAUTIONS: Information to be provided to the patient).

General Precautions

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

Endocrine and Metabolism

Patients treated with REBIF may develop new or worsening thyroid laboratory abnormalities. Caution should be exercised when administering REBIF to patients with pre-existing thyroid disorders. Patients treated with REBIF should be carefully monitored for evidence of thyroid dysfunction (most often presenting as hypothyroidism or hyperthyroidism), and development of thyroid auto-antibodies. Thyroid testing is recommended at baseline and if abnormal, every 6-12 months following initiation of therapy. If normal, routine testing is not needed but should be performed if clinical findings of thyroid dysfunction appear.

Neurologic (including seizures)

Caution should be exercised when administering REBIF (interferon-beta-1a) to patients with pre-existing seizures disorder. For patients without a pre-existing seizure disorder who develop seizures during therapy, an etiologic basis should be established and appropriate anti-convulsant therapy instituted prior to continuing treatment with REBIF. The effect of REBIF administration on the medical management of patients with seizure disorder is unknown.

Depression

Rebif should be used with caution in patients with depression, a condition that is common in people with multiple sclerosis. Depression, suicidal ideation, and suicide attempts have been reported to occur with increased frequency in patients receiving interferon products, including REBIF. Depressive symptoms associated with interferon beta may often be an atypical syndrome, occurring more frequently early in the course of treatment and not associated with all of the usual clinical symptoms of depression. Patients treated with Rebif should be advised to immediately report any symptoms of depression and/or suicidal ideation to their prescribing physician. Patients developing depression during Rebif therapy should be monitored closely and cessation of therapy should be considered.

Hepatic Injury

Isolated, life-threatening cases of acute hepatic failure have been reported with REBIF therapy. Symptomatic hepatic dysfunction, primarily presenting as jaundice, has been reported as a rare complication of REBIF therapy. Several possible mechanisms may explain the effect of REBIF on the liver (including direct toxicity, indirect toxicity via release of cytokines and/or autoimmunity). Asymptomatic elevations of transaminases (particularly ALT) is common with interferon therapy (see ADVERSE REACTIONS). In clinical trials with REBIF, the majority of these elevations were below 2.5 times the upper limit of normal [ULN] with 1-3% of patients developing elevations above 5 times ULN. In the absence of clinical symptoms, serum ALT levels should be monitored at baseline, every month for the first 6 months and every 6 months thereafter. 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). Dose reduction or discontinuation should be considered if ALT rises 5 times above

the ULN and gradually re-escalated when enzyme levels have normalized. Treatment with REBIF should be stopped if icterus or other clinical symptoms of hepatic dysfunction appear.

Immune (including hypersensitivity, autoimmunity, immunogenicity)

Anaphylaxis has been reported as a rare complication of REBIF use. Other allergic reactions have included skin rash, angioedema, and urticaria, and have ranged from mild to severe without a clear relationship to dose or duration of exposure. Several allergic reactions, some severe, have occurred after prolonged use.

Neutralising antibodies (NAbs) to REBIF may develop during the first 24 months of therapy in a small proportion of patients, the precise incidence of which is uncertain. Neutralising antibodies have been associated with a reduced clinical benefit, as evaluated by MRI parameters and multiple sclerosis relapse rate; however, the clinical significance of NAbs development in individual patients remains uncertain. Treatment decisions should be based on the assessment of clinical efficacy by the clinician in view of available NAbs data. A poor clinical course associated with persistent NAbs should prompt reconsideration of REBIF therapy. Neutralising antibodies to REBIF are cross-reactive to different forms of interferon beta.

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 and continued therapy with REBIF. Symptoms of the flu-like syndrome associated with REBIF may prove stressful to patients with cardiac conditions.

Special Populations

Pregnant Women: REBIF should not be administered in case of pregnancy and lactation. There are no adequate and well-controlled clinical studies of REBIF in pregnant women. In cynomolgous monkeys administered doses approximately 2 times the cumulative weekly human dose (based on either body weight or surface area), REBIF treatment was associated with significant increases in embryolethal or abortifacient effects either during the period of organogenesis (gestation day 21-89) or later in pregnancy. There were no fetal malformations or other evidence of teratogenesis noted in these studies; however, it is not known if teratogenic effects can occur in humans. These effects are consistent with the abortifacient effects of other type I interferons. Patients should be advised about the abortifacient potential of REBIF.

Nursing Women: It is not known whether REBIF is excreted in human milk and is not known if interferon beta-1a can cross the gastrointestinal mucosa. Because of the potential for serious adverse reactions in nursing infants, a decision should be made either to discontinue nursing or to discontinue REBIF therapy.

Pediatrics: There is limited experience with REBIF in children under 18 years of age with MS.

Geriatrics: There is no controlled clinical experience with REBIF in patients with multiple sclerosis over 65 years of age.

Patients with Special Diseases and Conditions: Caution should be exercised and close monitoring conducted when administering REBIF to patients with severe renal failure, or severe myelosuppression, or cardiac disease.

Monitoring and Laboratory Tests

Laboratory abnormalities are associated with the use of interferons. Therefore, in addition to those laboratory tests normally required for monitoring patients with multiple sclerosis, when initiating REBIF therapy, liver enzymes should be monitored at baseline, every month for the first 6 months and every 6 months thereafter (see WARNINGS AND PRECAUTIONS – Hepatic Injury). Complete blood cell counts with white blood cell differential, and platelet counts are also recommended at baseline 1, 3 and 6 months, and every 6 months thereafter in the absence of clinical symptoms. As patients being treated with REBIF may develop new or worsening thyroid abnormalities (see WARNINGS AND PRECAUTIONS – Endocrine and Metabolism), testing of thyroid function should be performed at baseline and every 6 months. In case of abnormal results or in patients with a past history of thyroid dysfunction, any necessary treatment should be administered and more frequent testing should be performed as clinically indicated (see ADVERSE REACTIONS).

Information to be Provided to the Patient

Patients should be advised not to stop or modify their treatment unless instructed by their physician.

Patients should be informed of the potential risk of liver injury during REBIF therapy, and be informed about the signs and symptoms of such injury, such as loss of appetite with malaise, fatigue, nausea, vomiting, abdominal pain, dark urine, jaundice or pruritus, and be informed of the requirement for frequent laboratory testing (see WARNINGS AND PRECAUTIONS – Hepatic Injury). They should be advised to consult their physician immediately if such symptoms arise.

Flu-like symptoms (fever, headache, chills, muscle and joint aches, and fatigue) are the most common adverse reactions following initiation of therapy with REBIF. Acetaminophen or ibuprofen may be used for relief of flu-like symptoms. Patients should contact their physician or pharmacist if they experience any undesirable effects.

Depression may occur in patients with multiple sclerosis and may occur while patients are taking REBIF. Patients receiving REBIF should be instructed to inform their doctor immediately if they have feelings of sadness, unusual tiredness, trouble concentrating, or if they think about committing suicide.

Female patients should be advised about the abortifacient potential of REBIF and instructed to take adequate contraceptive measures (see CONTRAINDICATIONS and see WARNINGS AND PRECAUTIONS).

Injection site reactions are commonly experienced by patients during therapy (see ADVERSE REACTIONS). In general, they do not require discontinuation of therapy, but the nature and severity of all reported reactions should be carefully assessed. Patient understanding and use of aseptic self-injection technique and procedures should be periodically re-evaluated.

Instruction on self-injection technique and procedures: patients should be instructed in the use of aseptic technique when administering REBIF. Appropriate instruction for self-injection should be given including careful review of the REBIF patient leaflet. The first injection should be performed under the supervision of an appropriately qualified health care professional. Patients should be advised of the importance of rotating sites of injection with each dose, to minimize the likelihood of severe injection site reactions or necrosis and not to inject into an area that appears abnormal. Patients should be advised to consult with their physician should they develop multiple lesions and/or experience any break in the skin, which may be associated with swelling or drainage of fluid from the injection site, as a decision may be required to discontinue REBIF until healing has occurred. Patients with single lesions may be advised to continue provided that necrosis is not too extensive. Patients should be cautioned against the re-use of needles or syringes and instructed in safe disposal procedures. A puncture resistant container for disposal of used needles and syringes should be supplied to the patient along with instructions for safe disposal of full containers.

Certain laboratory tests may change. The number of white blood cells or platelets may decrease, but no increased risk of infections or bleeding has been observed.

As REBIF may cause changes in thyroid function, patients should be informed of the symptoms of thyroid dysfunction such as difficulty concentrating, feeling abnormally cold or hot, gaining or losing weight unexpectedly, feeling unusually tired or nervous and unusual very dry skin.

REBIF may cause skin reactions such as rash, hives or urticaria, and itching or pruritus associated with redness, which may be a local allergic reaction. Rarely (in less than 1% of patients) these skin and/or allergic reactions can become generalized and very severe, associated with difficulty breathing, cough, swelling of the mouth or throat, fainting, dizziness, low blood pressure, heart palpitations, hives, itching, abdominal pain, vomiting and diarrhea. Patients should be informed that if this occurs, REBIF should be discontinued and prompt medical care is needed, since severe allergic reactions may be potentially life threatening.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

The most common adverse reactions which can occur during REBIF therapy are mild to moderate flu-like symptoms, injection site reactions, reduction in white blood cell count and

elevation of liver enzymes. Depending on the severity and persistence of the reactions, the dose may be lowered or temporarily interrupted, at the discretion of the physician.

Less common reactions include erythematous skin rash with pruritus, anemia, depression and thyroid dysfunction. Uncommonly, cases of infection and skin ulceration/necrosis at the site of injection have been reported with long term treatment (see WARNINGS AND PRECAUTIONS: Information to be Provided to the Patient).

Serious adverse hepatic reactions such as hepatitis, with or without jaundice, have been rarely (≤1/1,000 to ≥1/10,000) reported and isolated cases of acute hepatic failure have been reported (see WARNINGS AND PRECAUTIONS).

Thyroid dysfunction, may present as hypothyroidism or hyperthyroidism, is generally transient and mild, and may occur during the first year of treatment, particularly in patients with pre-existing thyroiditis (see WARNINGS AND PRECAUTIONS: Monitoring and Laboratory Tests).

Anaphylaxis has very rarely (≤1/10,000) been observed with the use of REBIF (see WARNINGS AND PRECAUTIONS).

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Study 25632 (REBIF New HSA-free Formulation): Adverse Drug Reactions

Study 25632 was performed to assess the immunogenicity and safety of the New FBS-free/HSA-free Formulation of interferon beta-1a (Rebif® New HSA-free Formulation), administered subcutaneously three times per week in accordance with the current product label.

The adverse events experienced during ninety-six weeks of Study 25632 are listed below, by MedDRA (Version 8.0) System Organ Class.

Adverse Events[(a)] Experienced by at least 1% of the Patients Enrolled in Study 25632 for Ninety-six Weeks

System Organ Class	Preferred Term	RNF 44 mcg TIW Subjects (n=260)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	Influenza like illness	176 (67.7)
	Injection site erythema	63 (24.2)
	Injection site haemorrhage	25 (9.6)
	Fatigue	24 (9.2)
	Chills	18 (6.9)
	Pyrexia	18 (6.9)
	Injection site pain	17 (6.5)
	Asthenia	16 (6.2)
	Injection site pruritus	5 (1.9)
	Pain	5 (1.9)

	Hyperthermia	4 (1.5)
	Injection site rash	3 (1.2)
	Injection site swelling	3 (1.2)
NERVOUS SYSTEM DISORDERS	Headache	98 (37.7)
	Dizziness	19 (7.3)
	Hypoaesthesia	8 (3.1)
	Migraine	8 (3.1)
	Burning sensation	4 (1.5)
	Paraesthesia	4 (1.5)
	Hypertonia	3 (1.2)
	Tremor	3 (1.2)
INFECTIONS AND INFESTATIONS	Upper respiratory tract infection	23 (8.8)
	Nasopharyngitis	17 (6.5)
	Viral upper respiratory tract infection	15 (5.8)
	Urinary tract infection	14 (5.4)
	Rhinitis	12 (4.6)
	Influenza	10 (3.8)
	Sinusitis	8 (3.1)
	Tonsillitis	8 (3.1)
	Herpes simplex	6 (2.3)
	Dental caries	4 (1.5)
	Ear infection	4 (1.5)
	Cystitis	3 (1.2)
	Pharyngitis	3 (1.2)
GASTROINTESTINAL DISORDERS	Nausea	26 (10.0)
	Diarrhoea	17 (6.5)
	Vomiting	13 (5.0)
	Dyspepsia	12 (4.6)
	Abdominal pain	10 (3.8)
	Abdominal pain upper	10 (3.8)
	Toothache	7 (2.7)
	Constipation	6 (2.3)
	Flatulence	5 (1.9)
	Gastritis	3 (1.2)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	Back pain	26 (10.0)
	Arthralgia	21 (8.1)
	Pain in extremity	20 (7.7)
	Myalgia	12 (4.6)
	Muscle spasms	9 (3.5)
	Osteochondrosis	4 (1.5)
	Neck pain	3 (1.2)
INVESTIGATIONS	Alanine aminotransferase increased	19 (7.3)
	Aspartate aminotransferase increased	15 (5.8)
	Blood creatine phosphokinase increased	8 (3.1)
	White blood cell count decreased	8 (3.1)
	Hepatic enzyme increased	7 (2.7)
	Body temperature increased	5 (1.9)
	Neutrophil count decreased	5 (1.9)
	Transaminases increased	4 (1.5)
	Weight decreased	4 (1.5)
	Anti-thyroid antibody positive	3 (1.2)
	Blood thyroid stimulating hormone increased	3 (1.2)

PSYCHIATRIC DISORDERS	Insomnia	13 (5.0)
	Anxiety	12 (4.6)
	Depression	9 (3.5)
	Depressed mood	5 (1.9)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	Neutropenia	18 (6.9)
	Lymphopenia	9 (3.5)
	Leukopenia	7 (2.7)
	Anaemia	4 (1.5)
	Iron deficiency anaemia	4 (1.5)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	Urticaria	5 (1.9)
	Dermatitis contact	4 (1.5)
	Erythema	4 (1.5)
	Night sweats	3 (1.2)
	Pruritus	3 (1.2)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	Contusion	7 (2.7)
	Limb injury	4 (1.5)
	Joint sprain	3 (1.2)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	Breast pain	3 (1.2)
	Menstruation irregular	3 (1.2)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	Pharyngolaryngeal pain	6 (2.3)
	Epistaxis	5 (1.9)
	Dyspnoea	4 (1.5)
EYE DISORDERS	Eye pain	6 (2.3)
	Vision blurred	5 (1.9)
VASCULAR DISORDERS	Hypertension	6 (2.3)
	Hypotension	6 (2.3)
CARDIAC DISORDERS	Palpitations	5 (1.9)
EAR AND LABYRINTH DISORDERS	Ear pain	4 (1.5)
	Vertigo	3 (1.2)
ENDOCRINE DISORDERS	Hyperthyroidism	4 (1.5)

[(a)]Treatment Emergent Adverse Events

No new or unexpected treatment emergent adverse events (TEAEs) were observed in the REBIF New HSA-free Formulation Cohort compared to the Historical HSA-containing Formulation Cohort (Historical Cohort). The Historical Cohort consisted of patients from three phase III clinical trials (Study GF6789, Study GF6954 and Study 21125) who were administered identical dosing of the previous HSA- and FBS-containing formulation of interferon beta 1a (44 µg tiw) during the 24-month/96-week period. For the purposes of these comparisons, the Historical Cohort TEAE data for 24-months/96-weeks of treatment was recoded in MedDRA version 8.0 (Clinical Trial Report Study 25632: 96-week Analysis). Overall, the proportion of subjects experiencing TEAEs was similar between the REBIF New HSA-free Formulation Cohort (95.0%) and the Historical Cohort (99.7%). With regard to severity, the majority (97%) of AEs in the REBIF New HSA-free Formulation Cohort were mild (70%) or moderate (27%). To facilitate comparison of the REBIF New HSA-free Formulation Cohort safety profile with that of the Historical Cohort the common AEs of interferon beta-1a were pre-specified into groups of MedDRA preferred terms. The pre-specified AE groups were "cytopenia", "flu like syndrome", "hepatic disorders", "hypersensitivity reactions", "injection site reactions", "depression and suicidal ideation," "skin rashes" and "thyroid disorders". Specific differences were observed in some of these eight pre-specified AE groups known to be associated with interferon beta-1a. The adverse event profile of REBIF New HSA-free Formulation was generally comparable with that observed in the historical trials with the original formulation of interferon-beta-1a. Events related to the flu-like syndrome were reported in 71.5% of REBIF New HSA-free Formulation subjects and in 69.0%, 55.4% and 49.0% of subjects in protocols 6789, 6954

and 21125 respectively. Local injection site reactions were 30.8% in REBIF New HSA-free Formulation Cohort and in 85.8% to 92.4% in the historical trials. Events related to depression and suicidal ideation were reported in 6.5% of REBIF New HSA-free Formulation subjects compared with 22.7% to 36.3% in the historical trials.

In addition to the above listed adverse events, the following events have been experienced less frequently (i.e. in less than 1% of the study population) during the 96 weeks of treatment.

Adverse Events[(a)] Experienced by less than 1% of Patients Enrolled in Study 25632 during Ninety-six weeks of follow-up

System Organ Class	Preferred Term	RNF 44 mcg TIW Subjects (n=260)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	Feeling cold	2 (0.8)
	Injection site inflammation	2 (0.8)
	Injection site irritation	2 (0.8)
	Oedema peripheral	2 (0.8)
	Chest pain	1 (0.4)
	Cyst	1 (0.4)
	Feeling hot	1 (0.4)
	Infusion site pain	1 (0.4)
	Injection site desquamation	1 (0.4)
	Injection site induration	1 (0.4)
	Injection site necrosis	1 (0.4)
	Injection site oedema	1 (0.4)
	Injection site reaction	1 (0.4)
	Malaise	1 (0.4)
	Non-cardiac chest pain	1 (0.4)
	Thirst	1 (0.4)
NERVOUS SYSTEM DISORDERS	Coordination abnormal	2 (0.8)
	Hemiparesis	2 (0.8)
	Muscle spasticity	2 (0.8)
	Sinus headache	2 (0.8)
	Somnolence	2 (0.8)
	Syncope	2 (0.8)
	Amnesia	1 (0.4)
	Autonomic nervous system imbalance	1 (0.4)
	Cognitive disorder	1 (0.4)
	Dysgeusia	1 (0.4)
	Dysgraphia	1 (0.4)
	Lethargy	1 (0.4)
	Loss of consciousness	1 (0.4)
	Motor dysfunction	1 (0.4)
	Neuralgia	1 (0.4)
	Optic neuritis	1 (0.4)
	Restless legs syndrome	1 (0.4)
	Syncope vasovagal	1 (0.4)
	Tension headache	1 (0.4)
INFECTIONS AND INFESTATIONS	Bronchitis acute	2 (0.8)
	Gastroenteritis	2 (0.8)
	Otitis externa	2 (0.8)
	Pharyngitis streptococcal	2 (0.8)
	Pneumonia	2 (0.8)
	Pulpitis dental	2 (0.8)
	Salpingitis	2 (0.8)
	Acute sinusitis	1 (0.4)
	Acute tonsillitis	1 (0.4)
	Bacterial food poisoning	1 (0.4)
	Blister infected	1 (0.4)

	Bronchitis	1 (0.4)
	Campylobacter infection	1 (0.4)
	Cervicitis	1 (0.4)
	Dry socket	1 (0.4)
	Furuncle	1 (0.4)
	Gastroenteritis escherichia coli	1 (0.4)
	Genital candidiasis	1 (0.4)
	Gingival abscess	1 (0.4)
	Hordeolum	1 (0.4)
	Injection site infection	1 (0.4)
	Kidney infection	1 (0.4)
	Laryngitis	1 (0.4)
	Localised infection	1 (0.4)
	Lower respiratory tract infection	1 (0.4)
	Nail candida	1 (0.4)
	Onychomycosis	1 (0.4)
	Oral fungal infection	1 (0.4)
	Osteomyelitis acute	1 (0.4)
	Paronychia	1 (0.4)
	Parotitis	1 (0.4)
	Penile infection	1 (0.4)
	Periodontal infection	1 (0.4)
	Peritonsillar abscess	1 (0.4)
	Pilonidal cyst	1 (0.4)
	Pyelonephritis	1 (0.4)
	Pyelonephritis acute	1 (0.4)
	Pyelonephritis chronic	1 (0.4)
	Tinea versicolour	1 (0.4)
	Tooth infection	1 (0.4)
	Tracheitis	1 (0.4)
	Vaginal candidiasis	1 (0.4)
	Vaginal mycosis	1 (0.4)
GASTROINTESTINAL DISORDERS	Coeliac disease	2 (0.8)
	Abdominal discomfort	1 (0.4)
	Abdominal distension	1 (0.4)
	Aerophagia	1 (0.4)
	Anal haemorrhage	1 (0.4)
	Colitis	1 (0.4)
	Faecal incontinence	1 (0.4)
	Food poisoning	1 (0.4)
	Gastritis erosive	1 (0.4)
	Gastroduodenitis	1 (0.4)
	Gingival bleeding	1 (0.4)
	Gingival oedema	1 (0.4)
	Gingivitis	1 (0.4)
	Mouth ulceration	1 (0.4)
	Odynophagia	1 (0.4)
	Pancreatitis	1 (0.4)
	Periodontitis	1 (0.4)
	Periproctitis	1 (0.4)
	Peritonitis	1 (0.4)
	Stomach discomfort	1 (0.4)
	Tongue discolouration	1 (0.4)
	Tooth impacted	1 (0.4)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	Chest wall pain	2 (0.8)
	Musculoskeletal stiffness	2 (0.8)
	Sensation of heaviness	2 (0.8)
	Arthropathy	1 (0.4)
	Bone pain	1 (0.4)
	Bursitis	1 (0.4)
	Fibromyalgia	1 (0.4)
	Groin pain	1 (0.4)
	Joint stiffness	1 (0.4)
	Muscle fatigue	1 (0.4)
	Muscle tightness	1 (0.4)

	Muscle twitching	1 (0.4)
	Musculoskeletal pain	1 (0.4)
	Myositis	1 (0.4)
	Night cramps	1 (0.4)
	Osteoarthritis	1 (0.4)
	Osteopenia	1 (0.4)
	Osteoporosis	1 (0.4)
	Shoulder pain	1 (0.4)
INVESTIGATIONS	Lymphocyte count decreased	2 (0.8)
	Thyroid function test abnormal	2 (0.8)
	Weight increased	2 (0.8)
	Blood cholesterol increased	1 (0.4)
	Blood creatinine increased	1 (0.4)
	Blood thyroid stimulating hormone decreased	1 (0.4)
	Haemoglobin decreased	1 (0.4)
	Heart rate increased	1 (0.4)
	Hepatic enzyme abnormal	1 (0.4)
	Red blood cell count decreased	1 (0.4)
	Serum ferritin increased	1 (0.4)
	Thyroxine free decreased	1 (0.4)
	Tri-iodothyronine free decreased	1 (0.4)
PSYCHIATRIC DISORDERS	Dyssomnia	2 (0.8)
	Panic attack	2 (0.8)
	Sleep disorder	2 (0.8)
	Hypomania	1 (0.4)
	Irritability	1 (0.4)
	Tension	1 (0.4)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	Lymphadenopathy	2 (0.8)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	Acne	2 (0.8)
	Alopecia	2 (0.8)
	Dermatitis allergic	2 (0.8)
	Rash	2 (0.8)
	Anhidrosis	1 (0.4)
	Dermal cyst	1 (0.4)
	Dermatitis atopic	1 (0.4)
	Eczema	1 (0.4)
	Exanthem	1 (0.4)
	Haemorrhage subcutaneous	1 (0.4)
	Heat rash	1 (0.4)
	Hypotrichosis	1 (0.4)
	Livedo reticularis	1 (0.4)
	Pigmentation disorder	1 (0.4)
	Pityriasis	1 (0.4)
	Pruritus generalized	1 (0.4)
	Skin irritation	1 (0.4)
	Skin ulcer	1 (0.4)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	Fall	2 (0.8)
	Post procedural pain	2 (0.8)
	Arthropod bite	1 (0.4)
	Back injury	1 (0.4)
	Caustic injury	1 (0.4)
	Concussion	1 (0.4)
	Drug toxicity	1 (0.4)
	Excoriation	1 (0.4)
	Face injury	1 (0.4)
	Humerus fracture	1 (0.4)
	Injury	1 (0.4)
	Joint dislocation	1 (0.4)
	Ligament sprain	1 (0.4)
	Muscle strain	1 (0.4)
	Near drowning	1 (0.4)
	Radius fracture	1 (0.4)
REPRODUCTIVE SYSTEM	Amenorrhoea	2 (0.8)

AND BREAST DISORDERS	Dysmenorrhoea	2 (0.8)
	Erectile dysfunction	2 (0.8)
	Menorrhagia	2 (0.8)
	Ovarian cyst	2 (0.8)
	Premenstrual syndrome	2 (0.8)
	Breast discharge	1 (0.4)
	Cervical polyp	1 (0.4)
	Endometriosis	1 (0.4)
	Fibrocystic breast disease	1 (0.4)
	Menometrorrhagia	1 (0.4)
	Menstrual disorder	1 (0.4)
	Ovarian cyst ruptured	1 (0.4)
	Uterine cervical erosion	1 (0.4)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	Cough	2 (0.8)
	Haemoptysis	1 (0.4)
	Increased upper airway secretion	1 (0.4)
	Pulmonary congestion	1 (0.4)
	Rhinitis allergic	1 (0.4)
	Rhinitis seasonal	1 (0.4)
	Rhinorrhoea	1 (0.4)
	Sleep apnoea syndrome	1 (0.4)
	Upper respiratory tract congestion	1 (0.4)
EYE DISORDERS	Blepharitis	2 (0.8)
	Eye irritation	2 (0.8)
	Conjunctivitis	1 (0.4)
	Diplopia	1 (0.4)
	Dry eye	1 (0.4)
	Myopia	1 (0.4)
	Retinal degeneration	1 (0.4)
	Visual brightness	1 (0.4)
	Vitreous disorder	1 (0.4)
	Vitreous floaters	1 (0.4)
VASCULAR DISORDERS	Essential hypertension	1 (0.4)
	Flushing	1 (0.4)
	Haematoma	1 (0.4)
	Hot flush	1 (0.4)
	Peripheral coldness	1 (0.4)
	Raynaud's phenomenon	1 (0.4)
CARDIAC DISORDERS	Angina pectoris	2 (0.8)
	Tachycardia	2 (0.8)
	Angina unstable	1 (0.4)
RENAL AND URINARY DISORDERS	Nocturia	2 (0.8)
	Renal colic	2 (0.8)
	Dysuria	1 (0.4)
	Micturition urgency	1 (0.4)
	Neurogenic bladder	1 (0.4)
	Pollakiuria	1 (0.4)
	Proteinuria	1 (0.4)
	Urinary hesitation	1 (0.4)
	Urine odour abnormal	1 (0.4)
EAR AND LABYRINTH DISORDERS	Ear discomfort	1 (0.4)
	Middle ear effusion	1 (0.4)
ENDOCRINE DISORDERS	Goitre	2 (0.8)
	Cushing's syndrome	1 (0.4)
	Hypothyroidism	1 (0.4)
	Thyroiditis chronic	1 (0.4)
HEPATOBILIARY DISORDERS	Cholecystitis	2 (0.8)
	Cholecystitis chronic	1 (0.4)
	Hepatic function abnormal	1 (0.4)
	Hepatic pain	1 (0.4)
	Hepatic steatosis	1 (0.4)
	Hepatitis toxic	1 (0.4)
	Hepatotoxicity	1 (0.4)
METABOLISM AND	Anorexia	2 (0.8)

NUTRITION DISORDERS	Dehydration	1 (0.4)
	Diabetes mellitus non-insulin-dependent	1 (0.4)
	Hyperglycaemia	1 (0.4)
	Hypokalaemia	1 (0.4)
	Lactose intolerance	1 (0.4)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	Uterine leiomyoma	2 (0.8)
	Fallopian tube neoplasm	1 (0.4)
	Tracheal neoplasm	1 (0.4)
IMMUNE SYSTEM DISORDERS	Seasonal allergy	2 (0.8)
CONGENITAL, FAMILIAL AND GENETIC DISORDERS	Factor VIII deficiency	1 (0.4)

[(a)]Treatment Emergent Adverse Events

Study 25827 (REBIF New HSA-free Formulation): Adverse Drug Reactions

The safety and tolerability of the New HSA-free Formulation of interferon beta-1a was compared to the previously marketed HSA- and FBS-containing formulation of REBIF as a secondary objective of the study. Both formulations were well tolerated when administered in subcutaneous doses of 44 µg in this study. There were no deaths or SAEs. All subjects who were administered with either study drug experienced mild Treatment Emergent Adverse Events (TEAEs). Of those TEAEs reported, 59.3% and 65.7% were probably related to the administration of the previously marketed REBIF formulation and the New HSA-free Formulation of interferon beta-1a, respectively. The nature and severities of AEs were similar for both study drugs, and were consistent with the known safety profile of previously marketed REBIF formulation. There appeared to be a higher frequency of pain associated TEAEs after administration of previously marketed REBIF formulation, and more episodes of pyrexia, and associated symptoms, after administration of the HSA-free interferon beta-1a. Injection site reactions, particularly redness, were observed after administration of both of the study drugs. Pain at the administration site and the incidence of injection site reactions however lower after injection of the HSA-free interferon beta-1a compared to previously marketed REBIF formulation.

Study GF6789 (PRISMS): **Adverse Reactions**

The adverse events experienced during the first two years of Study GF6789 are listed below, by WHOART System Organ Class. The most common amongst the injection site reactions was in the form of injection site inflammation. The majority of the other injection site reactions were also mild in the 2 REBIF groups. Necrosis was reported in 8 patients treated with REBIF. Two of these patients were in the 66 µg weekly and six in the 132 µg weekly groups. All patients completed the planned treatment period, with only 1 requiring temporary dose reductions and another patient stopping treatment for 2 weeks. Those that required treatments, received antibiotics.

Long-term Follow-up (LTFU) data up to 8 years for the PRISMS study has been collected in the retrospective study 22930. LTFU was attended by 68.2% of the original PRISMS study cohort (382/560 patients). 72.0% (275/382) were still receiving IFNbeta-1a s.c., with 74.3% (101/136) of those originally randomized to receive the 44 microg dose and 70.7% (87/123) the 22 microg dose. Overall, 19.7% of patients progressed to secondary progressive MS between baseline and

LTFU (75/381). No new safety concerns were identified and treatment was generally well tolerated.

Adverse Events Experienced by at least 1% of the Patients Enrolled in Study GF6789 (PRISMS– Year 1 and 2)

Body System	Preferred Term	Placebo (n=187)	REBIF 66 µg weekly (n=189)	REBIF 132 µg weekly (n=184)
APPLICATION SITE DISORDERS	Injection Site Inflammation	15.0%	65.6%	65.8%
	Injection Site Reaction	13.4%	31.2%	34.8%
	Injection Site Pain	14.4%	20.1%	22.8%
	Injection Site Bruising	11.2%	3.7%	5.4%
	Injection Site Mass	0.5%	3.2%	3.8%
	Injection Site Bleeding	0.5%	2.1%	2.2%
	Injection Site Necrosis		1.1%	3.3%
	Injection Site Abscess		1.1%	2.2%
BODY AS A WHOLE - GENERAL DISORDERS	Influenza-Like Symptoms	51.3%	56.1%	58.7%
	Fatigue	35.8%	32.8%	41.3%
	Fever	15.5%	24.9%	27.7%
	Leg Pain	14.4%	10.1%	13.0%
	Rigors	5.3%	6.3%	13.0%
	Sweating Increased	6.4%	6.9%	8.2%
	Chest Pain	5.3%	5.8%	7.6%
	Allergic Reaction	5.3%	4.8%	6.0%
	Pain	6.4%	2.6%	2.7%
	Malaise	1.1%	4.2%	5.4%
	Asthenia	2.1%	3.2%	2.2%
	Hot Flushes	2.1%	1.6%	2.7%
	Back Pain	2.7%	2.1%	1.1%
	Temperature Changed Sensation	1.1%	0.5%	0.5%
	Oedema Peripheral	1.1%		0.5%
	Necrosis Ischaemic			1.1%
CARDIOVASCULAR DISORDERS, GENERAL	Hypotension	3.2%	1.6%	1.6%
	Hypertension	2.7%	1.1%	1.6%
	Heart Murmur	0.5%	1.1%	0.5%
	Oedema Dependent		2.1%	
CENTR & PERIPH NERVOUS SYSTEM DISORDERS	Headache	62.6%	64.6%	70.1%
	Paraesthesia	18.7%	19.6%	16.3%
	Dizziness	17.6%	14.3%	16.3%
	Hypoaesthesia	12.8%	12.2%	7.6%
	Migraine	9.1%	6.3%	7.6%
	Hypertonia	5.3%	7.4%	6.0%
	Vertigo	7.0%	5.8%	5.4%
	Ataxia	7.5%	4.2%	4.9%
	Muscle Contractions Involuntary	7.5%	4.2%	3.3%
	Dysaesthesia	4.8%	3.2%	4.9%
	Coordination Abnormal	2.1%	5.3%	3.8%
	Convulsions	2.1%	4.8%	3.8%
	Gait Abnormal	2.7%	4.2%	3.8%
	Sensory Disturbance	4.8%	3.2%	1.6%
	Cramps Legs	3.2%	2.1%	2.7%
	Tremor	0.5%	3.2%	1.6%
	Speech Disorder	2.7%	1.1%	1.1%
	Dysphonia	1.1%	0.5%	2.2%
	Trigeminal Neuralgia	0.5%	0.5%	1.6%
	Dyskinesia		0.5%	1.6%
	Faecal Incontinence		2.1%	
	Convulsions Grand Mal		1.1%	
COLLAGEN DISORDERS	Auto-Antibody Response	1.1%	0.5%	1.1%
ENDOCRINE DISORDERS	Thyroid Disorder	3.2%	4.2%	6.0%
	T4 Increased	2.1%	2.6%	2.2%
	Thyroid Stim. Hormone Decreased	1.1%	1.1%	2.2%
	T3 Increased	0.5%	2.1%	1.1%
	T4 Decreased	1.1%	2.1%	0.5%

GASTRO-INTESTINAL SYSTEM DISORDERS	Nausea	23.0%	24.9%	24.5%
	Abdominal Pain	17.1%	22.2%	19.6%
	Diarrhoea	18.7%	17.5%	19.0%
	Vomiting	12.3%	12.7%	12.0%
	Constipation	10.2%	10.1%	7.1%
	Dyspepsia	9.6%	5.8%	8.2%
	Tooth Disorder	5.9%	5.8%	7.6%
	Tooth Ache	6.4%	5.8%	6.0%
	Gastroenteritis	7.5%	5.8%	4.3%
	Mouth Dry	1.1%	0.5%	4.9%
	Gastritis	2.7%	1.1%	2.2%
	Flatulence	2.7%	2.1%	0.5%
	Gastro-Intestinal Disorder Nos	2.7%	2.1%	0.5%
	Gingivitis	2.1%	0.5%	2.2%
	Stomatitis Ulcerative	1.1%	3.2%	0.5%
	Dysphagia	1.6%	1.1%	1.1%
	Haemorrhoids		2.1%	0.5%
	Change In Bowel Habits		1.1%	1.1%
	Haemorrhage Rectum	1.6%	0.5%	
	Appendicitis	1.1%	0.5%	
	Enteritis	0.5%		1.1%
	Glossitis		1.6%	
	Melaena			1.6%
	Tongue Ulceration		1.6%	
	Eructation		1.1%	
HEARING AND VESTIBULAR DISORDERS	Ear Ache	7.5%	3.2%	4.9%
	Tinnitus	3.2%	2.6%	1.6%
	Ear Disorder Nos	1.1%	2.1%	1.1%
	Vestibular Disorder	1.1%		1.1%
HEART RATE AND RHYTHM DISORDERS	Palpitation	4.3%	2.1%	2.7%
	Tachycardia	2.1%	1.1%	1.6%
LIVER AND BILIARY SYSTEM DISORDERS	Sgpt Increased	4.3%	19.6%	27.2%
	Sgot Increased	3.7%	10.1%	17.4%
	Hepatic Function Abnormal	1.6%	3.7%	9.2%
	Bilirubinaemia	0.5%	2.6%	2.2%
	Hepatomegaly			1.1%
METABOLIC AND NUTRITIONAL DISORDERS	Phosphatase Alkaline Increased	3.7%	4.8%	3.3%
	Weight Decrease	3.2%	4.8%	3.8%
	Hypocalcaemia	4.8%	4.2%	2.2%
	Weight Increase	3.2%	2.6%	1.6%
	Hypoglycaemia	1.6%	1.1%	1.6%
	Hypokalaemia	3.2%		
	Oedema Legs	2.1%	0.5%	0.5%
	Serum Iron Decreased	2.1%	1.1%	
	Blood Urea Decreased	0.5%	1.6%	0.5%
	Bun Increased	0.5%	1.1%	1.1%
	Glycosuria	1.1%	0.5%	1.1%
	Hypoproteinaemia		1.6%	
	Hypercalcaemia			1.1%
	Npn Increased	1.1%		
MUSCULO-SKELETAL SYSTEM DISORDERS	Myalgia	19.8%	24.9%	25.0%
	Back Pain	19.8%	23.3%	24.5%
	Arthralgia	17.1%	15.3%	19.0%
	Skeletal Pain	10.2%	14.8%	9.8%
	Muscle Weakness	13.4%	8.5%	8.7%
	Arthrosis	2.1%	2.1%	2.7%
	Tendinitis	0.5%	2.6%	1.1%
	Arthritis	0.5%	2.6%	
	Bursitis	0.5%	2.1%	0.5%
	Arthropathy		1.1%	0.5%
	Torticollis		0.5%	1.1%
PLATELET, BLEEDING & CLOTTING DISORDERS	Thrombocytopenia	1.6%	1.6%	8.2%
	Epistaxis	3.2%	2.6%	2.2%
	Purpura	2.7%	0.5%	1.1%
	Haematoma	1.1%	1.6%	
	Thrombocythaemia		1.1%	
PSYCHIATRIC DISORDERS	Depression	27.8%	20.6%	23.9%

	Insomnia	21.4%	19.6%	23.4%
	Anxiety	5.9%	4.8%	7.6%
	Nervousness	6.4%	5.3%	6.0%
	Anorexia	3.7%	4.8%	3.3%
	Somnolence	0.5%	3.7%	4.9%
	Sleep Disorder	2.1%	3.7%	2.2%
	Emotional Lability	3.2%	2.1%	1.1%
	Amnesia	1.6%	2.1%	1.1%
	Suicide Attempt	1.6%	1.6%	1.6%
	Agitation	0.5%	0.5%	2.2%
	Libido Decreased	1.1%	1.1%	1.1%
	Concentration Impaired	0.5%	1.6%	0.5%
	Confusion	1.6%		1.1%
	Paroniria		0.5%	1.1%
RED BLOOD CELL DISORDERS	Anaemia	2.7%	2.6%	4.9%
	Polycythaemia	0.5%	1.6%	
REPRODUCTIVE DISORDERS, FEMALE	Menstrual Disorder	3.7%	4.8%	4.3%
	Vaginitis	5.9%	2.6%	3.3%
	Dysmenorrhoea	4.8%	2.6%	1.1%
	Menorrhagia	1.1%	0.5%	2.7%
	Intermenstrual Bleeding	1.6%	1.6%	0.5%
	Amenorrhoea	1.6%	1.1%	0.5%
	Breast Neoplasm Female	1.6%	0.5%	1.1%
	Leukorrhoea		1.6%	
	Ovarian Cyst	0.5%		1.1%
	Pregnancy Unintended	1.1%		0.5%
	Uterine Fibroid	0.5%	1.1%	
	Breast Neoplasm Malignant Female	1.1%		
	Mastitis	1.1%		
REPRODUCTIVE DISORDERS, MALE	Impotence	2.1%	2.1%	2.7%
RESISTANCE MECHANISM DISORDERS	Herpes Simplex	8.0%	4.8%	5.4%
	Infection Fungal	7.5%	3.7%	5.4%
	Infection	6.4%	5.8%	3.3%
	Otitis Media	5.3%	3.2%	1.6%
	Moniliasis	1.6%	2.6%	3.3%
	Infection Viral	2.1%	2.1%	2.2%
	Herpes Zoster	1.1%	1.1%	2.2%
	Abscess	1.1%	1.1%	
	Infection Parasitic			1.1%
RESPIRATORY SYSTEM DISORDERS	Rhinitis	59.9%	52.4%	50.5%
	Pharyngitis	38.5%	34.9%	28.3%
	Upper Resp Tract Infection	32.6%	36.0%	29.3%
	Coughing	21.4%	14.8%	19.0%
	Sinusitis	15.5%	7.9%	9.8%
	Bronchitis	9.6%	10.6%	9.2%
	Tracheitis	5.9%	2.6%	6.5%
	Laryngitis	3.2%	2.6%	3.8%
	Dyspnoea	2.1%	1.6%	2.2%
	Throat Tightness		3.2%	1.1%
	Asthma	1.6%		2.2%
	Bronchospasm	0.5%	1.1%	1.6%
	Hyperventilation	2.1%		1.1%
	Pneumonia	2.7%	0.5%	
SECONDARY TERMS	Fall	16.0%	16.9%	15.8%
	Bite	3.2%	3.2%	
	Food Poisoning		1.6%	
	Varicella			1.1%
SKIN AND APPENDAGES DISORDERS	Pruritus	11.8%	9.0%	12.5%
	Rash	6.4%	6.9%	8.2%
	Rash Erythematous	3.2%	6.9%	4.9%
	Alopecia	5.3%	4.2%	3.3%
	Eczema	3.7%	5.3%	3.3%
	Skin Dry	3.7%	3.2%	5.4%
	Rash Maculo-Papular	1.6%	4.8%	4.3%
	Acne	3.7%	2.1%	3.3%
	Skin Disorder	2.1%	3.7%	3.3%
	Skin Hypertrophy	3.2%	1.1%	4.3%

	Skin Discolouration	4.3%	1.1%	2.7%
	Dermatitis Fungal	2.1%	2.1%	0.5%
	Urticaria	2.7%	1.1%	0.5%
	Nail Disorder	1.1%	1.1%	0.5%
	Onychomycosis	1.1%	0.5%	1.1%
	Folliculitis	0.5%	1.6%	
	Psoriasis	0.5%	1.6%	
	Dermatitis		0.5%	1.1%
	Furunculosis	0.5%		1.1%
	Hair Disorder Nos		1.6%	
	Photosensitivity Reaction	0.5%	1.1%	
	Pityriasis Rosea	0.5%		1.1%
	Verruca	1.1%		0.5%
	Dermatitis Lichenoid	1.1%		
	Rash Pustular	1.1%		
	Vitiligo	1.1%		
URINARY SYSTEM DISORDERS	Urinary Tract Infection	18.7%	18.0%	16.8%
	Cystitis	12.3%	5.8%	6.5%
	Micturition Frequency	3.7%	1.6%	6.5%
	Haematuria	3.7%	2.6%	2.7%
	Urinary Incontinence	1.6%	3.7%	1.6%
	Albuminuria	1.6%	3.2%	1.6%
	Micturition Disorder	1.6%	2.1%	2.2%
	Dysuria	1.1%	1.6%	2.2%
	Renal Pain	2.1%		2.2%
	Urinary Retention	2.1%	2.1%	
	Urine Abnormal	1.1%	1.1%	1.6%
	Face Oedema	1.6%		1.6%
	Micturition Urgency	1.1%	1.1%	1.1%
	Nocturia		0.5%	1.1%
VASCULAR (EXTRACARDIAC) DISORDERS	Flushing	3.2%	1.6%	2.2%
	Vascular Disorder		0.5%	1.1%
	Peripheral Ischaemia	1.1%		
VISION DISORDERS	Vision Abnormal	7.0%	7.4%	13.0%
	Eye Pain	8.0%	6.3%	4.9%
	Conjunctivitis	6.4%	5.8%	4.9%
	Diplopia	3.2%	1.6%	2.2%
	Xerophthalmia		2.6%	0.5%
	Eye Infection	1.1%	0.5%	1.1%
	Photophobia	0.5%	1.1%	1.1%
	Conjunctival Discolouration	1.1%		
	Photopsia	1.1%		
WHITE CELL AND RES DISORDERS	Lymphopenia	11.2%	20.1%	28.8%
	Leucopenia	3.7%	12.7%	22.3%
	Lymphadenopathy	8.0%	11.1%	12.0%
	Granulocytopenia	3.7%	11.6%	15.2%
	Leukocytosis	4.3%	5.3%	4.3%
	Monocytosis	2.7%	4.8%	4.3%
	Eosinophilia	2.1%	3.7%	1.1%
	Wbc Abnormal Nos	0.5%	3.2%	2.7%
	Lymphadenopathy Cervical	1.6%	1.6%	1.6%
	Lymphocytosis	1.1%	1.6%	0.5%

In addition to the above listed adverse events, the following events have been experienced less frequently (i.e. in less than 1% of the study population) during years 1 and 2 of treatment.

Adverse Events Experienced by less than 1% of the Patients Enrolled in Study GF6789 (PRISMS– Year 1 and 2)

Body System	Preferred Term
APPLICATION SITE DISORDERS	Injection Site Atrophy
BODY AS A WHOLE - GENERAL DISORDERS	Scar
	Oedema

	Syncope
	Abdomen Enlarged
	Anaphylactoid Reaction
	Carpal Tunnel Syndrome
	Nasal Polyp
	Oedema Genital
CARDIOVASCULAR DISORDERS, GENERAL	Hypotension Postural
CENTR & PERIPH NERVOUS SYSTEM DISORDERS	Convulsions Local
	Extrapyramidal Disorder
	Hypotonia
	Nerve Root Lesion
	Neuralgia
	Optic Neuritis
	Paralysis
	Paresis
	Scotoma
	Visual Field Defect
ENDOCRINE DISORDERS	Hypothyroidism
	Sialoadenitis
FOETAL DISORDERS	Hernia Congenital
	Death Foetal
GASTRO-INTESTINAL SYSTEM DISORDERS	Appetite Increased
	Saliva Increased
	Tooth Caries
	Colitis
	Crohn's Disease
	Gastroesophageal Reflux
	Gi Neoplasm Benign
	Gum Hyperplasia
	Hiccup
	Intestinal Obstruction
	Irritable Bowel Syndrome
	Rectal Prolapse
	Stomatitis
	Stomatitis Aphthous
HEARING AND VESTIBULAR DISORDERS	Hearing Decreased
	Hyperacusis
	Motion Sickness
	Deafness
HEART RATE AND RHYTHM DISORDERS	Arrhythmia
	Bradycardia
	Cardiac Arrest
	Extrasystoles
	Sick Sinus Syndrome
LIVER AND BILIARY SYSTEM DISORDERS	Cholecystitis
	Cholelithiasis
	Gamma-Gt Increased
METABOLIC AND NUTRITIONAL DISORDERS	Hypercholesterolaemia
	Thirst
	Hyperlipaemia
	Hypernatraemia
	Oedema Generalised
MUSCULO-SKELETAL SYSTEM DISORDERS	Malformation Foot
	Osteoporosis
MYO ENDO PERICARDIAL & VALVE DISORDERS	Angina Pectoris
NEOPLASM	Basal Cell Carcinoma
	Colon Carcinoma
	Lipoma
PLATELET,BLEEDING & CLOTTING DISORDERS	Dissem. Intravasc. Coagulation
	Embolism Arterial
	Embolism Pulmonary
	Thrombosis Arterial Arm
PSYCHIATRIC DISORDERS	Apathy
	Dreaming Abnormal
	Hallucination
	Psychosis Manic-Depressive

	Thinking Abnormal
RED BLOOD CELL DISORDERS	Hyperhaemoglobinaemia
	Splenomegaly
REPRODUCTIVE DISORDERS, FEMALE	Cervicitis
	Endometriosis
	Lactation Nonpuerperal
	Vaginal Haemorrhage
	Bacterial Growth Genital Asymptom
	Breast Neoplasm Benign Female
	Cervical Dysplasia
	Endometrial Disorder
	Menopausal Symptoms
	Ovarian Disorder
	Premenstrual Tension
	Uterovaginal Prolapse
REPRODUCTIVE DISORDERS, MALE	Breast Discharge
	Epididymitis
	Sexual Function Abnormal
	Testicular Pain
	Testis Disorder
RESISTANCE MECHANISM DISORDERS	Infection Bacterial
	Moniliasis Genital
	Sepsis
RESPIRATORY SYSTEM DISORDERS	Sputum Increased
	Atelectasis
	Pneumonitis
	Stridor
SECONDARY TERMS	Cyst Nos
	Heat Intolerance
	Spinal Cord Compression
	Abrasion Nos
	Asthma Extrinsic
	Cytomegalus Virus Infection
	Heat Stroke
	Lumbar Disc Lesion
	Malaria
SKIN AND APPENDAGES DISORDERS	Pigmentation Abnormal
	Rosacea
	Bullous Eruption
	Hair Texture Abnormal
	Hyperkeratosis
	Hypertrichosis
	Paronychia
	Rhagades
	Seborrhoea
	Skin Reaction Localised
	Skin Ulceration
	Sweat Gland Disorder
	Vesicular Rash
SPECIAL SENSES OTHER, DISORDERS	Taste Perversion
URINARY SYSTEM DISORDERS	Pyelonephritis
	Polyuria
VASCULAR (EXTRACARDIAC) DISORDERS	Thrombophlebitis Arm Superficial
	Vein Distended
	Claudication Intermittent
	Thrombophlebitis
	Vascular Malformation Cerebral
VISION DISORDERS	Accommodation Abnormal
	Conjunctival Haemorrhage
	Blindness
	Blindness Temporary
	Cataract
	Iritis
	Keratitis
	Meibomianitis
	Retinal Disorder
	Uveitis

WHITE CELL AND RES DISORDERS	Immunoglobulins Increased

After 2 years, the placebo patients were switched to REBIF, and along with the patients for the REBIF treatment groups, they were treated for an additional two years. Listed below by WHOART System Organ Class, are the proportion of patients reporting the most common adverse events ongoing from years 1 and 2 or started during years 3 and 4 of treatment. The results are similar to those obtained in the original phase of the study. The findings indicate that the incidence of interferon-related adverse events diminishes somewhat with continued exposure to the medication.

Cases of necrosis were rare and not a cause of drop-out. For REBIF 66 µg weekly, there was one episode of skin necrosis per 92 years of exposure or per 14 100 injections. The comparable figures for REBIF 132 µg weekly are 1 episode of necrosis per 61 years of exposure or per 9 300 injections.

Adverse Events Experienced by at least 1% of the Patients Enrolled in Study GF6789 (PRISMS– Ongoing from Year 1 and 2 or Started During Year 3 and 4)

Body System	Preferred Term	Placebo/66 (n=85)	Placebo/132 (n=87)	REBIF 66 µg weekly (n=167)	REBIF 132 µg weekly (n=167)
APPLICATION SITE DISORDERS	Injection Site Inflammation	65.9%	65.5%	56.9%	66.5%
	Injection Site Reaction	28.2%	37.9%	29.9%	31.7%
	Injection Site Pain	18.8%	21.8%	15.0%	13.8%
	Injection Site Bruising	5.9%	6.9%	2.4%	6.0%
	Injection Site Mass	3.5%	4.6%	4.8%	3.6%
	Injection Site Necrosis	2.4%	1.1%	1.8%	3.0%
	Injection Site Abscess	1.2%	2.3%	1.8%	1.2%
	Injection Site Bleeding	2.4%		0.6%	1.8%
	Skin Nodule				1.2%
BODY AS A WHOLE - GENERAL DISORDERS	Influenza-Like Symptoms	42.4%	60.9%	50.3%	42.5%
	Fatigue	34.1%	36.8%	24.6%	27.5%
	Fever	14.1%	14.9%	15.6%	12.0%
	Leg Pain	8.2%	12.6%	6.6%	7.8%
	Pain	4.7%	14.9%	4.2%	4.2%
	Rigors	5.9%	6.9%	4.2%	7.8%
	Sweating Increased	5.9%	3.4%	5.4%	3.6%
	Malaise	3.5%	3.4%	3.0%	5.4%
	Asthenia	1.2%	2.3%	4.8%	3.6%
	Chest Pain	2.4%	5.7%	3.6%	2.4%
	Allergic Reaction	2.4%	4.6%	3.0%	2.4%
	Hot Flushes	3.5%	1.1%	1.8%	2.4%
	Oedema Peripheral	3.5%	2.3%	0.6%	0.6%
	Temperature Changed Sensation	1.2%		1.2%	2.4%
	Scar		2.3%	1.2%	1.2%
	Carpal Tunnel Syndrome		1.1%	0.6%	
	Anaphylactic Shock		1.1%		
	Choking		1.1%		
	Necrosis Ischaemic	1.2%			
	Pallor	1.2%			
CARDIOVASCULAR DISORDERS, GENERAL	Hypertension	3.5%	5.7%	4.2%	4.2%
	Hypotension	1.2%	1.1%	1.8%	2.4%
	Oedema Dependent	3.5%	1.1%	1.2%	0.6%
	Cardiac Failure Left	1.2%			
	Hypotension Postural		1.1%		
CENTR & PERIPH NERVOUS SYSTEM DISORDERS	Headache	44.7%	55.2%	46.7%	46.7%
	Dizziness	4.7%	11.5%	13.2%	12.6%
	Hypertonia	14.1%	11.5%	10.8%	9.6%
	Paraesthesia	15.3%	13.8%	10.2%	7.8%

	Hypoaesthesia	7.1%	13.8%	7.2%	9.0%
	Migraine	8.2%	9.2%	6.6%	5.4%
	Ataxia	2.4%	8.0%	5.4%	7.2%
	Vertigo	7.1%	8.0%	3.6%	3.0%
	Muscle Contractions Involuntary	4.7%	3.4%	5.4%	2.4%
	Gait Abnormal	2.4%	2.3%	4.8%	2.4%
	Dysaesthesia	2.4%	3.4%	2.4%	2.4%
	Tremor	2.4%	2.3%	3.6%	1.8%
	Convulsions	2.4%	1.1%	3.0%	2.4%
	Coordination Abnormal	4.7%		3.6%	0.6%
	Cramps Legs	1.2%	2.3%	1.2%	3.0%
	Sensory Disturbance	4.7%	1.1%	1.2%	1.2%
	Speech Disorder		4.6%	1.8%	1.2%
	Faecal Incontinence			3.0%	0.6%
	Paresis		1.1%	1.2%	1.2%
	Extrapyramidal Disorder	1.2%			0.6%
	Hyperkinesia		1.1%		0.6%
	Ms Aggravated	1.2%			0.6%
	Paralysis	1.2%			0.6%
	Ptosis				1.2%
	Aphasia	1.2%			
	Hemiplegia		1.1%		
	Visual Field Defect		1.1%		
COLLAGEN DISORDERS	Auto-Antibody Response		1.1%	1.2%	1.8%
	Arthritis Rheumatoid Aggravated		1.1%		
ENDOCRINE DISORDERS	Thyroid Disorder	4.7%	8.0%	4.2%	6.6%
	T4 Increased	4.7%	1.1%	3.0%	2.4%
	Thyroid Stim. Hormone Decreased	3.5%	1.1%	0.6%	3.0%
	Hypothyroidism	2.4%		0.6%	1.8%
	T3 Increased		1.1%	1.2%	1.2%
	T4 Decreased	2.4%		1.2%	0.6%
	Goitre	1.2%		1.2%	0.6%
	Hyperthyroidism			1.2%	1.2%
FOETAL DISORDERS	Hernia Congenital		1.1%	1.2%	
GASTRO-INTESTINAL SYSTEM DISORDERS	Nausea	12.9%	19.5%	10.8%	11.4%
	Abdominal Pain	8.2%	16.1%	13.2%	10.8%
	Diarrhoea	5.9%	8.0%	12.0%	9.0%
	Constipation	14.1%	9.2%	6.0%	7.2%
	Vomiting	3.5%	9.2%	3.0%	6.0%
	Dyspepsia	7.1%	5.7%	3.0%	3.6%
	Gastroenteritis	2.4%	4.6%	4.2%	4.2%
	Tooth Ache	2.4%	4.6%	3.0%	4.8%
	Tooth Disorder	1.2%	3.4%	3.0%	6.0%
	Haemorrhoids	1.2%	1.1%	2.4%	1.8%
	Dysphagia	1.2%	2.3%	0.6%	1.2%
	Gastritis	1.2%		1.2%	1.2%
	Gastro-Intestinal Disorder Nos		4.6%	0.6%	
	Stomatitis Ulcerative	1.2%	1.1%	1.2%	0.6%
	Flatulence	2.4%	1.1%		0.6%
	Gastroesophageal Reflux		2.3%	0.6%	0.6%
	Appendicitis	1.2%		0.6%	0.6%
	Melaena		2.3%	0.6%	
	Mouth Dry				1.8%
	Colitis				1.2%
	Enterocolitis				1.2%
	Eructation	1.2%		0.6%	
	Gingivitis		1.1%		0.6%
	Glossitis				1.2%
	Irritable Bowel Syndrome		1.1%	0.6%	
	Oesophagitis		1.1%		0.6%
	Stomatitis		1.1%		0.6%
	Abdominal Adhesions	1.2%			
	Achalasia Cardiae		1.1%		
	Crohn's Disease	1.2%			
	Gi Haemorrhage		1.1%		
	Peptic Ulcer		1.1%		
	Saliva Increased		1.1%		

HEARING AND VESTIBULAR DISORDERS	Tinnitus	2.4%	3.4%	3.6%	1.8%
	Ear Ache	4.7%	3.4%	1.2%	1.2%
	Ear Disorder Nos	2.4%	1.1%		1.8%
	Hearing Decreased	1.2%		0.6%	1.2%
	Deafness		2.3%		0.6%
	Hyperacusis	1.2%	1.1%		
	Deafness Nerve	1.2%			
	Otosclerosis	1.2%			
HEART RATE AND RHYTHM DISORDERS	Palpitation	2.4%	2.3%	3.0%	2.4%
	Tachycardia	1.2%	2.3%	1.2%	
LIVER AND BILIARY SYSTEM DISORDERS	Sgpt Increased	11.8%	14.9%	13.8%	12.6%
	Sgot Increased	4.7%	9.2%	6.6%	6.0%
	Hepatic Function Abnormal	7.1%	4.6%	2.4%	3.0%
	Bilirubinaemia	1.2%		1.2%	0.6%
	Hepatic Enzymes Increased	1.2%	1.1%		
	Gamma-Gt Increased	1.2%			
	Hepatitis	1.2%			
	Jaundice		1.1%		
METABOLIC AND NUTRITIONAL DISORDERS	Weight Increase	4.7%	9.2%	3.6%	1.8%
	Phosphatase Alkaline Increased	8.2%	1.1%	2.4%	4.8%
	Weight Decrease	3.5%	4.6%	3.6%	3.6%
	Blood Urea Decreased	3.5%		2.4%	1.2%
	Hypoglycaemia	2.4%	1.1%	2.4%	0.6%
	Oedema Legs	2.4%	1.1%	2.4%	0.6%
	Glycosuria			1.8%	1.2%
	Hypercholesterolaemia		1.1%	1.2%	1.2%
	Hyperproteinaemia			0.6%	1.8%
	Npn Increased	2.4%		0.6%	0.6%
	Hyperglycaemia			1.8%	
	Hypocalcaemia	1.2%		0.6%	0.6%
	Hypoproteinaemia	2.4%		0.6%	
	Serum Iron Decreased	2.4%	1.1%		
	Hypokalaemia		2.3%		
	Hyperkalaemia		1.1%		
	Hyperlipaemia	1.2%			
MUSCULO-SKELETAL SYSTEM DISORDERS	Back Pain	14.1%	20.7%	20.4%	22.2%
	Myalgia	21.2%	23.0%	15.6%	14.4%
	Arthralgia	16.5%	18.4%	12.6%	18.0%
	Muscle Weakness	12.9%	17.2%	7.2%	9.6%
	Skeletal Pain	8.2%	11.5%	7.2%	6.6%
	Arthritis		5.7%	2.4%	2.4%
	Arthrosis	1.2%	2.3%	1.8%	2.4%
	Tendinitis	2.4%		1.2%	1.2%
	Bursitis			1.8%	0.6%
	Arthropathy			1.2%	0.6%
	Bone Disorder		1.1%		
	Ischial Neuralgia		1.1%		
	Malformation Foot	1.2%			
NEOPLASM	Breast Fibroadenosis	1.2%		0.6%	
PLATELET,BLEEDING & CLOTTING DISORDERS	Thrombocytopenia	3.5%	1.1%	1.8%	3.6%
	Haematoma	3.5%	1.1%	1.8%	1.8%
	Epistaxis		2.3%	1.8%	0.6%
	Thrombocythaemia	1.2%		1.2%	
	Thrombosis	1.2%			
PSYCHIATRIC DISORDERS	Depression	29.4%	27.6%	23.4%	25.1%
	Insomnia	22.4%	21.8%	16.2%	21.6%
	Nervousness	7.1%	8.0%	6.6%	4.8%
	Anxiety	3.5%	6.9%	4.8%	3.0%
	Emotional Lability	4.7%	3.4%	3.0%	2.4%
	Sleep Disorder	1.2%	5.7%	3.6%	1.8%
	Anorexia	4.7%	1.1%	3.0%	2.4%
	Somnolence	2.4%		2.4%	4.2%
	Amnesia	1.2%	2.3%	3.0%	0.6%
	Depression Aggravated			2.4%	0.6%
	Concentration Impaired			1.2%	1.2%
	Suicide Attempt	1.2%			1.8%
	Agitation			1.8%	

	Confusion		2.3%		0.6%
	Libido Decreased	1.2%	1.1%	0.6%	
	Apathy	1.2%			
	Paroniria	1.2%			
	Personality Disorder		1.1%		
	Psychosis Manic-Depressive	1.2%			
	Teeth-Grinding	1.2%			
RED BLOOD CELL DISORDERS	Anaemia	7.1%	9.2%	3.6%	6.6%
	Polycythaemia	1.2%		1.8%	
	Anaemia Hypochromic	1.2%			
	Marrow Hyperplasia		1.1%		
REPRODUCTIVE DISORDERS, FEMALE	Menstrual Disorder	5.9%	6.9%	6.6%	2.4%
	Amenorrhoea	3.5%		0.6%	1.8%
	Breast Neoplasm Female	2.4%	2.3%	1.2%	0.6%
	Menorrhagia	1.2%	1.1%	1.8%	0.6%
	Vaginitis		3.4%	1.2%	0.6%
	Dysmenorrhoea	1.2%	2.3%	1.2%	
	Intermenstrual Bleeding		2.3%	1.8%	
	Uterine Fibroid	1.2%		1.2%	1.2%
	Menopausal Symptoms	1.2%		1.8%	
	Vaginal Haemorrhage	1.2%	1.1%	0.6%	0.6%
	Ovarian Cyst	1.2%		0.6%	0.6%
	Breast Neoplasm Malignant Female		2.3%		
	Endometriosis	1.2%		0.6%	
	Pregnancy Unintended	1.2%			0.6%
	Breast Neoplasm Benign Female	1.2%			
	Cervicitis		1.1%		
	Uterine Inflammation		1.1%		
REPRODUCTIVE DISORDERS, MALE	Impotence	7.1%		3.0%	2.4%
	Epididymitis		1.1%	0.6%	
	Testicular Pain		1.1%		
RESISTANCE MECHANISM DISORDERS	Infection Fungal	4.7%	1.1%	6.6%	5.4%
	Herpes Simplex	2.4%	6.9%	5.4%	1.2%
	Infection	3.5%	1.1%	4.8%	2.4%
	Infection Viral	4.7%		3.0%	3.0%
	Otitis Media	4.7%		1.2%	2.4%
	Herpes Zoster			1.2%	1.8%
	Moniliasis		1.1%	0.6%	1.8%
	Abscess		1.1%		0.6%
	Infection Parasitic	1.2%			0.6%
	Moniliasis Genital		1.1%		
	Sepsis	1.2%			
RESPIRATORY SYSTEM DISORDERS	Rhinitis	38.8%	29.9%	39.5%	33.5%
	Upper Resp Tract Infection	18.8%	14.9%	22.8%	20.4%
	Pharyngitis	23.5%	12.6%	19.8%	15.0%
	Coughing	5.9%	11.5%	8.4%	13.8%
	Sinusitis	8.2%	11.5%	5.4%	10.2%
	Bronchitis	1.2%	9.2%	4.2%	8.4%
	Tracheitis	1.2%		2.4%	3.0%
	Laryngitis		3.4%	3.6%	
	Dyspnoea	2.4%	2.3%	1.2%	1.2%
	Asthma	1.2%	1.1%		0.6%
	Hyperventilation	2.4%			0.6%
	Pneumonia			1.2%	0.6%
	Bronchospasm			1.2%	
	Pneumonitis	1.2%			
SECONDARY TERMS	Trauma Nos	15.3%	5.7%	14.4%	11.4%
	Fall	3.5%	5.7%	2.4%	4.8%
	Cyst Nos	2.4%	1.1%	1.2%	2.4%
	Bite	2.4%	2.3%	0.6%	1.8%
	Post-Operative Wound Infection	1.2%	2.3%	1.2%	
	Post-Operative Pain	1.2%	1.1%	0.6%	0.6%
	Food Poisoning		1.1%	0.6%	
	Post-Operative Haemorrhage	2.4%			
	Surgical Procedure			1.2%	
	Metastases Nos		1.1%		
SKIN AND APPENDAGES	Pruritus	3.5%	5.7%	7.8%	9.6%

DISORDERS	Rash	3.5%	8.0%	6.6%	6.0%
	Skin Disorder	2.4%	4.6%	7.2%	3.0%
	Eczema	2.4%	3.4%	7.2%	3.0%
	Skin Dry	2.4%	3.4%	3.0%	5.4%
	Acne	4.7%	1.1%	3.6%	3.0%
	Alopecia	4.7%	2.3%	3.6%	1.8%
	Rash Erythematous	3.5%	2.3%	4.8%	1.2%
	Dermatitis Fungal	1.2%	2.3%	2.4%	0.6%
	Rash Maculo-Papular	2.4%	1.1%	1.2%	1.8%
	Skin Hypertrophy	1.2%	2.3%	0.6%	1.8%
	Psoriasis	1.2%	2.3%	1.8%	
	Verruca	1.2%	1.1%		2.4%
	Onychomycosis		1.1%	1.2%	1.2%
	Folliculitis		1.1%	1.8%	
	Furunculosis		1.1%		1.8%
	Nail Disorder		1.1%		1.8%
	Photosensitivity Reaction	1.2%		0.6%	1.2%
	Urticaria	1.2%	1.1%		1.2%
	Dermatitis	1.2%			1.2%
	Rosacea		1.1%	0.6%	0.6%
	Skin Discolouration			0.6%	1.2%
	Hair Disorder Nos		1.1%	0.6%	
	Papilloma	1.2%	1.1%		
	Pilonidal Cyst	1.2%		0.6%	
	Bullous Eruption	1.2%			
	Dermographia		1.1%		
	Hyperkeratosis		1.1%		
SPECIAL SENSES OTHER, DISORDERS	Taste Perversion	1.2%			1.8%
URINARY SYSTEM DISORDERS	Urinary Tract Infection	8.2%	14.9%	16.2%	13.8%
	Cystitis	5.9%	6.9%	9.6%	6.6%
	Haematuria	1.2%	4.6%	3.0%	4.8%
	Micturition Frequency	1.2%	3.4%	1.8%	4.8%
	Urinary Incontinence		5.7%	3.0%	1.8%
	Urinary Retention	2.4%	2.3%	2.4%	0.6%
	Urine Abnormal	4.7%		1.8%	1.2%
	Dysuria	1.2%		1.8%	1.8%
	Micturition Disorder	1.2%	1.1%	1.2%	1.8%
	Albuminuria	1.2%	1.1%	1.2%	1.2%
	Micturition Urgency	1.2%	1.1%	1.2%	1.2%
	Renal Calculus			1.2%	2.4%
	Pyelonephritis			1.2%	1.2%
	Renal Pain	1.2%	1.1%		1.2%
	Creatinine Decrease	1.2%			1.2%
	Face Oedema		1.1%		
	Pyuria	1.2%			
VASCULAR (EXTRACARDIAC) DISORDERS	Peripheral Ischaemia	1.2%	2.3%	1.8%	1.8%
	Flushing	1.2%	2.3%	1.8%	
	Telangiectasis			1.8%	
	Vascular Disorder			0.6%	1.2%
	Vein Varicose	1.2%	1.1%	0.6%	
	Thrombophlebitis			1.2%	
	Thrombophlebitis Deep		1.1%		
VISION DISORDERS	Vision Abnormal	5.9%	4.6%	4.2%	9.0%
	Eye Pain	1.2%	4.6%	5.4%	5.4%
	Conjunctivitis	1.2%	3.4%	3.6%	3.6%
	Xerophthalmia		1.1%	3.0%	0.6%
	Diplopia			1.8%	1.2%
	Eye Infection			0.6%	1.2%
	Lacrimal Duct Obstruction	1.2%		0.6%	
	Meibomianitis	1.2%	1.1%		
	Accommodation Abnormal		1.1%		
	Conjunctival Discolouration	1.2%			
	Keratitis	1.2%			
	Lacrimation Abnormal	1.2%			
WHITE CELL AND RES DISORDERS	Lymphopenia	22.4%	23.0%	19.8%	25.7%
	Leucopenia	16.5%	14.9%	12.0%	13.8%

Granulocytopenia	9.4%	10.3%	7.8%	12.0%
Lymphadenopathy	2.4%	14.9%	8.4%	10.2%
Leukocytosis	3.5%	3.4%	6.0%	3.6%
Monocytosis	4.7%	1.1%	1.8%	2.4%
Eosinophilia	3.5%	1.1%	1.2%	2.4%
Wbc Abnormal Nos	1.2%	1.1%	2.4%	1.2%
Lymphadenopathy Cervical		1.1%	0.6%	2.4%
Lymphocytosis	1.2%		1.8%	0.6%

In addition to the above listed adverse events, the following events have been experienced less frequently (i.e. in less than 1% of the study population) ongoing from years 1 and 2 or started during years 3 and 4 of treatment.

Adverse Events Experienced by less than 1% of the Patients Enrolled in Study GF6789 (PRISMS– Ongoing from Year 1 and 2 or Started During Year 3 and 4)

Body System	Preferred Term
APPLICATION SITE DISORDERS	Injection Site Atrophy
	Cellulitis
	Injection Site Fibrosis
	Skin Necrosis
BODY AS A WHOLE - GENERAL DISORDERS	Chest Pain Substernal
	Sarcoidosis
CARDIOVASCULAR DISORDERS, GENERAL	Aneurysm
	Circulatory Failure
	Heart Murmur
CENTR & PERIPH NERVOUS SYSTEM DISORDERS	Trigeminal Neuralgia
	Dyskinesia
	Dysphonia
	Nerve Root Lesion
	Neuralgia
	Neuropathy
	Scotoma
COLLAGEN DISORDERS	Antinuclear Factor Test Positive
ENDOCRINE DISORDERS	Glucocorticoids Increased
GASTRO-INTESTINAL SYSTEM DISORDERS	Change In Bowel Habits
	Enanthema
	Haemorrhage Rectum
	Hiccup
	Oesophageal Ulceration
	Periodontal Destruction
	Tongue Ulceration
	Tooth Caries
HEART RATE AND RHYTHM DISORDERS	Arrhythmia
	Extrasystoles
LIVER AND BILIARY SYSTEM DISORDERS	Cholelithiasis
	Hepatomegaly
METABOLIC AND NUTRITIONAL DISORDERS	Bun Increased
	Diabetes Mellitus
	Hypercalcaemia
	Oedema Generalised
	Vitamin B12 Deficiency
MUSCULO-SKELETAL SYSTEM DISORDERS	Myopathy
	Osteoporosis
MYO ENDO PERICARDIAL & VALVE DISORDERS	Myocardial Infarction
NEOPLASM	Bladder Carcinoma
	Ovarian Carcinoma
	Renal Carcinoma
PLATELET,BLEEDING & CLOTTING DISORDERS	Purpura
PSYCHIATRIC DISORDERS	Depression Psychotic
	Drug Dependence

RED BLOOD CELL DISORDERS	Hyperhaemoglobinaemia
	Packed Cell Volume Increased
REPRODUCTIVE DISORDERS, FEMALE	Cervical Uterine Polyp
	Cervix Lesion
	Fertility Decreased Female
	Premenstrual Tension
	Vulva Discomfort
REPRODUCTIVE DISORDERS, MALE	Hernia Inguinal
	Semen Abnormal
	Sexual Function Abnormal
	Testis Disorder
RESISTANCE MECHANISM DISORDERS	Toxoplasmosis
RESPIRATORY SYSTEM DISORDERS	Pleural Pain
	Pleurisy
	Pulmonary Congestion
SECONDARY TERMS	Abrasion Nos
	Heat Intolerance
	Lumbar Disc Lesion
	Medication Reaction Nos
	Nasal Septum Deviation
SKIN AND APPENDAGES DISORDERS	Dermatitis Contact
	Pigmentation Abnormal
	Pityriasis Rosea
	Hair Texture Abnormal
	Hypertrichosis
	Livedo Reticularis
	Photosensitivity Allergic React
	Rash Pustular
	Rhagades
	Skin Malformation
	Skin Reaction Localised
	Vesicular Rash
	Vitiligo
URINARY SYSTEM DISORDERS	Nocturia
	Cystitis Haemorrhagic
	Polyuria
	Renal Cyst
	Urethral Disorder
VASCULAR (EXTRACARDIAC) DISORDERS	Claudication Intermittent
	Ocular Haemorrhage
	Vascular Malformation Cerebral
	Vascular Malformation Peripheral
	Vein Distended
VISION DISORDERS	Blepharitis
	Corneal Ulceration
	Herpes Ocular
	Lacrimal Gland Disorder
	Mydriasis
	Retinal Disorder
	Uveitis

Asymptomatic laboratory abnormalities were reported frequently with interferon dosing over the 4 years. Of the abnormalities noted, the cytopenias and abnormalities of liver function showed dose-related differences. Lymphopenia occurred in 35% of high dose patients and 27% of low dose patients. Thrombocytopenia was seen in 2.6% of patients on low dose, and 8.2% of patients on high dose. Differences in the frequency of abnormal liver enzymes were seen which included elevated ALT (24% for low dose vs. 30% for high dose, p=0.07) and elevated AST (11% vs. 20%, p=0.03). Severe elevations are uncommon and not different between dose groups. These data suggest that there is only minimal evidence of significant dose-dependent lab abnormalities with interferon therapy in MS patients.

After 4 years of therapy, 23.7% of the low dose and 14.3% of the high-dose patients had developed persistent neutralising antibodies (p = 0.024, 44 µg vs. 22 µg), the vast majority of which (91%) developed within 24 months. The lower incidence in the high dose group may be due to the phenomenon of high-zone tolerance. While continuing interferon treatment, 20.0% of low-dose NAb+ patients reverted, while 25.7% of high-dose NAb+ patients reverted. The neutralising antibodies were associated with reduced clinical efficacy during years 3 and 4 and reduced MRI efficacy over 4 years.

Study GF6954 (SPECTRIMS): Adverse Reactions

The table below presents adverse events that were reported in at least 1% of the patients in any treatment group of Study GF6954; the AEs are listed by WHOART system organ class and preferred term (sorted by preferred term in order of frequency). The most frequently reported adverse event was injection site inflammation, which occurred in 67% of both treated groups compared to 16% for placebo. Lower frequencies of the closely associated but more symptomatic injection site reactions were reported in 3 to 4 times as many treated patients as placebo patients. Injection site necrosis was seen in 3.3% and 6.9% of patients in the 22 µg and 44 µg groups respectively, but almost always as a single event per patient. The rate of necrosis was 1/3 800 injections for high-dose and 1/9 600 for low-dose therapy. Liver function abnormalities were also reported 3 to 4 times more commonly with active therapy. The haematopoietic system was also affected, with increased reports of leucopenia, granulocytopenia and lymphopenia associated with active therapy and most prominently with the higher dose. These haematopoietic abnormalities are expected side-effects of interferon therapy. Increased reports of anaemia and thrombocytopenia were noted with treatment, but these events occurred in less than 10% of patients.

Adverse Events Experienced by at least 1% of the Patients Enrolled in Study GF6954 (SPECTRIMS– Year 3)

Body System	Preferred Term	Placebo (n=205)	Rebif 66 µg weekly (n=209)	Rebif 132 µg weekly(n=204)
APPLICATION SITE DISORDERS	Injection Site Inflammation	15.6%	66.5%	67.2%
	Injection Site Reaction	7.8%	21.1%	31.9%
	Injection Site Pain	18.0%	17.2%	22.5%
	Injection Site Bruising	16.1%	8.1%	9.8%
	Injection Site Necrosis		3.3%	6.9%
	Injection Site Mass	1.0%	1.9%	2.5%
	Injection Site Abscess		2.4%	2.5%
	Injection Site Bleeding		2.4%	1.5%
AUTONOMIC NERVOUS SYSTEM DISORDERS	Flushing	1.5%	1.9%	2.9%
BODY AS A WHOLE - GENERAL DISORDERS	Headache	56.6%	52.2%	63.2%
	Influenza-Like Symptoms	52.2%	50.7%	49.5%
	Fatigue	32.2%	33.0%	43.1%
	Fever	11.7%	14.4%	19.1%
	Leg Pain	9.3%	11.5%	12.3%
	Asthenia	9.8%	5.7%	12.3%
	Rigors	5.4%	7.7%	7.8%
	Chest Pain	5.9%	7.2%	6.4%
	Sweating Increased	4.4%	9.1%	5.4%
	Malaise	5.9%	4.3%	7.8%
	Pain	4.9%	5.3%	5.4%
	Allergic Reaction	5.9%	2.4%	3.9%
	Hot Flushes	3.4%	4.3%	2.5%
	Temperature Changed Sensation	3.4%	2.4%	3.9%
	Syncope	1.0%	2.4%	1.5%
	Scar	1.5%	0.5%	1.5%
CARDIOVASCULAR DISORDERS, GENERAL	Hypertension	2.9%	7.7%	7.8%
	Oedema Dependent	4.9%	5.7%	5.4%
	Oedema Peripheral	4.9%	5.7%	3.4%
	Oedema Legs	4.9%	1.9%	2.0%
	Hypotension	1.0%	1.9%	1.0%
CENTR & PERIPH NERVOUS SYSTEM DISORDERS	Hypertonia	26.8%	24.4%	30.4%
	Dizziness	18.0%	16.3%	17.2%
	Paraesthesia	13.2%	8.1%	9.3%
	Hypoaesthesia	9.3%	10.0%	8.3%
	Dysaesthesia	9.8%	6.2%	5.9%
	Ataxia	7.3%	6.7%	5.9%
	Gait Abnormal	6.8%	6.7%	5.9%
	Vertigo	5.9%	3.3%	4.9%
	Tremor	5.4%	3.8%	4.4%
	Migraine	3.4%	4.3%	4.9%
	Paresis	3.4%	3.3%	3.9%
	Muscle Contractions Involuntary	2.4%	3.8%	3.4%
	Ms Aggravated	1.5%	3.3%	3.4%
	Speech Disorder	2.4%	1.4%	1.0%
	Confusion	2.9%		1.5%
	Coordination Abnormal	1.0%	1.4%	2.0%
	Convulsions	1.0%	2.4%	0.5%
	Dysphonia	1.0%	1.0%	1.5%
	Sensory Disturbance	0.5%	0.5%	2.5%
	Trigeminal Neuralgia	2.4%	0.5%	0.5%
	Hyperkinesia	1.0%	1.4%	0.5%
ENDOCRINE DISORDERS	Thyroid Disorder	3.4%	3.3%	5.4%
	T4 Increased	0.5%	3.8%	2.0%
GASTRO-INTESTINAL SYSTEM DISORDERS	Nausea	26.3%	23.9%	17.6%
	Abdominal Pain	18.0%	14.8%	15.2%
	Diarrhoea	15.6%	18.7%	13.7%
	Constipation	19.0%	14.8%	13.2%
	Vomiting	8.3%	7.2%	6.9%

	Dyspepsia	7.3%	7.2%	5.9%
	Tooth Disorder	4.4%	5.3%	6.9%
	Anorexia	5.4%	5.3%	4.9%
	Gastroenteritis	7.3%	2.9%	5.4%
	Tooth Ache	3.4%	3.3%	2.5%
	Gastro-Intestinal Disorder Nos	3.9%	1.4%	2.9%
	Faecal Incontinence	3.9%	0.5%	3.4%
	Dysphagia	2.4%	2.4%	2.5%
	Mouth Dry	3.4%	1.9%	0.5%
	Gastritis	1.5%	1.4%	1.0%
	Flatulence	1.5%		1.5%
	Appetite Increased	1.0%	1.4%	
	Hiccup	1.0%		1.5%
	Oesophagitis	1.5%	0.5%	0.5%
	Gingival Bleeding		1.4%	
	Gingivitis	1.5%		
HEARING AND VESTIBULAR DISORDERS	Ear Ache	1.0%	2.4%	4.9%
	Tinnitus	2.0%	1.4%	2.0%
	Ear Disorder Nos	2.9%	1.4%	
HEART RATE AND RHYTHM DISORDERS	Palpitation	1.5%	3.3%	3.4%
	Tachycardia	0.5%	1.4%	0.5%
LIVER AND BILIARY SYSTEM DISORDERS	Sgpt Increased	7.3%	21.1%	23.0%
	Sgot Increased	3.4%	11.5%	13.2%
	Hepatic Enzymes Increased	1.0%	5.3%	6.4%
	Phosphatase Alkaline Increased	1.5%	3.8%	2.9%
	Hepatic Function Abnormal	1.5%	2.4%	3.4%
	Cholelithiasis		0.5%	1.5%
METABOLIC AND NUTRITIONAL DISORDERS	Weight Decrease	6.3%	4.8%	8.3%
	Weight Increase	3.4%	3.3%	2.0%
	Glycosuria	1.0%	1.4%	1.5%
	Hypercholesterolaemia	1.0%	1.0%	2.0%
	Hyperproteinaemia	1.0%	1.9%	0.5%
MUSCULO-SKELETAL SYSTEM DISORDERS	Myalgia	23.9%	24.9%	27.9%
	Arthralgia	25.4%	24.4%	23.0%
	Back Pain	22.4%	21.5%	22.1%
	Muscle Weakness	18.0%	17.2%	16.7%
	Skeletal Pain	8.8%	9.1%	7.4%
	Arthropathy	3.4%	3.8%	2.9%
	Tendinitis	2.0%	2.9%	3.9%
	Arthritis	2.0%	1.4%	2.9%
	Bursitis	2.0%	2.9%	1.0%
	Arthrosis	0.5%	3.3%	1.0%
NEOPLASM	Cervical Smear Test Positive			1.5%
PLATELET, BLEEDING & CLOTTING DISORDERS	Thrombocytopenia	0.5%	3.3%	6.4%
	Thrombocythaemia	1.5%	1.0%	1.5%
PSYCHIATRIC DISORDERS	Depression	28.8%	32.1%	34.8%
	Insomnia	22.0%	20.6%	23.5%
	Anxiety	7.3%	4.3%	5.4%
	Depression Aggravated	1.5%	7.2%	5.4%
	Somnolence	4.4%	4.3%	4.4%
	Nervousness	2.4%	1.9%	2.0%
	Emotional Lability	1.5%	2.4%	2.0%
	Amnesia	2.4%	1.0%	0.5%
	Suicide Attempt	1.5%	1.4%	1.0%
	Agitation	1.0%	0.5%	2.0%
	Libido Decreased		2.4%	
	Cyclothymic Reaction			1.5%
RED BLOOD CELL DISORDERS	Anaemia	3.9%	2.4%	9.3%
REPRODUCTIVE DISORDERS, FEMALE	Menstrual Disorder	5.4%	2.9%	3.4%
	Menorrhagia	2.9%	2.4%	2.5%
	Vaginitis	2.4%	1.4%	2.0%
	Amenorrhoea	0.5%	2.9%	0.5%
	Dysmenorrhoea	2.4%	1.0%	0.5%
	Menopausal Symptoms	0.5%	1.9%	1.5%
	Vaginal Haemorrhage	2.0%	0.5%	1.0%
	Breast Neoplasm Benign Female	1.5%	0.5%	0.5%
	Leukorrhoea		1.4%	

REPRODUCTIVE DISORDERS, MALE	Impotence	1.5%	1.0%	2.9%
RESISTANCE MECHANISM DISORDERS	Infection	3.9%	5.3%	6.4%
	Herpes Simplex	4.4%	6.2%	3.4%
	Infection Fungal	2.9%	2.9%	2.9%
	Moniliasis	2.0%	1.4%	3.4%
	Abscess	1.0%	2.4%	2.0%
	Infection Viral	1.5%	1.4%	2.0%
	Otitis Media	1.0%	0.5%	2.9%
	Herpes Zoster	0.5%	1.9%	0.5%
	Moniliasis Genital	1.0%	1.4%	0.5%
RESPIRATORY SYSTEM DISORDERS	Rhinitis	41.5%	38.3%	33.3%
	Upper Resp Tract Infection	33.2%	31.1%	26.0%
	Pharyngitis	20.0%	19.6%	17.2%
	Sinusitis	6.8%	7.2%	8.8%
	Coughing	6.3%	6.7%	5.4%
	Bronchitis	5.9%	3.8%	7.8%
	Tracheitis	6.3%	7.2%	3.9%
	Dyspnoea	3.9%	4.3%	0.5%
	Pneumonia	1.0%	2.9%	2.9%
	Epistaxis	2.0%	1.0%	3.4%
	Laryngitis	2.9%	1.4%	1.0%
SECONDARY TERMS	Trauma Nos	28.3%	24.9%	23.0%
	Fall	7.3%	5.7%	6.9%
	Post-Operative Pain	3.4%	1.9%	2.5%
	Bite	1.0%	2.4%	2.0%
	Food Poisoning	0.5%	2.4%	2.0%
	Abrasion Nos	0.5%	1.4%	1.5%
	Cyst Nos	0.5%	1.4%	0.5%
	Eye Burns	0.5%	1.4%	
SKIN AND APPENDAGES DISORDERS	Rash	6.3%	5.7%	8.8%
	Pruritus	5.9%	5.7%	8.8%
	Alopecia	4.9%	8.1%	4.4%
	Rash Erythematous	2.4%	8.6%	6.4%
	Eczema	5.9%	4.3%	2.9%
	Skin Dry	1.0%	5.7%	4.9%
	Skin Disorder	2.0%	4.3%	3.9%
	Dermatitis	2.9%	1.0%	1.5%
	Rash Maculo-Papular	2.0%	1.9%	1.5%
	Acne	1.0%	2.4%	1.5%
	Pruritic Rash	1.0%	1.9%	1.0%
	Skin Ulceration		1.4%	2.5%
	Seborrhoea	0.5%	1.4%	1.5%
	Skin Discolouration	1.5%	0.5%	1.5%
	Dermatitis Fungal	1.0%		2.0%
	Furunculosis	1.0%	1.4%	0.5%
	Nail Disorder		1.4%	1.5%
	Urticaria	2.4%	0.5%	
	Rosacea	0.5%	0.5%	1.5%
	Verruca	0.5%		1.5%
SPECIAL SENSES OTHER, DISORDERS	Taste Perversion	0.5%	1.9%	0.5%
URINARY SYSTEM DISORDERS	Urinary Tract Infection	26.3%	34.4%	27.0%
	Cystitis	12.7%	17.2%	10.8%
	Haematuria	4.4%	6.2%	5.4%
	Micturition Frequency	2.9%	5.3%	3.9%
	Urinary Incontinence	6.3%	3.3%	2.0%
	Albuminuria	3.4%	3.3%	3.4%
	Urinary Retention	4.4%	3.8%	1.0%
	Micturition Disorder	2.9%	3.3%	1.5%
	Creatinine Decrease	2.4%	1.4%	2.5%
	Dysuria	3.4%	1.9%	0.5%
	Micturition Urgency	2.0%	0.5%	0.5%
	Pyelonephritis	2.0%		1.0%
	Bun Increased		0.5%	1.5%
VASCULAR (EXTRACARDIAC) DISORDERS	Haematoma	6.3%	1.4%	3.4%
	Thrombophlebitis Deep		1.4%	0.5%

VISION DISORDERS	Vision Abnormal	11.7%	10.5%	4.9%
	Eye Pain	5.9%	6.7%	7.4%
	Conjunctivitis	3.4%	4.8%	2.5%
	Diplopia	2.9%	1.9%	2.0%
	Xerophthalmia	1.0%	1.9%	1.0%
	Eye Infection	2.0%	0.5%	1.0%
	Meibomianitis		1.4%	2.0%
WHITE CELL AND RES DISORDERS	Lymphopenia	15.1%	21.5%	26.0%
	Leucopenia	4.9%	11.0%	21.1%
	Granulocytopenia	2.0%	9.1%	13.2%
	Lymphadenopathy	3.9%	5.3%	7.8%
	Leukocytosis	4.4%	0.5%	2.9%
	Monocytosis	1.5%	1.4%	2.0%
	Eosinophilia	1.0%	1.4%	2.0%

In addition to the above listed adverse events, the following events have been experienced less frequently (i.e. in less than 1% of the study population) during the 3 years of treatment.

Adverse Events Experienced by less than 1% of the Patients Enrolled in Study GF6954 (SPECTRIMS– Year 3)

Body System	Preferred Term
APPLICATION SITE DISORDERS	Cellulitis
	Otitis Externa
	Skin Nodule
BODY AS A WHOLE - GENERAL DISORDERS	Allergy
	Choking
	Face Oedema
	Carpal Tunnel Syndrome
	Condition Aggravated
	Granulomatous Lesion
	Halitosis
	Necrosis Ischaemic
	Oedema
	Pallor
CARDIOVASCULAR DISORDERS, GENERAL	Heart Murmur
	Cyanosis
	Oedema Periorbital
CENTR & PERIPH NERVOUS SYSTEM DISORDERS	Anaesthesia Mouth
	Cramps Legs
	Neuralgia
	Coma
	Dyskinesia
	Lower Motor Neurone Lesion
	Neuropathy
	Paralysis
	Paraplegia
	Convulsions Grand Mal
	Hemianopia
	Hyperaesthesia
	Nystagmus
	Optic Atrophy
	Scotoma
	Stupor
	Visual Field Defect
COLLAGEN DISORDERS	Auto-Antibody Response
ENDOCRINE DISORDERS	Thyroid Stim. Hormone Decreased
	Hypothyroidism
	T3 Increased
	Goitre
	Hyperthyroidism
	T4 Decreased
	Thyroiditis

FOETAL DISORDERS	Hernia Congenital
GASTRO-INTESTINAL SYSTEM DISORDERS	Stomatitis Ulcerative
	Appendicitis
	Gastroesophageal Reflux
	Haemorrhoids
	Change In Bowel Habits
	Enteritis
	Abdomen Enlarged
	Colitis
	Gastric Ulcer
	Haemorrhage Rectum
	Melaena
	Tenesmus
	Tongue Discolouration
	Abdominal Adhesions
	Anus Disorder
	Duodenal Ulcer
	Faeces Discoloured
	Gi Haemorrhage
	Leukoplakia Oral
	Mucositis Nos
	Oesophagospasm
	Saliva Altered
	Saliva Increased
	Salivary Duct Obstruction
	Salivary Gland Enlargement
	Stomatitis
	Teeth-Grinding
	Tongue Ulceration
HEARING AND VESTIBULAR DISORDERS	Hearing Decreased
	Deafness
	Motion Sickness
	Vestibular Disorder
HEART RATE AND RHYTHM DISORDERS	Fibrillation Atrial
	Arrhythmia
	Bradycardia
LIVER AND BILIARY SYSTEM DISORDERS	Bilirubinaemia
	Hepatomegaly
	Cholangitis
	Gall Bladder Disorder
	Gamma-Gt Increased
METABOLIC AND NUTRITIONAL DISORDERS	Blood Urea Decreased
	Hypercalcaemia
	Hyperkalaemia
	Thirst
	Vitamin B12 Deficiency
	Hypokalaemia
	Oedema Generalised
	Dehydration
	Gout
	Hyperglycaemia
	Hyperuricaemia
	Hypocalcaemia
	Hypoglycaemia
	Hypoglycaemic Reaction
	Lipodystrophy
	Npn Increased
MUSCULO-SKELETAL SYSTEM DISORDERS	Osteoporosis
	Torticollis
	Avascular Necrosis Femoral Head
	Myositis
	Synovitis
MYO ENDO PERICARDIAL & VALVE DISORDERS	Angina Pectoris
NEOPLASM	Basal Cell Carcinoma
	Brain Neoplasm Benign
	Breast Neoplasm Malignant Female

	Cervical Uterine Polyp
	Gi Neoplasm Benign
	Lipoma
	Thyroid Neoplasm Malignant
PSYCHIATRIC DISORDERS	Concentration Impaired
	Aggressive Reaction
	Paroniria
	Depersonalization
	Drug Abuse
	Euphoria
	Paranoid Reaction
	Sleep Disorder
	Snoring
RED BLOOD CELL DISORDERS	Anaemia Hypochromic
	Polycythaemia
	Packed Cell Volume Increased
	Splenomegaly
REPRODUCTIVE DISORDERS, FEMALE	Cervical Dysplasia
	Intermenstrual Bleeding
	Mastitis
	Uterine Fibroid
	Breast Discharge
	Endometrial Hyperplasia
	Ovarian Cyst
	Uterine Haemorrhage
	Uterovaginal Prolapse
	Vaginal Discomfort
	Vaginal Neoplasm Benign
REPRODUCTIVE DISORDERS, MALE	Prostatic Disorder
	Semen Abnormal
	Ejaculation Failure
	Epididymitis
	Hernia Inguinal
	Testicular Pain
RESISTANCE MECHANISM DISORDERS	Infection Bacterial
	Sepsis
RESPIRATORY SYSTEM DISORDERS	Asthma
	Bronchospasm
	Pneumonitis
	Chronic Obstruct Airways Disease
	Pleurisy
	Pulmonary Congestion
	Respiratory Insufficiency
	Sleep Apnoea
	Pleural Effusion
	Pulmonary Eosinophilia
	Pulmonary Oedema
	Sputum Increased
	Throat Tightness
SECONDARY TERMS	Post-Operative Haemorrhage
	Post-Operative Wound Infection
	Surgical Procedure
	Asthma Extrinsic
	Bone Metastases
	Lumbar Disc Lesion
	Nasal Septum Deviation
	Varicella
SKIN AND APPENDAGES DISORDERS	Photosensitivity Reaction
	Psoriasis
	Rash Psoriaform
	Bullous Eruption
	Rash Pustular
	Hyperkeratosis
	Onychomycosis
	Dermatitis Contact
	Hypertrichosis
	Skin Odor Abnormal

	Vesicular Rash
	Chloasma
	Erythema Induratum
	Erythema Multiforme
	Erythema Nodosum
	Folliculitis
	Hair Disorder Nos
	Heat Rash
	Livedo Reticularis
	Melanosis
	Nail Discolouration
	Photosensitivity Allergic React
	Piloerection
	Pilonidal Cyst
	Pruritus Genital
	Skin Atrophy
	Skin Hypertrophy
	Sweating Decreased
SPECIAL SENSES OTHER, DISORDERS	Parosmia
URINARY SYSTEM DISORDERS	Polyuria
	Renal Pain
	Nocturia
	Urethral Disorder
	Urine Abnormal
	Bladder Discomfort
	Cystitis Haemorrhagic
	Hydronephrosis
	Renal Calculus
	Renal Cyst
	Renal Function Abnormal
VASCULAR (EXTRACARDIAC) DISORDERS	Peripheral Ischaemia
	Embolism Pulmonary
	Vascular Disorder
	Vasculitis
	Vein Distended
	Cerebral Haemorrhage
	Cerebrovascular Disorder
	Phlebitis
	Subarachnoid Haemorrhage
	Thrombophlebitis
	Vascular Malformation Peripheral
	Vein Varicose
VISION DISORDERS	Blepharitis
	Photophobia
	Accommodation Abnormal
	Cataract
	Retinal Disorder
	Blindness
	Glaucoma
	Blepharospasm
	Blindness Temporary
	Conjunctival Discolouration
	Conjunctival Haemorrhage
	Corneal Deposits
	Corneal Opacity
	Exophthalmos
	Eyelid Retraction
	Herpes Ocular
	Uveitis
WHITE CELL AND RES DISORDERS	Lymphadenopathy Cervical
	Wbc Abnormal Nos
	Basophilia

Study GF7480 (ETOMS): Adverse Reactions

In Study GF7480, adverse events were reported more frequently in patients assigned REBIF than in those assigned placebo. These events included injection-site inflammation (60% vs 12%), fever (28% vs 12%), myalgia (17% vs 9%) and chills (11% vs 5%). Serious adverse events were reported in five patients in the placebo group and six in the interferon beta-1a group.

Study 21125 (EVIDENCE): Adverse Reactions

Study 21125 was a direct comparative trial of IFN beta-1a 44 µg tiw (REBIF) vs. IFN beta-1a 30 µg im qw (Avonex®) in RRMS patients. Of the 677 patients randomized, 339 patients received REBIF 44 µg sc tiw and 338 patients were randomized to AVONEX 30 µg im qw. The following tables present AE frequencies for only the REBIF-treated group coded in MedDRA version 8.0.

There were a total of 2682 AEs reported by the subjects who received REBIF, the majority of which were mild in severity. The most commonly reported AEs were injection site disorders, flu-like symptoms (headache, fever, chills, fatigue, malaise, arthralgia and myalgia), white blood cell abnormalities and elevated hepatic transaminases (AST and ALT), all of which are well-known reactions to interferon and are included in the product label for REBIF.

Adverse Events[(a)] Experienced By at Least 1% of the REBIF-Treated Patients Enrolled in Study 21125 (EVIDENCE) During Forty-Eight Weeks

System organ class	Preferred Term	REBIF 44 µg TIW Subjects (n=339)
General disorders and administration site conditions	Injection site erythema	45.1 %
	Influenza like illness	44.2 %
	Injection site reaction	27.1 %
	Fatigue	17.1 %
	Injection site pain	14.2 %
	Injection site haemorrhage	10.0 %
	Injection site irritation	8.3 %
	Pain	5.0 %
	Pyrexia	5.0 %
	Asthenia	3.5 %
	Chest pain	3.2 %
	Chills	3.2 %
	Injection site inflammation	2.4 %
	Gait disturbance	1.2 %
	Injection site mass	1.2 %
	Injection site pruritus	1.2 %
	Malaise	1.2 %
Infections and infestations	Rhinitis	17.7 %
	Upper respiratory tract infection	15.9 %
	Sinusitis	11.2 %
	Viral infection	8.0 %
	Urinary tract infection	7.4 %
	Bronchitis	5.0 %
	Gastroenteritis viral	4.1 %
	Ear infection	2.9 %
	Herpes simplex	2.1 %
	Localised infection	1.8 %
	Lower respiratory tract infection	1.8 %
	Pharyngitis	1.8 %
	Tooth abscess	1.8 %
	Vaginal candidiasis	1.5 %
	Acute tonsillitis	1.2 %
	Eye infection	1.2 %

	Gastroenteritis	1.2 %
	Otitis media	1.2 %
	Vaginal infection	1.2 %
Nervous system disorders	Headache	37.5 %
	Dizziness	9.1 %
	Hypoaesthesia	5.6 %
	Migraine	4.7 %
	Paraesthesia	4.7 %
	Hemiparesis	2.7 %
	Muscle spasticity	2.7 %
	Balance disorder	2.1 %
	Sinus headache	1.8 %
	Paresis	1.5 %
	Tremor	1.5 %
Musculoskeletal and connective tissue disorders	Arthralgia	10.6 %
	Back pain	8.8 %
	Myalgia	8.8 %
	Pain in extremity	3.8 %
	Musculoskeletal stiffness	3.5 %
	Muscle spasms	2.9 %
	Musculoskeletal pain	2.4 %
	Neck pain	1.8 %
	Tendonitis	1.5 %
	Arthritis	1.2 %
Psychiatric disorders	Depression	15.9 %
	Insomnia	14.2 %
	Anxiety	3.5 %
	Mood swings	1.5 %
	Affect lability	1.2 %
	Depressed mood	1.2 %
	Irritability	1.2 %
	Nervousness	1.2 %
	Sleep disorder	1.2 %
Investigations	Alanine aminotransferase increased	12.1 %
	Aspartate aminotransferase increased	7.7 %
	Hepatic enzyme increased	3.8 %
	White blood cell count decreased	3.8 %
	Blood creatine phosphokinase increased	3.2 %
	Lymphocyte count decreased	2.4 %
	Neutrophil count decreased	2.4 %
	Weight decreased	2.4 %
	Blood pressure increased	1.5 %
	Thyroxine increased	1.5 %
	Weight increased	1.5 %
	Blood alkaline phosphatase increased	1.2 %
	Blood calcium decreased	1.2 %
	Red blood cell count decreased	1.2 %
Gastrointestinal disorders	Nausea	10.3 %
	Diarrhoea	5.9 %
	Constipation	5.0 %
	Abdominal pain upper	4.4 %
	Abdominal pain	2.7 %
	Vomiting	2.7 %
	Toothache	1.8 %
	Dyspepsia	1.5 %
	Faecal incontinence	1.2 %
	Gastrooesophageal reflux disease	1.2 %
	Stomach discomfort	1.2 %
Skin and subcutaneous tissue	Rash	4.1 %

	Pruritus	3.2 %
	Alopecia	2.4 %
	Dry skin	1.8 %
	Hyperhidrosis	1.2 %
	Night sweats	1.2 %
	Rash pruritic	1.2 %
Respiratory, thoracic and mediastinal disorders	Pharyngolaryngeal pain	5.0 %
	Cough	4.4 %
	Nasal congestion	2.7 %
	Sinus congestion	2.7 %
	Dyspnoea	2.1 %
	Epistaxis	1.8 %
Injury, poisoning and procedural complications	Traumatic haematoma	4.4 %
	Joint sprain	1.8 %
	Laceration	1.2 %
Reproductive system and breast disorders	Dysmenorrhoea	2.7 %
	Menstruation irregular	2.7 %
	Menorrhagia	1.5 %
	Amenorrhoea	1.2 %
	Metrorrhagia	1.2 %
Eye disorders	Eye pain	2.4 %
	Vision blurred	2.1 %
	Conjunctivitis	1.5 %
Blood and lymphatic system disorders	Lymphadenopathy	2.7 %
	Leukopenia	2.4 %
	Anaemia	2.1 %
	Lymphopenia	1.5 %
Renal and urinary disorders	Micturition urgency	1.5 %
	Urinary incontinence	1.5 %
	Pollakiuria	1.2 %
Ear and labyrinth disorders	Vertigo	1.8 %
	Tinnitus	1.2 %
Vascular disorders	Hypertension	2.7 %
	Hot flush	1.5 %
Cardiac disorders	Palpitations	1.8 %
Metabolism and nutrition disorders	Anorexia	1.2 %

[(a)]Treatment Emergent Adverse Events

In addition to the above listed adverse events, the following events have been experienced less frequently (i.e. in less than 1% of the study population) during the 48 weeks of treatment.

Adverse Events[(a)] Experienced by Less than 1% of the REBIF-Treated Patients Enrolled in Study 21125 (EVIDENCE) During Forty-Eight Weeks

System organ class	Preferred Term
General disorders and administration site conditions	Chest discomfort
	Injection site discolouration
	Injection site rash
	Injection site swelling
	Nodule
	Feeling hot
	Injection site vesicles
	Temperature intolerance
	Thirst
	Circadian rhythm sleep disorder
	Cyst
	Difficulty in walking
	Drug withdrawal syndrome
	Facial pain
	Feeling jittery
	Hernia
	Injection site induration
	Injection site necrosis

	Injection site photosensitivity reaction
	Injection site ulcer
	Oedema peripheral
Infections and infestations	Fungal infection
	Onychomycosis
	Vaginal mycosis
	Abscess limb
	Cystitis
	Dental caries
	Nasopharyngitis
	Paronychia
	Pharyngitis streptococcal
	Pneumonia
	Abscess
	Bacterial infection
	Bacteriuria
	Fungal skin infection
	Gastrointestinal fungal infection
	Herpes zoster
	Infection parasitic
	Injection site cellulitis
	Laryngitis
	Malaria
	Postoperative infection
	Skin candida
	Skin infection
	Tinea infection
	Tonsillitis
	Tooth infection
	Wound infection
Nervous system disorders	Coordination abnormal
	Dysgeusia
	Neuralgia
	Restless legs syndrome
	Amnesia
	Carpal tunnel syndrome
	Cognitive disorder
	Disturbance in attention
	Hyperaesthesia
	Multiple sclerosis
	Sciatica
	Somnolence
	Syncope
	Aphasia
	Burning sensation
	Dizziness postural
	Dyskinesia
	Dystonia
	Head discomfort
	Lethargy
	Muscle contractions involuntary
	Myoclonus
	Sensory disturbance
	Syncope vasovagal
Musculoskeletal and connective tissue disorders	Muscle twitching
	Sensation of heaviness
	Arthropathy
	Bone pain
	Bursitis
	Intervertebral disc disorder
	Joint stiffness
	Bone disorder
	Costochondritis
	Flank pain
	Ganglion

	Joint effusion
	Osteoporosis
	Pain in jaw
	Periarthritis
	Spinal osteoarthritis
	Torticollis
Psychiatric disorders	Apathy
	Confusional state
	Suicidal ideation
	Anxiety disorder
	Libido decreased
	Nightmare
	Suicide attempt
	Tension
Investigations	Anti-thyroid antibody
	Blood glucose increased
	Blood thyroid stimulating hormone decreased
	Blood urine present
	Blood albumin increased
	Blood thyroid stimulating hormone increased
	Glucose urine
	Haematocrit decreased
	Haemoglobin decreased
	Neutrophil count
	Thyroid function test abnormal
	Tri-iodothyronine increased
	Blood iron decreased
	Blood phosphorus decreased
	Blood potassium increased
	Lymphocyte count abnormal
	Monocyte count increased
	Neutrophil count increased
	Platelet count decreased
	Platelet count increased
	Protein total increased
	Thyroxine decreased
	White blood cell count
	White blood cell count increased
Gastrointestinal disorders	Dry mouth
	Mouth ulceration
	Abdominal distension
	Abdominal pain lower
	Dysphagia
	Gastritis
	Abdominal tenderness
	Anorectal disorder
	Aphthous stomatitis
	Change of bowel habit
	Colitis
	Colonic polyp
	Diverticulum
	Enteritis
	Flatulence
	Gingivitis
	Halitosis
	Irritable bowel syndrome
	Oesophagitis
	Oral pain
	Salivary hypersecretion
	Stomatitis
	Tongue discolouration
	Tooth disorder
Skin and subcutaneous tissue disorders	Acne
	Rash erythematous
	Dermatitis allergic

	Livedo reticularis
	Rash maculo-papular
	Skin disorder
	Urticaria
	Alopecia areata
	Blister
	Cold sweat
	Dermatitis
	Dermatitis bullous
	Dermatitis contact
	Eczema
	Ephelides
	Erythema
	Exanthem
	Hypotrichosis
	Nail disorder
	Onychorrhexis
	Palmar erythema
	Photosensitivity allergic reaction
	Pruritus allergic
	Rash scaly
	Rash vesicular
	Rosacea
	Skin discolouration
	Skin nodule
Respiratory, thoracic and mediastinal disorders	Rhinitis allergic
	Rhinorrhoea
	Asthma
	Dysphonia
	Postnasal drip
	Rales
	Wheezing
	Breath sounds decreased
	Nasal discomfort
	Nasopharyngeal disorder
	Pleurisy
	Productive cough
	Rhinitis seasonal
	Rhonchi
Injury, poisoning and procedural complications	Arthropod bite
	Excoriation
	Fall
	Pain trauma activated
	Animal bite
	Joint dislocation
	Joint injury
	Post procedural pain
	Tooth injury
	Accident
	Anaemia postoperative
	Ankle fracture
	Arthropod sting
	Foot fracture
	Hand fracture
	Injury
	Limb injury
	Muscle injury
	Muscle strain
	Nerve injury
	Post procedural complication
	Sunburn
	Thermal burn
Reproductive system and breast disorders	Breast mass
	Sexual dysfunction
	Breast pain

	Endometriosis
	Genital disorder female
	Oligomenorrhoea
	Ovarian cyst
	Pelvic pain
	Pruritus genital
	Scrotal pain
	Vaginal discharge
	Vaginal prolapse
	Vulvovaginal discomfort
Eye disorders	Photopsia
	Visual disturbance
	Diplopia
	Dry eye
	Eye disorder
	Vitreous floaters
	Accommodation disorder
	Conjunctivitis allergic
	Eye irritation
	Ocular hyperaemia
	Optic atrophy
	Visual acuity reduced
Blood and lymphatic system disorders	Neutropenia
	Bone marrow depression
	Lymphadenitis
	Microcytic anaemia
	Monocytosis
Renal and urinary disorders	Glycosuria
	Dysuria
	Nocturia
	Urine odour abnormal
	Bladder disorder
	Ketonuria
	Proteinuria
	Renal colic
	Stress incontinence
	Urinary retention
	Urinary tract disorder
Ear and labyrinth disorders	Ear disorder
	Ear pain
	Meniere's disease
	Motion sickness
	Vertigo positional
Vascular disorders	Flushing
	Haematoma
	Phlebitis
	Varicose vein
Cardiac disorders	Tachycardia
	Arrhythmia
	Bundle branch block right
	Supraventricular tachycardia
Metabolism and nutrition disorders	Hypokalaemia
	Diabetes mellitus
	Hypercholesterolaemia
	Hypertriglyceridaemia
	Hypocalcaemia
	Hypoglycaemia
	Increased appetite
	Ketoacidosis
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Thyroid neoplasm
	Basal cell carcinoma
	Breast cancer
	Breast neoplasm
	Fibroadenoma of breast
	Uterine leiomyoma

Immune system disorders	Hypersensitivity
	Seasonal allergy
Hepatobiliary disorders	Hepatitis
	Cholecystitis
	Hepatocellular damage
Endocrine disorders	Hypothyroidism
	Goitre
Congenital, familial and genetic disorders	Colour blindness
Pregnancy, puerperium and perinatal conditions	Abortion spontaneous

[(a)]Treatment Emergent Adverse Events

Clinical Trials: Summary of Adverse Reactions

Studies with REBIF have included patients with Relapsing Remitting Multiple Sclerosis and secondary progressive forms of MS, disability ranging from none to severe, and age ranging from 18 to 60 at study start.

Post-Market Adverse Drug Reactions

The vast majority of the adverse reactions of REBIF in multiple sclerosis have been identified from the clinical trials and are summarized in the above placebo-controlled study tables.
The adverse reactions reported with marketed use of REBIF that are not already mentioned in the clinical study tables are shown below. These reactions have been identified during post-marketing surveillance and their exact frequency is unknown.

General disorders and administration site conditions: Injection site necrosis

Infections and infestations: Injection site infections, including cellulitis which could be severe and injection site abscesses

Immune system disorders: Anaphylactic reaction

Psychiatric disorders: Suicide attempt

Nervous system disorders: Seizures, transient neurological symptoms (i.e. hypoesthesia, muscle spasm, paresthesia, difficulty in walking, musculoskeletal stiffness) that may mimic multiple sclerosis exacerbations

Vascular disorders: Thromboembolic events

Blood and lymphatic system disorders: Thrombotic thrombocytopenic purpura, haemolytic uraemic syndrome

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

Hepatobiliary disorders: Hepatitis with or without icterus

Skin and subcutaneous tissue disorders: Angioedema (Quincke's edema), urticaria, erythema multiforme, erythema multiforme-like skin reactions, hair loss, Stevens-Johnson Syndrome

DRUG INTERACTIONS

No formal drug interaction studies have been conducted with REBIF 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 ACTH has not been studied systematically. Clinical studies indicate that multiple sclerosis patients can receive REBIF and corticosteroids or ACTH during relapses. REBIF should not be mixed with other drugs in the same syringe.

DOSAGE AND ADMINISTRATION

RELAPSING FORMS OF MULTIPLE SCLEROSIS:
Before initiating a patient on REBIF therapy, please review completely the CONTRAINDICATIONS section of this Product Monograph.

Recommended Dose and Dosage Adjustment

The recommended dose is 44 μg given 3 times per week by subcutaneous injection. The dose can be reduced to 22 μg tiw if the patient is not able to tolerate the higher dose.

Treatment should be initiated under supervision of a physician experienced in the treatment of the disease. When first starting treatment with REBIF, in order to allow tachyphylaxis to develop thus reducing adverse events, it is recommended that 20% of the total dose be administered during the initial 2 weeks of therapy, 50% of total dose be administered in week 3 and 4, and the full dose from the fifth week onwards.

Please also review the WARNINGS AND PRECAUTIONS section and ensure appropriate monitoring of patients with depression, hepatic dysfunction, a history of seizures, cardiac disease, renal dysfunction, thyroid dysfunction, myelosuppression, and female patients of child-bearing potential.

At the present time, it is not known for how long patients should be treated. Safety and efficacy with REBIF have been demonstrated following 4 years of treatment. Therefore, it is recommended that patients should be evaluated after 4 years of treatment with REBIF and a decision for longer-term treatment be made on an individual basis by the treating physician.

Missed Dose

Should a dose be missed, the patient should be advised to continue to inject from the day of the next scheduled dose. The patient should not take a double dose to make up for the missed dose.

Administration

Patients should be advised of REBIF side-effects and instructed on the use of aseptic technique when administering REBIF. The REBIF Patient Leaflet should be carefully reviewed with all patients, and patients should be educated on self-care and advised to keep the Leaflet for continued reference during REBIF therapy.

Preparation of Solution: Liquid formulation in a pre-filled syringe

The liquid formulation in a pre-filled syringe is ready for use. These syringes are graduated to facilitate therapy initiation. The pre-filled syringes contain 8.8 µg, 22 µg and 44 µg of REBIF New HSA-free Formulation respectively. The pre-filled syringes are ready for subcutaneous use only.

Preparation of Solution: Rebif®RebiDose™ Solution for Injection in a pre-filled pen

The liquid formulation in the Rebif®RebiDose™ pre-filled pen is ready for use. Rebif®RebiDose™ pre-filled pens contain 8.8 µg, 22 µg and 44 µg of REBIF New HSA-free Formulation respectively. Rebif®RebiDose™ pre-filled pens are ready for subcutaneous use only. For administration, follow the instructions provided in the REBIF Patient Leaflet.

Preparation of Solution: Liquid formulation in a pre-filled cartridge

The liquid formulation in a pre-filled cartridge is ready for use with the RebiSmart™ autoinjection device. For administration, follow the instructions given in the package leaflet and in the instructions manual which is provided with each RebiSmart™ autoinjection device. The pre-filled cartridge that contains 66 µg/1.5 mL is designed to deliver three doses of 22 µg/0.5 mL and the pre-filled cartridge that contains 132 µg/1.5 mL is designed to deliver three doses of 44 µg/0.5 mL of REBIF. The pre-filled cartridges are for subcutaneous use only.

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre

One medically-confirmed case of REBIF overdose has been reported in over 450,000 patient-years of exposure to REBIF, and concerned a subject who injected himself with seven syringes of REBIF 44 µg (total dose of 308 µg) in a suicide attempt. Symptoms included a modest rise in body temperature (to 37.5°C), diffuse erythema of the limbs and abdomen with rigors. The subject was treated with 500 mg of acetyl-salicylic acid dl-lysine intravenously, and haematologic screening revealed no abnormalities of hepatic function, thyroid function, or indices of inflammation. The event was not considered serious. There is no known antidote for an overdose of REBIF. The subject should be hospitalised for observation and appropriate supportive treatment administered.

ACTION AND CLINICAL PHARMACOLOGY

REBIF (Interferon beta-1a) is a purified, sterile glycoprotein product produced by recombinant DNA techniques and formulated for use by injection. The active ingredient of REBIF is produced by genetically engineered Chinese Hamster Ovary (CHO) cells. Interferon beta-1a is a highly purified glycoprotein that has 166 amino acids and an approximate molecular weight of 22,500 daltons. It contains a single N-linked carbohydrate moiety attached to Asn-80 similar to that of natural human Interferon beta.

The specific activity of REBIF is approximately 0.27 million international units (MIU)/μg Interferon beta-1a. The unit measurement is derived by comparing the antiviral activity of the product to an in-house natural hIFN-β NIH standard that is obtained from human fibroblasts (BILS 11), which has been calibrated against the NIH natural hIFN-β standard (GB 23-902-531).

General: Interferons are a family of naturally occurring proteins, which have molecular weights ranging from 15,000 to 21,000 daltons. Three major classes of interferons have been identified: alpha, beta, gamma. Interferon beta, Interferon alpha and Interferon gamma have overlapping yet distinct biologic activities.

Mechanism of Action

Interferon beta-1a acts through various mechanisms:

- Immunomodulation through an induction of cell membrane components of the major histocompatibility complex i.e., MHC Class I antigens, an increase in natural killer (NK) cell activity, and an inhibition of IFN-γ induced MHC Class II antigen expression, as well as a sustained reduction in TNF level.
- Antiviral effect through the induction of proteins like 2'-5' oligoadenylate synthetase and p78.
- Antiproliferative effect through direct cytostatic activity and indirect through antitumoral immune response enhancement.

The mechanism of action of REBIF in relapsing forms of multiple sclerosis is still under investigation.

STORAGE AND STABILITY

Refer to the date indicated on the labels for the expiry date. REBIF New HSA-free Formulation liquid in a pre-filled syringe, pre-filled cartridge or Rebif®RebiDose™ pre-filled pen should be stored at 2-8°C. REBIF New HSA-free Formulation in pre-filled syringes, pre-filled cartridges

or Rebif®RebiDose™ pre-filled pens may be stored for a limited period at room temperature (up to 25°C), but not more than 1 month. Do not freeze.

SPECIAL HANDLING INSTRUCTIONS

The liquid in the pre-filled syringe and Rebif®RebiDose™ pre-filled pen is ready for use.

The liquid in the pre-filled cartridge is ready for use with the RebiSmart™ autoinjection device. The RebiSmart™ autoinjection device should be stored in the device storage box when stored with a REBIF pre-filled cartridge.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Solution for injection in a pre-filled syringe

REBIF New HSA-free Formulation is available as a liquid formulation, in pre-filled syringes. Two package strengths are available: 22 µg /0.5 mL and 44 µg / 0.5mL. The pre-filled syringes are supplied as 3-packs. The pre-filled syringes are for subcutaneous use only.

Initiation packs are available for the initial 4 weeks of treatment (see DOSAGE AND ADMINISTRATION). The initiation pack contains six syringes of 8.8 µg/0.2 mL and six syringes of 22 µg/0.5 mL.

Rebif®RebiDose™ pre-filled pen

REBIF New HSA-free Formulation is available as a liquid formulation, in pre-filled pens called Rebif®RebiDose™. Two package strengths are available: 22 µg /0.5 mL and 44 µg / 0.5mL. It is supplied as a pack of 12 pens. Rebif®RebiDose™ pre-filled pens are for subcutaneous use only.

Initiation packs are available for the initial 4 weeks of treatment (see DOSAGE AND ADMINISTRATION). The initiation pack contains six pre-filled pens of 8.8 µg/0.2 mL and six pre-filled pens of 22 µg/0.5 mL.

Solution for injection in a pre-filled cartridge

REBIF New HSA-free Formulation is available as a liquid formulation, in pre-filled cartridges. Two package strengths are available: 66 µg/1.5 mL and 132 µg /1.5 mL. The pre-filled cartridge that contains 66 µg/1.5 mL is designed to deliver three doses of 22 µg/0.5 mL and the pre-filled cartridge that contains 132 µg/1.5 mL is designed to deliver three doses of 44 µg/0.5 mL of REBIF. The pre-filled cartridges are supplied as 4 pre-filled cartridges per box. The pre-filled cartridge is ready for use with the RebiSmart™ autoinjection device for subcutaneous administration only.

Initiation packs are available for the initial 4 weeks of treatment (see DOSAGE AND ADMINISTRATION). The initiation pack for the recommended therapeutic dose of 44 µg contains two cartridges of 132 µg/1.5 mL. The cartridges provided in the initiation pack will be injected with the RebiSmart™ autoinjection device. The RebiSmart™ autoinjection device is programmed to deliver 20% of the total dose during the initial 2 weeks of therapy (6 injections in total) and 50% of the total dose in the week 3 and 4 (6 injections in total).

The route of administration for Relapsing forms of Multiple Sclerosis is subcutaneous.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Proper or Common Name: BAN: Interferon beta-1a
INN: Interferon beta-1a
USAN: Interferon beta-1a

Structural Formula: The full amino acid sequence is as follows:

1 Met-Ser-Tyr-Asn-Leu-Leu-Gly-Phe-Leu-Gln
11 Arg-Ser-Ser-Asn-Phe-Gln-Cys-Gln-Lys-Leu
21 Leu-Trp-Gln-Leu-Asn-Gly-Arg-Leu-Glu-Tyr
31 Cys-Leu-Lys-Asp-Arg-Met-Asn-Phe-Asp-Ile
41 Pro-Glu-Glu-Ile-Lys-Gln-Leu-Gln-Gln-Phe
51 Gln-Lys-Glu-Asp-Ala-Ala-Leu-Thr-Ile-Tyr
61 Glu-Met-Leu-Gln-Asn-Ile-Phe-Ala-Ile-Phe
71 Arg-Gln-Asp-Ser-Ser-Ser-Thr-Gly-Trp-Asn*
81 Glu-Thr-Ile-Val-Glu-Asn-Leu-Leu-Ala-Asn
91 Val-Tyr-His-Gln-Ile-Asn-His-Leu-Lys-Thr
101 Val-Leu-Glu-Glu-Lys-Leu-Glu-Lys-Glu-Asp
111 Phe-Thr-Arg-Gly-Lys-Leu-Met-Ser-Ser-Leu
121 His-Leu-Lys-Arg-Tyr-Tyr-Gly-Arg-Ile-Leu
131 His-Tyr-Leu-Lys-Ala-Lys-Glu-Tyr-Ser-His
141 Cys-Ala-Trp-Thr-Ile-Val-Arg-Val-Glu-Ile
151 Leu-Arg-Asn-Phe-Tyr-Phe-Ile-Asn-Arg-Leu
161 Thr-Gly-Tyr-Leu-Arg-Asn

* Asn-80 N-glycosylation site

Molecular Weight: Approximately 22,500 daltons, identical to the natural human IFN-beta

Physical Form: IFN-beta-1a is a glycoprotein of 166 amino acids, it has 3 cysteines at positions 17, 31 and 141, a single disulphide bridge and an N-linked carbohydrate moiety primarily of the biantennary complex type attached to Asn-80.

Bulk hIFN-beta-1a is a clear, colourless to yellowish solution.

pH: 3.5 – 4.5 for the pre-filled syringe/3.5 - 4.1 for the pre-filled cartridge

COMPOSITION

Solution for injection in a pre-filled syringe and Rebif®RebiDose™ pre-filled pen

The liquid formulation is supplied in syringes and Rebif®RebiDose™ pre-filled pens containing 0.2 mL or 0.5 mL of solution. Each syringe contains Interferon beta-1a, mannitol, poloxamer-188, methionine, benzyl alcohol and 0.01 M sodium acetate buffer, as indicated in the table below.

Interferon beta-1a	Mannitol	Poloxamer-188	Methionine	Benzyl alcohol	0.01M Sodium acetate buffer
8.8 µg	9.0 mg	0.1 mg	0.024 mg	1.0 mg	q.s. to 0.2 mL
22 µg	22.5 mg	0.25 mg	0.06 mg	2.5 mg	q.s. to 0.5 mL
44 µg	22.5 mg	0.25 mg	0.06 mg	2.5 mg	q.s. to 0.5 mL

Solution for injection in a pre-filled cartridge

The liquid formulation is supplied in cartridges containing 1.5 mL of solution. Each cartridge contains Interferon beta-1a, mannitol, poloxamer-188, methionine, benzyl alcohol and 0.01 M sodium acetate buffer, as indicated in the table below.

Interferon beta-1a	Mannitol	Poloxamer-188	Methionine	Benzyl alcohol	0.01M Sodium acetate buffer
66 µg	83.25 mg	0.93 mg	0.22 mg	9.25 mg	q.s. to 1.5 mL
132 µg	83.25 mg	0.93 mg	0.22 mg	9.25 mg	q.s. to 1.5 mL

CLINICAL TRIALS

REBIF has been tested in five large, well-controlled studies of 2577 patients with 1539 on active therapy.

Study GF6789 (PRISMS: Prevention of Relapses and Disability by Interferon β-1a Subcutaneously in relapsing-remitting Multiple Sclerosis)

A total of 560 patients diagnosed with clinically definite or laboratory-supported relapsing-remitting multiple sclerosis EDSS 0-5 with at least a 1-year history before study entry and a history of 2 or more acute exacerbations in the 2 years prior to study entry were enrolled and randomized to 3 treatments (placebo, 22 µg REBIF, or 44 µg REBIF) in a ratio of 1:1:1. About 90% of patients completed the 2 years of treatment, and entered the extension phase: 167 from the original 44 µg tiw group, 167 from the original 22 µg tiw group, and 172 from the original placebo group. Prior to the start of the extension phase and without knowledge of study results, all patients from the original placebo group were re-randomized to receive either 22 or 44 µg tiw (85 randomized to 22 µg, and 87 randomized to 44 µg). The patients from the original 22 and 44 µg tiw groups continued their treatment as originally randomized. Of the original 560 patients

enrolled in the study, 445 (79%) remained in the study to the end of year 4. Less than 10 % of patients treated with active therapy withdrew for adverse events over 4 years.

REBIF 66 µg weekly (22 µg, 3x/week) and 132 µg weekly (44 µg, 3x/week) had a significant effect on the primary outcome measure by reducing relapse count compared to placebo. The relapse rate reduction continued during years 3 and 4 of therapy. Patients converting to REBIF from placebo demonstrated a 52-53% reduction in relapse rate compared to years on placebo. Over 4 years, REBIF 132 µg weekly was superior to REBIF 66 µg weekly in reducing relapses and although this difference did not achieve statistical significance (p= 0.069), neither was the study powered to demonstrate a significant difference between two active treatment arms. REBIF 132 µg weekly reduced the time to onset of progression of disability by 18 months compared to placebo crossover patients. High dose REBIF also reduced the number of EDSS 1-point changes made by a patient compared to placebo and compared to REBIF 66 µg weekly. Both doses strongly diminished the MRI active lesion development and the accumulation of lesion burden over time compared to placebo. REBIF 132 µg weekly was significantly more effective on MRI outcomes than REBIF 66 µg weekly. These data demonstrate a continued benefit of REBIF therapy up to 4 years and provide further evidence of a dose-effect relationship in MS. Whereas after two years of therapy, there had been a consistent trend in favour of the high dose which was statistically significant for MRI active lesions, further observation to 4 years showed that these trends continued and for the majority of endpoints became statistically significant. Finally, patients treated early (study start) attained more benefit at 4 years than those delaying treatment until the start of year 3.

Exacerbation rate during Years 1-4: ITT (Intent to treat)

Time Period	Estimated annual exacerbation rate		
	Placebo/ REBIF (n=187)	REBIF 66 µg weekly (n=189)	REBIF 132 µg weekly (n=184)
Years 1-4	1.02	0.80	0.72
	Treatment comparison		p-value*
Years 1-4	REBIF 132 µg vs. placebo/REBIF REBIF 66 µg vs. placebo/REBIF REBIF 66 µg vs. REBIF 132 µg		0.0001 0.0001 0.069
*Poisson Regression model with effects for treatment and center and treatment by center interaction			

Exacerbation count during years 1-2 and years 3-4 [all patients treated with placebo during years 1-2 (placebo switch patients)]

Time period	Statistics	Placebo/REBIF 66 µg weekly (n=85)	Placebo/REBIF 132 µg weekly (n=87)
Years 1-2	Mean (SD) Median Range	2.60 (2.11) 2 (0.00, 10.00)	2.57 (1.99) 2 (0.00, 8.00)
Years 3-4	Mean (SD) Median Range	1.21 (1.55) 1 (0.00, 9.00)	1.23 (1.24) 1 (0.00, 6.00)
Change from Years 1-2 to Years 3-4	Mean (SD) Median	-1.39 (2.47) -1	-1.34 (1.85) -1

	Range p-value*	(-10.00, 9.00) 0.0001	(-6.00, 2.00) 0.0001
*p-value from Wilcoxon Signed-Rank test			

Proportion of exacerbation-free patients at the end of year 4: ITT

Time Period	Number and proportion of exacerbation-free patients		
	Placebo/ REBIF n/N* (%)	REBIF 66 µg weekly n/N* (%)	REBIF 132 µg weekly n/N* (%)
Year 4	12/180 (6.67)	26/181 (14.36)	34/179 (18.99)
	Treatment comparison		p-value[#]
Year 4	REBIF 132 µg vs. placebo/ REBIF REBIF 66 µg vs. placebo/ REBIF REBIF 66 µg vs. REBIF 132 µg		0.0002 0.0158 0.0159
*Exclude patients lost to follow-up without any exacerbation count # p-value is from a logistic regression model with effects for treatment and center.			

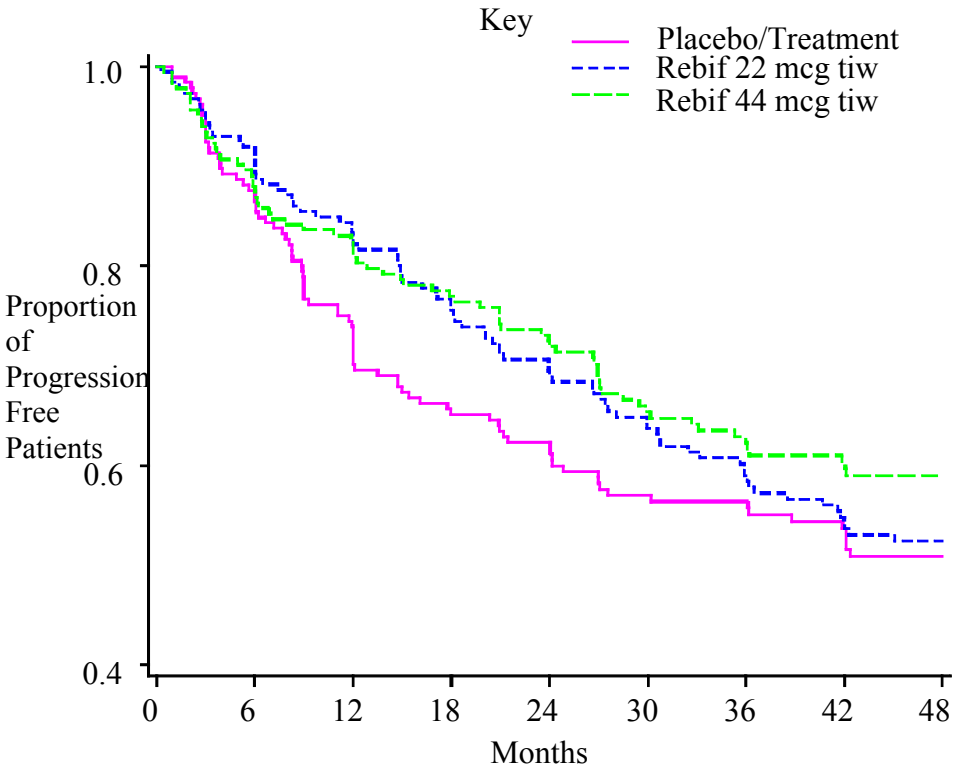
Time to first exacerbation (from 2 year database)

	Placebo	REBIF		p-value	
Efficacy parameters		66 µg/ week	132 µg/ week	REBIF 66 µg/wk vs Placebo	REBIF 132 µg/wk vs Placebo
Median time to first exacerbation (months)	4.5	7.6	9.6	0.0008	<0.0001

Time to second exacerbation (from 4 year database) and proportion with second relapses: ITT years 1-4

Time Period	Time to second exacerbation	Placebo/ REBIF N=187	REBIF 66 µg weekly n=189	REBIF 132 µg weekly n=184
Years 1-4	First quartile in days (months) Median in days (months)	216 (7.1) 449 (14.8)	329 (10.8) 702 (23.1)	359 (11.8) 965 (31.7)
		Treatment comparison		p-value[#]
Years 1-4		REBIF 132 µg vs. placebo REBIF 66 µg vs. placebo REBIF 132 µg vs. REBIF 66 µg		0.0001 0.0058 0.0460
The first quartile and median time to second exacerbation are Kaplan-Meier estimates. # p-value is from a Cox proportional hazards model with effects for treatment and center.				

Time to Confirmed Progression in Disability: Kaplan-Meier Curves by 3-Treatment Group



Time to progression for the ITT group shows that REBIF 132 µg weekly compared to placebo/treatment has a significant prolongation of the time to progression (p=0.047). This prolongation is 18 months for REBIF 132 µg weekly and 12 months for REBIF 66 µg weekly. There was no significant difference between the 132 µg/week dose and the 66 µg/week dose in the time to confirmed progression (p=0.333). Only the 132 µg/week dose was effective at reducing the time to confirmed EDSS progression in the ITT analysis. The time to first confirmed progression did not differ significantly between the 66 µg/week dose and the placebo crossover ITT group (p=0.289).

Proportion of progression-free patients at the end of Year 4: ITT

	Number and proportion of progression free patients		
Time Period	Placebo/REBIF n/N (%)	REBIF 66 µg weekly n/N (%)	REBIF 132 µg weekly n/N (%)
Year 4	74/161 (46%)	88/173 (51%)	92/164 (56%)
	Treatment comparison		p-value[#]
Year 4	REBIF 132 µg vs. placebo/REBIF REBIF 66 µg vs. placebo/REBIF REBIF 132 µg vs. REBIF 66 µg		0.0702 0.4101 0.3090
Excludes patients lost to follow-up without any confirmed progression. * p-value is from a logistic regression model with effects for treatment and center.			

Number of confirmed EDSS changes during Years 1-4: ITT

	Estimated confirmed annual progression rate *		
Time Period	Placebo/REBIF n=187	REBIF 66 µg weekly n=189	REBIF 32 µg weekly n=184
Years 1-4	0.24	0.22	0.17
	Treatment comparison		p-value[#]
Years 1- 4	REBIF 132 µg vs. placebo/REBIF REBIF 66 µg vs. placebo/REBIF REBIF 132 µg vs. REBIF 66 µg		0.0048 0.5227 0.0295
* from a Poisson regression model with effects for treatment and center.			

Effect on MRI scans in multiple sclerosis:

The MRI data show a highly significant effect of interferon therapy on BOD (burden of disease) and MRI activity measures, a highly significant dose effect on both BOD and MRI activity measures for patients treated with 132 µg weekly vs. 66 µg weekly after 4 years (p=0.009 and p<0.0001 respectively), an overall net reduction in BOD of 6.2% over 4 years in patients treated with 132 µg weekly, and that patients originally treated with the high dose of REBIF retain an overall significant benefit on BOD and activity measures compared to patients treated with placebo followed by 132 µg weekly for two years (p=0.003).

Percent change in burden of disease during Years 1-4: 4-treatment groups

Time period	Statistics	Placebo/REBIF 66 µg weekly	Placebo/REBIF 132 µg weekly	REBIF 66 µg/ week	REBIF 132 µg/ week
Years 1-4	N Mean (SD) Median Range	57 16.3 (31.0) 9.7 (-24.9, 151.5)	49 13.0 (31.0) 7.2 (-31.7, 124.6)	117 20.4 (71.3) 3.4 (-64.1, 351.0)	111 2.4 (34.5) -6.2 (-53.1, 188.1)
Time period	Treatment comparison			p-value*	
Years 1-4	REBIF 132 µg vs. placebo/REBIF 132 µg REBIF 66 µg vs. placebo/REBIF 66 µg REBIF 132 µg vs. REBIF 66 µg			0.0027 0.1125 0.0089	
* p-value from an ANCOVA on ranks with effects for treatment and center adjusting for baseline burden of disease					

Mean Number of T2 Active Lesions per Patient per Scan During Years 1-4 and 3-4: 4-Treatment Groups

Time Period	Statistics	Treatment Group			
		Placebo/REBIF 22 µg tiw	Placebo/REBIF 44 µg tiw	REBIF 22 µg tiw	REBIF 44 µg tiw
Years 1-4	N Mean (SD) Median Range	90 4.0 (4.9) 2.0 (0.0, 26.5)	92 4.0 (4.0) 2.7 (0.0, 19.0)	180 2.6 (4.0) 1.3 (0.0, 22.3)	180 1.5 (3.3) 0.5 (0.0, 27.5)
Years 3-4	n Mean (SD) Median Range	80 2.0 (3.3) 0.5 (0.0, 19.5)	75 1.8 (2.8) 1.0 (0.0, 12.0)	161 2.1 (3.5) 1.0 (0.0, 19.0)	150 1.2 (3.3) 0.0 (0.0, 23.5)
Time Period	Treatment Comparison			p-value (a)	
Years 1-4	REBIF 44 µg tiw vs Placebo/ REBIF 44 µg tiw REBIF 22 µg tiw vs Placebo/ REBIF 22 µg tiw REBIF 44 µg tiw vs REBIF 22 µg tiw			< 0.0001 0.0009 <0.0001	
Years 3-4	REBIF 44 µg tiw vs Placebo/REBIF 44 µg tiw REBIF 22 µg tiw vs Placebo/REBIF 22 µg tiw REBIF 44 µg tiw vs REBIF 22 µg tiw			0.0007 0.8006 <0.0001	
(a) p-value from and ANOVA on ranks with effects for treatment and center					

Requirement for steroids:
During the first two years, the proportion of patients requiring steroids for MS (excluding non-MS indications) was higher in the placebo group (more than 50%) than in either of the 2 REBIF groups (around 40% in each group). For patients on therapy for 4 years, the majority (76.4%) of steroid courses were for MS indications and over 90% of MS-related courses were for the treatment of exacerbations. Comparison of the rate of steroid use for actively treated patients over years 1-4 indicates a significantly lower rate in the 132 µg weekly group compared with the 66 µg weekly group ($p = 0.032$), providing supportive evidence of a dose-effect relationship for interferon therapy in MS.

Hospitalization for multiple sclerosis:
During the first two years, the observed mean number of hospitalizations for MS in the REBIF 66 and 132 µg weekly groups represented reductions of 21% and 48%, respectively, from that in the placebo group. The number of hospitalizations per patient was 0.48 for placebo, 0.38 for 22µg tiw and 0.25 for 44 µg tiw. Only the difference between 44 µg tiw and placebo was statistically significant ($p=0.038$). After four years on study, comparison of the hospitalization rates was performed on only the two groups receiving active therapy during years 1-4. It revealed no significant difference between groups with a mean value of 0.2 (median = 0) and 0.1(median = 0) hospitalizations/patient/year for 66 and 132 µg groups, respectively. The lack of significant difference could in part be due to the low number of events overall even though the rate of 66 µg is double that of 132 µg.

<u>Study GF7999 (OWIMS: Once Weekly Interferon beta-1a for Multiple Sclerosis)</u>

A total of 293 patients diagnosed with clinically definite or laboratory-supported relapsing MS with at least a one-year history, one or more exacerbations in the previous two years, 3 or more lesions on MRI at the pre-study scan, and an EDSS between 0 and 5.0 were enrolled and randomized to the 3 treatments (placebo, 22 µg REBIF, or 44 µg REBIF) in a ratio of 1:1:1. The patients were treated once weekly by subcutaneous injection. About 92% of patients completed 48 weeks, and very few patients withdrew from the study due to adverse events.

MRI as a measure of MS activity was evaluated in two ways: number of active lesions on T_2-weighted and T_1-weighted gadolinium enhanced MRI scans at Weeks 4, 8, 12, 16, 20 and 24 during treatment (and compared to baseline) and the burden of disease evaluated in all patients using the T_2-weighted sequence at the same time points. Further T_2-weighted MRIs were conducted at Weeks 48 and 96.

MRI disease activity:
A non-significant decrease compared with placebo in combined active lesions per patient per scan was noted for the 22 µg QW dose (29.6%), and a modest yet significant reduction was apparent with the 44 µg QW dose (53.5%). A dose-effect was also noted in other MRI parameters: the percentage of MRI scans showing combined active lesions was 50%, 45% and 33% for placebo, REBIF 22 µg QW and REBIF 44 µg QW (not statistically significant). Only the highest dose of REBIF was associated with a significant reduction in the proportion of active scans ($p=0.02$), T2 active lesions alone and T1-Gd enhancing lesions alone ($p<0.01$) as compared to placebo.

MRI disease burden:
Over 1 year of treatment, the change from baseline in burden of disease (total PD/T2 lesion area) differed significantly between both active treatment groups and placebo. Burden of disease increased from baseline in the placebo groups and decreased in the active treatment groups, (decreased by 2.0% and 1.4% for REBIF 22 µg and 44 µg QW, respectively, and no statistical difference was seen between the two groups).

Exacerbation frequency:
No reduction was evident with the 22 µg QW dose, and a 19% reduction was seen with the 44 µg QW dose, a difference that did not reach statistical significance ($p=0.21$), although the study was not powered for this outcome.

Conclusion:
While some modest MRI effect was seen, no significant clinical benefit was seen over the one-year study duration. This study suggests that once weekly administration at doses of 22 or 44 µg does not provide significant benefit in established RRMS.

Study GF6954 SPECTRIMS: Secondary Progressive Efficacy Clinical Trial of Recombinant Interferon beta-1a (Serono) in Multiple Sclerosis)

GF6954 was a large randomized, double-blind, placebo-controlled three-year study performed to examine the effects of REBIF on key outcome parameters in a patient population with more advanced multiple sclerosis disease.

GF6954 was conducted in 22 centres in Europe, Canada, and Australia. A total of 618 patients (229 men and 389 women) aged 18-55 years with secondary progressive MS (EDSS 3-6.5) were randomized to receive REBIF 66 µg weekly (22 µg, 3x/week), 132 µg weekly (44 µg, 3x/week) or matching placebo as SC injections for 3 years. To reduce the occurrence of anticipated side effects, the dose was increased gradually: 20% of the assigned dose was given for two to four weeks, then 50% for two to four weeks, and the full dose thereafter.

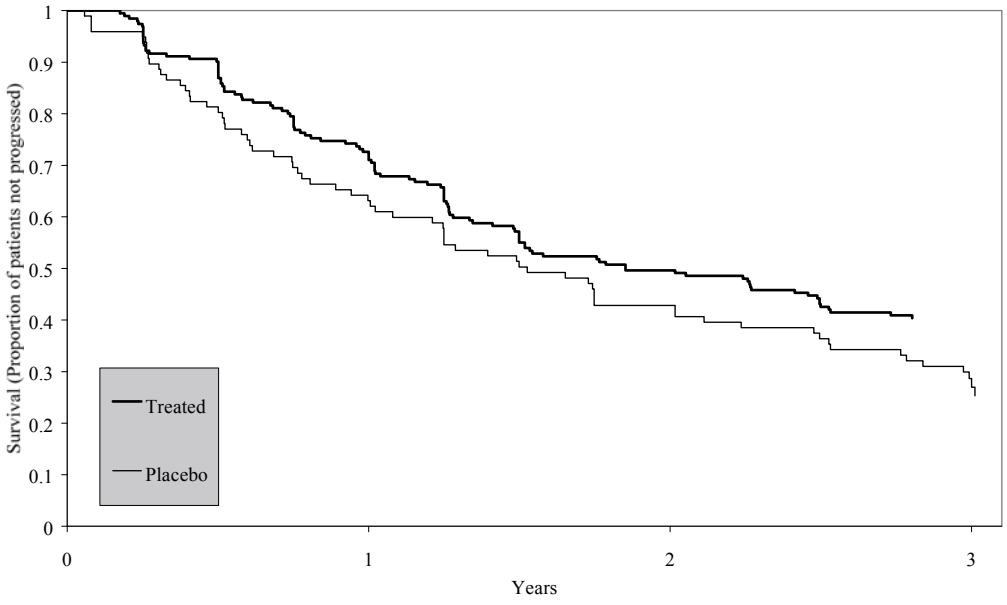
The primary efficacy endpoint was the effect of treatment on the deterioration of disability. The deterioration of disability was prospectively defined as the time to progression in disability by at least 1.0 point on the EDSS, or a deterioration of 0.5 point if the baseline EDSS was $\geq$ 5.5, confirmed at two consecutive visits three months apart. Secondary outcome measures included relapse count, MS lesion activity measures on MRI and the change in total MRI lesion burden. Several tertiary outcome measures were also evaluated.

A total of 571 patients (92.4%) completed the 3-year study, with 96.5% of all possible data collected. The proportions of patients completing were similar in the placebo (90.7%), REBIF 66 µg (93.3%), and REBIF 132 µg (93.1%) groups. Of the 112 patients who discontinued prematurely, only 47 (7.6% of the overall population) were lost to follow-up. All analyses were based on intent-to-treat principles.

Clinical endpoints:
The primary outcome measure was time to confirmed progression in disability, with the main comparison being between REBIF 132 µg tiw and placebo. Although a trend in favour of therapy was noted for the primary outcome, this difference was not statistically significant (p=0.146). An unexpected treatment by sex interaction was noted (p=0.035) which clouds interpretation.

The differential effect of treatment, based on whether or not patients had relapses during the 2 years before entry to the study, was also examined. After the sex-treatment interaction was identified, Serono investigated other possible baseline factors that could have possibly been related to the sex-treatment interaction. As part of this investigation, a number of clinically relevant baseline disease and demographic factors were each investigated in order to see if the sex-treatment interaction remained in the presence of these factors. As part of this process, it was noted that the number of relapses in the two years prior to the study also showed an interaction with treatment. The effect of treatment (both groups combined) on time to progression was analysed separately for "relapsing" and "non-relapsing" patients. This analysis indicated that the benefit for the combined treatment group was greater for relapsing patients (n=293) as opposed to non-relapsing patients (n=325). The hazard ratio for progression was 0.74 in the relapsing patients (p=0.055), while the hazard ratio was 1.01 in the non-relapsing patients (p=0.934). The corresponding odds ratios for proportion progressing in the treated relapsing and non-relapsing patients were 0.52 (p=0.027) and 1.07 (p =0.802), respectively.

Proportion of Patients progressing in Relapsing SPMS cohort: Combined Treatment groups compared to Placebo



Secondary endpoints:

The three secondary endpoints were exacerbation count per patient, MRI activity and burden of disease.

Table 1: Secondary endpoints results

	Placebo	REBIF 66 µg	REBIF 132 µg	p value 66 µg vs. placebo	p value 132 µg vs. placebo
Exacerbation count per patient at 3 years	2.05 ± 2.14	1.44 ± 1.63	1.46 ± 1.68	<0.001	<0.001
Relapse Rate (number per year)	0.71	0.50	0.50	<0.001	<0.001
T2 Active lesions per patient per scan (median)	0.67	0.20	0.17	<0.0001	<0.0001
T2 New lesions per patient per scan (median)	0.33	0.17	0.00	<0.0001	<0.0001
T2 Newly enlarging lesions per patient per scan (median)	0.17	0.00	0.00	<0.0001	<0.0001
Mean % T2 active scans	46%	28%	24%	<0.001	<0.001
% patients with no T2 active scans during treatment	24%	36%	41%	<0.001	<0.001

% Change in BOD (median)	+10.0	-0.5	-1.3	<0.001	<0.001

Both doses of REBIF conferred significant benefits, reducing the relapse rate by approximately 30% ($p<0.001$), reducing T2 activity by 70-75% ($p<0.001$), and the percentage change in BOD increased by 10% in the placebo group while decreasing by 1.3% and 0.5% in the low and high dose groups respectively ($p<0.001$ for both doses compared to placebo).

Allied to the T2 active lesion counts were significant effects of treatment on the proportion of active scans (66% reduction, $p<0.001$) and the proportion of patients who did not have any active lesions on their scans during the study (71% increase, $p<0.001$). The comparison of relapsing vs. non-relapsing patients revealed differences in both baseline MR characteristics and on-study behaviour and treatment response.

For the pre-study relapsing group of patients, treatment was more effective on the secondary outcome measures than for the non-relapsing sub-group, as occurred for the primary endpoint.

Table 2. Summary of on-study behaviour of Relapsing vs. Non-relapsing patients

	Relapsing pre-study			Non-relapsing pre-study		
Dose of REBIF	132 µg	66 µg	Placebo	132 µg	66 µg	Placebo
Total number of patients per group	98	97	98	106	112	107
% progressing at the end of the study	59	56	70	58	63	61
Relapse rate (number per year)	0.67***	0.57***	1.08	0.36	0.43	0.39
T2 activity (median)	0.17***	0.17***	1.17	0.17*	0.20	0.33
% Change in BOD (median)	-1.3***	-1.5***	11.8	-1.4***	1.2	8.4
***: $p<0.001$, **: $p<0.01$, *: $p<0.05$ compared with placebo						

Tertiary endpoints:

Other relapse related outcome measures including time to first relapse ($p=0.032$), time between first and second relapse ($p=0.002$), relapse severity ($p=0.049$), need for steroid treatment ($p=0.005$) and need for hospitalisation ($p=0.005$), were all favourably affected by REBIF 132 µg treatment. The only relapse related measure which was not significantly affected by 132 µg therapy was relapse duration.

Composite Score:

In a disorder such as MS, there are often multiple outcomes that may measure different impacts of the disease. These measures may be independent of one another but each may also be important to the overall benefit to the patient. A statistical method exists to combine these measures in one composite score. The value of this measure is that if all outcomes are favourably affected, a strong result is seen while if there are some outcomes with good effect and others without, the composite score will not show a treatment effect. In this study the five outcomes that were combined were time to progression, relapse count, T2 activity, change in BOD and IDSS

(Integrated Disability Status Score). The composite score of these outcomes showed a highly significant result ($p<0.001$) in favour of REBIF at both doses.

Study GF7480 (ETOMS: Early Treatment of Multiple Sclerosis)

A total of 309 patients with clinically probable or laboratory supported definite MSwere randomized in this clinical trial to receive either 22 µg of REBIF once a week by S.C. injections or matching placebo for 2 years. Patients were to have their first MS attack in the 3 months preceding study entry and have MRI scan strongly suggestive of MS. About 78% of these patients received the allocated treatment during the 2-year study period and 90% remained on study until the end of 2 years. Over 85% of patients stopping blinded study treatment did so after having their second MS attack on study. Very few patients withdrew due to adverse events.

The treatment efficacy was determined by comparing the rate of patients converting to clinically definite MS (CDMS) in the active arm versus placebo. MRI as a measure of disease activity was evaluated by the number of new T2 lesions and the proportion of patients without MRI active scans.

Conversion to CDMS:
A significant reduction in the proportion of patients converting to CDMS was observed in the treated group as compared to placebo (34% versus 45% respectively; $p=0.047$). The time to the second relapse increased significantly from 252 days in patients treated with placebo to 569 days for patients treated with REBIF ($p=0.034$). The annual relapse rate was significantly lower in the REBIF group (0.33) as compared to the placebo group (0.43) with a p value of 0.045.

MRI disease measures:
A significant decrease compared with placebo in the number of new T2 lesions was observed in patients treated with REBIF 22 µg once a week (median 2.0 versus 3.0 respectively; $p<0.001$). The proportion of patients with no MRI active scan was significantly higher in the REBIF group (16%) than in the placebo group (6%) with a significant statistical difference ($p=0.005$). No difference between the study groups was observed for T1 active lesions. The total T2 lesion volume as compared to the baseline value increased of 8.8% in the placebo group while a decrease of 13% was observed in patients treated with REBIF 22 µg once a week; the difference being statistically significant ($p=0.002$).

Conclusion:
This study demonstrated that 22 µg of REBIF injected once weekly significantly reduced the risk of a second relapse leading to the conversion to CDMS in patients with a first episode highly suggestive of MS. The clinical benefit was confirmed by a significant impact on MRI lesion activity and accumulation of disease burden.

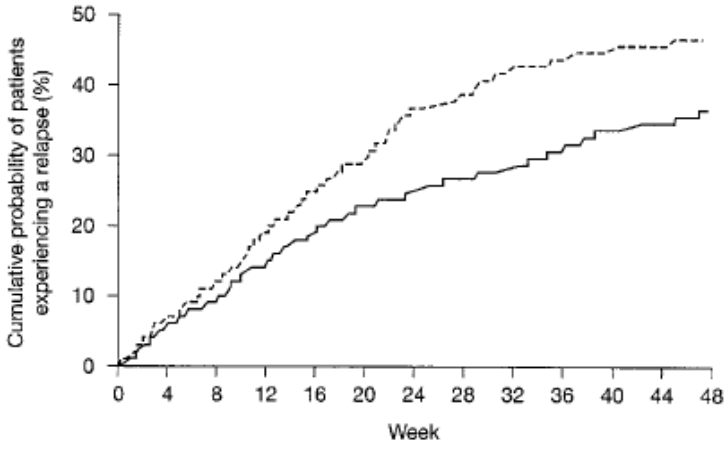
Study 21125 (EVIDENCE: Evidence for Interferon Dose Effect: European-North American Comparative Efficacy Study)

This was an open-label, randomized, multicenter, parallel-group comparator study. Patients eligible for inclusion were clinically definite or laboratory-supported definite relapsing-remitting multiple sclerosis patients, with EDSS scores ranging from 0 to 5.5, clinically active disease defined as two or more relapses in the previous two years, and had no previous treatment with interferon. Patients were randomized to treatment with either IFN beta-1a 44 µg tiw given by s.c. injection (REBIF) or IFN beta-1a 30 µg qw given by i.m. injection (AVONEX) for a duration of 48 weeks. Neurologists blinded to treatment performed clinical evaluations, and assessors blinded to treatment performed central MRI evaluations. The primary efficacy endpoint was the proportion of patients who remained exacerbation-free at 24 weeks. The principal secondary endpoint was the mean number of combined unique (CU) active MRI lesions per patient per scan defined as T1 or T2 active.

Patient population:
Of the 677 patients randomized, 339 patients received REBIF 44 µg SC three times a week (tiw) and 338 patients were assigned to AVONEX® 30 µg IM once a week (qw). One patient randomized to the AVONEX group did not receive treatment. No statistically significant differences were noted in demographics between the randomized groups. A high percentage of both REBIF and AVONEX patients completed 24 weeks (95.0% and 96.4% respectively) and 48 weeks (92.6% and 93.7% respectively) of treatment.

Efficacy results:
Patients treated with REBIF were significantly more likely to remain relapse free after 24 weeks than patients treated with AVONEX (74.9% vs. 63.3% respectively). The odds ratio adjusted for center was=1.9, $p<0.001$. Thirty-two percent fewer patients on REBIF relative to AVONEX experienced a new relapse during this 24-week period. After 48 weeks, a significantly higher proportion of REBIF treated patients remained relapse free as compared to the AVONEX treated patients (62% vs 52%, respectively, p=0.009; adjusted odds ratio=1.5, p=0.009).

Time to first relapse was prolonged over the course of the 48 week study for patients treated with REBIF, HR=0.7, 95% CI 0.55-0.88, p=0.003.



Hazard ratio = 0.70 (p = 0.003). Solid line = interferon (IFN) β-1a 44 µg tiw; dotted line = IFNβ-1a 30 µg once weekly.

The absolute count of relapses by severity was less for REBIF treated patients compared to AVONEX treated patients for each level of severity. The rate of steroid use to treat relapses for REBIF patients was approximately half that of AVONEX patients during the 24-week period (p=0.004).

The MRI outcome measures provided strong support for the clinical findings There was approximately a one-third relative reduction in MRI CU lesion activity for REBIF compared to AVONEX over the 24-week treatment period (0.8 vs 1.2 respectively, p<0.001). Other MRI activity measures showed similar benefits favoring REBIF over 24 and 48 weeks (p<0.001). The mean number of T1 enhancing and T2 active lesions per patient per scan was significantly reduced in the REBIF group (p<0.001). In addition, the mean proportion of patients with no active scans in the REBIF treated group was significantly higher for CU, T2 and T1 lesion assessments over 24 and 48 weeks (CU, T2, and T1, p<0.001).

Safety results:
Treatment was generally well tolerated in both treatment groups, with the majority of adverse events in both groups considered mild. The most common adverse events experienced in this study were well described consequences of IFN administration. They included flu-like symptoms (42% on REBIF and 49% on AVONEX; p = 0.089), injections site disorders (83% for REBIF and 28% for AVONEX; p<0.001), hepatic dysfunction (18% on REBIF and 10% on AVONEX; p=0.002), and leukopenia (6% on REBIF and <1% on AVONEX; p<0.05).

There were 21 patients that experienced serious adverse events in the REBIF group (6%) and 18 in the AVONEX group (5%), and 9 of the events were considered related to treatment. Treatment discontinuation because of adverse events occurred in 16 of the REBIF patients (4.7%) and 14 of the AVONEX patients (4.2%).

Conclusion:
This randomized controlled study demonstrated a greater efficacy of REBIF compared with AVONEX on both relapse and MRI outcomes over 48 weeks. Despite considerable differences in dosing regimens, the overall safety profiles of the treatments were similar with differences noted only in the incidence of specific safety events, and there was no dose-limiting toxicity.

Study 25632 (REBIF New HSA-free Formulation)

This was a multi-national, 96-week, single-arm, open-label study, with patients treated with the New HSA-free Formulation of REBIF three times a week. The primary objective of the study was to compare the immunogenicity of the new FBS-free/HSA-free interferon-beta-1a (REBIF) formulation (RNF) to historical data. Patients with a relapsing form of MS according to the McDonald criteria, an EDSS<6.0 and no prior interferon beta therapy were enrolled.

The data from study 25632 ("REBIF New HSA-free Formulation Cohort") is compared to historical data from the 44 µg tiw treatment arms of studies 6789 (PRISMS), 6954

(SPECTRIMS) and 21125 (EVIDENCE) (collectively referred to as the "Historical Cohort"). These studies were selected for comparison as they were pivotal controlled studies in patients with MS and included a treatment arm with identical dosing and route of administration. In study 21125, REBIF was also supplied in an identical format, pre-filled syringes. Studies 6789 and 21125 were conducted only in a relapsing MS population and study 6954 was conducted in an SPMS (with or without superimposed relapses) population.

Subject Disposition:
A total of 282 subjects were screened for trial entry, of whom 260 were enrolled between 25 Jan 2005 and 6 Jun 2005. All 260 enrolled subjects received trial medication and were included in the REBIF New HSA-free Formulation Cohort Safety Population; one had no post-baseline NAb data and was therefore excluded from the ITT Population. Considering the REBIF New HSA-free Formulation Cohort Safety Population, 207 subjects (79.6%) completed treatment and 224 subjects (86.2%) completed the trial. Adverse events were the most frequent reason for early discontinuation.

Demographics and Baseline Characteristics:
The median age of the 260 enrolled subjects in the REBIF New HSA-free Formulation Cohort was 34 (range: 18 to 58), and the majority of the subjects (71.5%) were female, which is consistent with the MS population. Almost all of the subjects were White (253/260 [97.3%]). The majority of subjects had RRMS (97.3%), while 6 subjects had SPMS with superimposed relapses and one subject had PPMS. Duration of MS varied across the subjects with a median of 5.45 years (range: 0.2 to 33.2).

Seven hundred and twenty-seven (727) subjects treated with interferon beta-1a 44 µg tiw were included in the Historical Cohort (Studies 6789, 6954 and 21125). The median age of subjects in the REBIF New HSA-free Formulation Cohort was similar compared to Study 6789 and lower compared to Study 6954 (this is expected as this was an SPMS population) and Study 21125. Sex and race were similar between the REBIF New HSA-free Formulation and Historical Cohorts. Studies 6789 (n=184) and 21125 (n=339) enrolled subjects with RRMS (median EDSS scores: 2.48 and 2.34, respectively). Study 6954 (n=204) enrolled subjects with SPMS (median EDSS scores: 5.35).

Primary Endpoint Analysis:
At Week 96 or last assessment, 45 subjects (17.4%) were NAb-postive. Immunogenicity results were comparable with historical Rebif studies; the proportion of subjects NAb-free at Week 96 was similar or better than that observed in previous trials.

Safety Results:

No new or unexpected safety concerns were identified during 96 weeks of study 25632. Adverse events reported over 96 weeks were consistent with those reported by the Historical Cohort.

Overall, 247 of the 260 subjects (95.0%) in the REBIF New HSA-free Formulation Cohort experienced 1979 AEs. The system organ classes with the largest proportion of treatment

emergent AEs were "general disorders and administration site conditions" (223 subjects, 611 events) and "nervous system disorders" (123 subjects, 316 events). The majority of adverse events in the REBIF New HSA-free Formulation Cohort were mild (86.5%) or moderate (60.8%) in severity, and the majority of AEs were classified as possibly (70.8%) or probably related to treatment (52.7%).

Fifteen of the 260 subjects (15/260 [5.8%]) in the REBIF New HSA-free Formulation Cohort experienced 20 SAEs. One event reported as serious in more than one subject was depression (3 events in 3 subjects). The system organ classes with the largest proportion of SAEs were injury, poisoning and procedural complications (5 events in 5 subjects), psychiatric disorders (4 events in 4 subjects), reproductive system and breast disorders (3 events in 3 subjects) and gastrointestinal disorders (2 events in 2 subjects); for other SOCs, serious events were reported in no more than one subject. Five of the 20 SAEs experienced by the REBIF New HSA-free Formulation Cohort were considered possibly or probably related, and 15 events were considered unlikely or unrelated to treatment. No deaths were reported during this trial.

Thirty-one subjects (11.9%) discontinued treatment permanently because of adverse events, citing a total of 52 events as reasons for treatment discontinuation. A further 3 subjects became pregnant during the trial and consequently stopped treatment (one underwent an induced abortion and the other two gave birth to healthy children). Influenza-like symptoms and laboratory abnormalities known to be associated with interferon-beta treatment (elevations in liver function tests and cytopenia) were prominent among reasons for discontinuation. Two subjects discontinued treatment because of local injection site symptoms.

To facilitate the analysis of the safety data, adverse events commonly associated with IFN-β were prospectively classified into a series of pre-specified AE groups of related MedDRA preferred terms which best represented the AE of interest. These pre-specified AE groups were defined as "injection site reactions", "flu-like syndrome", "cytopenias", "hepatic disorders", "thyroid disorders", "depression and suicidal ideation", "skin rashes" and "hypersensitivity reactions". For "hepatic disorders" the Standard MedDRA Query was used adapted to the study population. The pre-specified AE group "flu-like syndrome" included all reports of "influenza-like illness" as well as at least two pre-specified preferred terms representing typical flu-like symptoms occurring concomitantly, i.e. within a 48-hour interval. The frequencies of these pre-specified AE groups for the REBIF New HSA-free Formulation Cohort were compared to those reported by the Historical Cohort during 96 weeks of treatment.

Pre-specified Treatment Emergent Adverse Events reported up to Week 96 or Month 24 for both the REBIF New HSA-free Formulation Cohort and the Historical Cohort

Pre-specified group	25632 REBIF HSA-free 44 µg TIW	6789 REBIF 44 µg TIW Subjects	6954 REBIF 44 µg TIW Subjects	21125 REBIF 44 µg TIW Subjects

	Subjects (n=260) n (%)	(n=184) n (%)	(n=204) n (%)	(n=339) n (%)
Cytopenia	35 (13.5)	71 (38.6)	81 (39.7)	44 (13.0)
Depression and Suicidal Ideation	17 (6.5)	55 (29.9)	74 (36.3)	77 (22.7)
Flu Like Syndrome	186 (71.5)	127 (69.0)	113 (55.4)	166 (49.0)
Hepatic Disorders	37 (14.2)	70(38.0)	67 (32.8)	63 (18.6)
Hypersensitivity Reactions	15 (5.8)	22 (12.0)	19 (9.3)	19 (5.6)
Injection Site Reaction (ISR)	80 (30.8)	170 (92.4)	176 (86.3)	291 (85.8)
Skin Rashes	16 (6.2)	44(23.9)	52 (25.5)	56 (16.5)
Thyroid Disorders	11 (4.2)	16 (8.7)	10 (4.9)	25 (7.4)

Injection tolerability is a key factor in treatment compliance, especially for a product, which must be administered chronically, where injection site reactions are a frequent cause of treatment discontinuation. The development of the REBIF New HSA-free Formulation has focused on improving injection site tolerance through targeted formulation enhancements. A near 3-fold improvement in local tolerability was observed following administration of the new formulation when compared to historical data. After 96 weeks of treatment, the REBIF New HSA-free Formulation Cohort experienced a much lower rate for the pre-specified AE group "injection site reactions" (30.8%) than the Historical Cohort (85.8% to 92.4%).

Overall, 226 subjects (86.9%) in the REBIF New HSA-free Formulation Cohort experienced at least one "pre-specified" adverse event. Events related to the flu-like syndrome were reported in 71.5% of REBIF New HSA-free Formulation subjects and in 69.0%, 55.4% and 49.0% of subjects in protocols 6789, 6954 and 21125 respectively. Local injection site reactions were 30.8% of subjects in the REBIF Cohort compared with 85.8% to 92.4% in the historical trials. Events related to depression and suicidal ideation affected 6.5% of REBIF New HSA-free Formulation subjects compared with 22.7% to 36.3% in the historical trials. Rates of cytopenia and hepatic disorders in the REBIF New HSA-free Formulation Cohort were 13.5% for REBIF New HSA-free Formulation, 13.0% for 21125, 38.6% for 6789 and 39.7% for 6954; hepatic disorders: 14.2% for REBIF New HSA-free Formulation, 18.6% for 21125, 38.0% for 6789 and 32.8% for 6954. Skin rashes were 6.2% in the REBIF New HSA-free Formulation group and 16.5% - 25.5% in historical populations. Rates of hypersensitivity reactions and thyroid disorders observed in the REBIF New HSA-free Formulation group were similar to those seen in the previous trials (hypersensitivity reactions: 5.8% for REBIF New HSA-free Formulation and 5.6% to 12.0% in historical groups; thyroid disorders: 4.2% for REBIF New HSA-free Formulation and 4.9% to 8.7% in historical trials).

Most of the laboratory parameters remained constant and within normal limits during the 96 weeks of treatment. The distribution of the haematology and biochemistry worst post-baseline CTCAE grades shift analyses from baseline to Week 96 were similar between the REBIF New HSA-free Formulation Cohort and the Historical Cohort. The majority of worst post-baseline CTCAE grades for haematology and biochemistry parameters were Grade 0 or 1, but a low frequency of grade 2 to 4 haematological toxicity, principally neutropenia, and hepatic transaminase elevation was observed, comparable to that of the Historical Cohort.

Conclusions:

Safety data generated during 96 weeks of treatment in study 25632 indicate that the new HSA-free formulation of IFN-β-1a possesses a safety profile qualitatively similar to that of the previously marketed HSA-containing REBIF formulation, represented by the Historical Cohort.

Table 3: Summary of studies in multiple sclerosis							
Study No.	Design	Indication	No. patients	Dose of IFN-beta-1a	Route of administration	Assessments	Key results
GF 6613 (phase II)	Randomized, open label, comparative	Relapsing-remitting MS	68 males and females	11 µg, 33 µg 3x / week (untreated observation followed by treatment)	SC	Efficacy (incl. MRI)	• ↓ MS activity (MRI) • ↓ relapse rate
GF 6789 - PRISMS (phase III)	Randomized, double-blind, placebo-controlled	Relapsing-remitting MS	560 males and females	22 µg, 44 µg or placebo 3x / week	SC	Safety Efficacy (incl. MRI)	• ↓ Relapse count • ↑ % relapse-free patients • ↓ progression in disability • ↓ MRI MS activity/BOD • Dose response over 4 y • Development of NAb associated with ↓ efficacy
GF 6954 - SPECTRIMS (phase III)	Randomized, double-blind, placebo-controlled	Secondary Progressive MS	619 males and females	22 µg, 44 µg or placebo 3x / week	SC	Safety Efficacy (incl. MRI)	• No significant effect on disability • Significant ↓ in relapse rate • Significant ↓ in T2 active lesions/BOD
GF 6976 (phase III)	Randomized, double-blind, placebo-controlled	Secondary Progressive MS	371 males and females	22 µg or placebo 1x / week	SC	Safety Efficacy	• No significant effect on disability
GF 7480 - ETOMS (phase III)	Randomized, double-blind, placebo-controlled	Laboratory-supported definite or clinically probable MS	309 males and females randomized, 308 received treatment	22 µg or placebo 1x / week	SC	Safety Efficacy (incl. MRI)	• Delay in time to conversion to MS • Significant ↓ in relapse rate • ↓ MRI activity and BOD
GF 7999 - OWIMS (phase III)	Randomized, double-blind, placebo-controlled	Relapsing MS	293 males and females	22 µg, 44 µg or placebo 1x / week	SC	Safety Efficacy (incl. MRI)	• ↓ MRI active lesions • ↓ BOD

Table 3: Summary of studies in multiple sclerosis							
Study No.	Design	Indication	No. patients	Dose of IFN-beta-1a	Route of administration	Assessments	Key results
GF 8000 (continuation of GF 6613, phase II)	Randomized, open label comparative	Relapsing-remitting MS	67 males and females	11 µg or 33 µg 3x / week	SC	Safety Efficacy (incl. MRI)	• No significant ↓ in MRI active lesions • Significant ↓ in T1 volume, T2 lesion no., relapse rate and disease progression 33 compared to 11 µg
IMP 21125 EVIDENCE (phase III)	Randomized, open label comparative	Relapsing-remitting MS	677 males and females	REBIF 44 µg tiw (n=338) or AVONEX 30 µg qw (n=338)	SC vs IM	Safety Efficacy (incl. MRI)	• ↑ % relapse-free patients and ↓ MRI active lesions REBIF compared to AVONEX
IMP 22930 (LTFU to GF 6789, phase IV)	Non-randomized, retrospective and punctual LTFU	Relapsing-remitting MS (at inclusion in GF 6789)	560 patients in the original PRISMS Study (No. GF 6793); 382 of those 560 patients were in the PRISMS LTFU study (IMP 22930), and 274 of those 382 patients had EDSS data available.	None (patients could continue on REBIF or switch to another disease modifying drug)	NA	Safety Efficacy (incl. MRI)	• ↑ time to progression; ↓ progression rate, BOD, relapse rate in patients originally randomized to 44 µg compared to placebo
IMP 22982 (phase IIIb)	Randomized, open label comparative	Relapsing-remitting MS	1883 males and females	REBIF 44 µg tiw with or without Rebiject™Mini, an auto-injector	SC	Safety	• No significant difference between manual injection and autoinjector use in % patients with grade 3-5 injection site reaction after 3 months
IMP 24207 (phase IV)	Non-randomized, open label prospective	MS	163 males and females	REBIF 44 µg tiw and influenza vaccine (single injection)	SC	Safety Efficacy (immune response to infuenza vaccination)	• No significant difference between treated and non-treated subjects in immunologic response to influenza vaccination

Table 3: Summary of studies in multiple sclerosis							
Study No.	Design	Indication	No. patients	Dose of IFN-beta-1a	Route of administration	Assessments	Key results
IMP 24735 (phase IV)	Randomized, open label comparative	Relapsing-remitting MS	764 males and females	REBIF 44 µg tiw or Copaxone 20 mg qd	SC	Safety Efficacy (incl. MRI)	• In this study the primary outcome was time to first relapse during 96 weeks of therapy with either Rebif or Copaxone. The results were not statistically different between Rebif and Copaxone (p =0.643). • The Study population had much less disease activity than expected in order to have 80% power to detect a 30% difference in time to first relapse. • The safety profile of Rebif and Copaxone observed in this trial was consistent with the product labelling of these marketed products.
24810 (phase IV)	Single-arm, open label	Relapsing-remitting MS	460 males and females	REBIF 44 µg tiw (clone 484-39)	SC	Safety Immunogenicity Pharmacodynamics	• Enrolment completed • Study ongoing
25632 - REBIF New HSA-free Formulation (phase IIIb):	Single-arm, open label	Relapsing-remitting MS	260 males and females	REBIF 44 µg tiw (clone 484-39 in FBS-free/HSA-free formulation)	SC	Immunogenicity Pharmacodynamics Safety	• Immunogenicity results were comparable with historical Rebif studies; at Week 96 or last assessment, 45 subjects (17.4%) were NAb positive

DETAILED PHARMACOLOGY

Animal Pharmacology

Animal Pharmacodynamics:
A study of the cardiovascular and respiratory effects of REBIF (Interferon beta-1a) has been carried out in a conventional anaesthetized, instrumented model in the rat. Bolus IV doses up to 11 μg/kg showed no effects on cardiac function, ECG, blood pressure or respiration.

REBIF has been tested in toxicology studies up to 3 months in duration in rats and up to 6 months in monkeys. No toxicities except for transient pyrexia were observed.

Acute and repeated dose toxicity studies in rat and cynomolgus monkey showing that doses up to 73 μg/kg IV or IM did not produce clinical signs of dysfunction of the nervous system, gastrointestinal tract and smooth muscle, or dysfunction of their physiological control. These acute experiments also showed that REBIF 73 μg/kg IV and IM caused transient pyrexia (in monkeys, this also occurred in the 13-week study at REBIF doses of 0.25-3.67 μg/kg IV).

Animal Pharmacokinetics:
The single dose kinetics of REBIF has been examined in the rat and monkey to validate their use in toxicity tests as a model for man. The outcome of these studies is confirmed by the comparability of the findings with the results of single dose studies of other hIFN-betas, and the information gained from them about kinetics after multiple dosing. Absorption from an SC or IM site is rapid, the bioavailability is about 30-40% and some circulating IFN-beta persists up to 24 hours in the cynomolgus monkey dosed SC. Slight accumulation occurred after twice daily SC or IM dosing.

Human Pharmacology

The following studies are based on the original REBIF formulation (HSA formulation). This formulation is being replaced with the REBIF New HSA-free Formulation described below (see Clinical Pharmacology Program with the HSA-Free Formulation of Interferon beta-1a)

Human Pharmacokinetics:
In a randomized, double-blind, placebo-controlled, cross-over study, 12 healthy volunteers were injected with a single dose of 22 μg REBIF by the IV, IM or SC route. The pharmacokinetic analysis showed that 22 μg REBIF administered by the IV route follows a two-compartment model with a short distribution half-life of approximately 5 minutes and an elimination half-life of about 5 h, (similar results have also been reported for IFN-beta-1b). Following IM or SC administration, REBIF showed a rather flat plasma concentration/time curve, (similar to the data obtained in rats and monkeys), with an absolute bioavailability of about 15%.

The bioavailability of human interferon beta following single-dose subcutaneous and intramuscular administration of recombinant human interferon beta-1a was compared. The pharmacokinetic parameters showed a high intersubject variability, but intramuscular and subcutaneous routes of administration demonstrated equivalent bioavailability.

Human Pharmacodynamics:
2'-5'-oligoadenylate synthetase is an enzyme shown to be produced in response to exposure to IFN both in vitro and in vivo. In the above mentioned randomized study, it was found to increase following REBIF administration, however, the mean peak elevation was independent of the route of administration. The increase in (2-5A) synthetase levels was maximal at 24 h (earlier samples were not collected) and levels were still significantly elevated 72 h after REBIF injection.

Previous work has shown these biomarkers to be of value in assessing the pharmacodynamics of interferons, but the relationship between serum IFN-beta concentration, measurable pharmacodynamic response and the mechanism(s) by which REBIF exerts therapeutic effects in multiple sclerosis remains essentially unknown.

Additional studies investigated the importance of increased frequency of administration. The results confirmed that more frequent administration (i.e., three times per week vs. once per week) elicits the optimal pharmacologic response.

Clinical Pharmacology Program with the HSA-free Formulation of Interferon beta-1a:

Human Pharmacokinetics:
The clinical pharmacology program compared the New HSA-free Formulation of REBIF to the previously marketed HSA-containing formulation of REBIF at a dose of 44 µg interferon beta-1a. The biocomparability assessment that was performed as a secondary objective of the study was influenced by the high variability of the PK parameters. Standard bioequivalence criteria were not met for C_{max} or AUC_{last}.

The table below represents summary of the results of a non-compartmental analysis between the previously marketed formulation of REBIF and the current HSA-free formulation of REBIF, based on Study 25394 and 25827.

Summary of Pharmacokinetic Parameters for REBIF Formulations Non-compartmental Analysis of the Evaluable Population. Dose of 44 µg/kg

METRIC	PREVIOUS REBIF WITH HSA	CURRENT REBIF HSA-FREE
T_{max} (h) (n=38)		
Median	0.33	0.25
Range	0.033 - 168.00	0.167 - 0.50
C_{max} (IU/mL) (n=38)		
Mean ± SD	11.8 ± 8.41	19.8 ± 12.26

Geometric Mean	10.22	17.10
Median	10.25	17.15
Median Range	3.8 – 53.0	6.6 – 71.0
AUCT (IU/mL*hr) (n=38)		
Mean ± SD	107.6 ± 248.1	109.0 ± 137.0
Geometric Mean	31.9	54.0
Median	31.35	47.2
Median Range	2.1 - 1300	2.63 - 676
Half-life (hr) (n=12)		
Mean ± SD	12.78 ± 6.66	13.32 ± 11.32
Geometric Mean	10.85	9.80
Geometric CV (%)	72.8	104.46
Range	2.91 – 25.56	1.49 – 38.59

Special Tolerance Studies in Human: In an open-label study in patients with malignant diseases unresponsive to standard therapies, REBIF (Interferon beta-1a) was given as a bolus IV injection on day 1, followed one week later by daily subcutaneous injections for 28 consecutive days at the following dose levels: 5.5, 11, 22, 44, 66 or 88 μg/m^2. Preliminary results indicate that the maximum tolerated dose is probably 44 μg/m^2.

TOXICOLOGY

The following studies are based on the original REBIF formulation (HSA formulation).

Acute Toxicity

In formal single dose tests in the mouse and rat, REBIF (Interferon beta-1a) doses of 37 μg/kg and 73 μg/kg administered by intravenous or intramuscular route showed no effects during life or at autopsy.

In a similar experiment in cynomolgus monkeys, REBIF doses of 73 μg/kg IV or IM produced only a 1-2°C rise in rectal temperature from 2 to 7 hours. No other effects were seen in the acute studies.

Repeated Dose Toxicity

All these experiments have been affected by the development of neutralizing antibodies against Interferon beta-1a (and the HSA carrier protein in the formulation).

In the rat, the principal findings were of local trauma at the sites of the repeated injections and of higher titre antibodies against HSA than against Interferon beta-1a by week 4, and increasing in incidence at week 13. The experiment using the IV route was marred by a number of accidental deaths mainly due to respiratory infection probably associated with tail (injection site) damage. Injection site lesions occurred in all groups, including the control group, and may have been

possibly consequent on several factors, including needle trauma and a local allergic reaction to heterologous proteins (Interferon beta-1a and/or HSA) which predisposed to local infection with daily venipuncture. The infections spread then to the lungs (bacterial emboli). The studies in the cynomolgus monkeys showed brief pyrexia on day 1 after all IV doses (0.917 μg - 3.67 μg/kg), which was not present subsequently. The other findings were of anti-HSA and anti Interferon beta-1a antibodies appearing by week 4, and local trauma at the injection sites in all groups, including controls. No other findings were recorded.

Genetic toxicity testing

REBIF has been shown to be neither mutagenic nor clastogenic.

Reproduction toxicity testing

A teratology study in monkeys was performed showing that REBIF is not teratogenic. An increased risk of abortion has been attributed to the interferons, based on observations with interferon alpha and interferon beta-1b. No information is available on the effects of the interferon beta-1a on male fertility.

In addition, a single dose toxicity study in Cynomolgus monkeys and a local tolerability study in rabbits were conducted using the new formulation (HSA-free drug substance and HSA-free drug product, respectively). These studies did not reveal any additional toxicity concerns.

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PART III: CONSUMER INFORMATION

REBIF®
(Interferon beta-1a)

Solution for injection in pre-filled syringes

This leaflet is part III of a three-part "Product Monograph" published when REBIF was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about REBIF. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
Your doctor has prescribed REBIF (interferon beta-1a) treatment for your relapsing forms of Multiple Sclerosis (MS). Interferons belong to a family of proteins, which occurs naturally in the body, and help regulate the body's immune system, slowing the progression of disease.

As with any prescription medication, there are things you need to know about your treatment and what to expect from it. The following is important patient information about administering REBIF, and where to get more information should you have questions.

This information relates only to the use of REBIF in the treatment of relapsing forms of Multiple Sclerosis. If you have been prescribed any MS treatment other than REBIF, or if you have been prescribed REBIF for the treatment of any other condition, these instructions will not apply.

In clinical trials using a placebo comparator, REBIF has been demonstrated to:

- reduce the number of relapses
- reduce the severity of relapses
- slow disability progression (prolonging the time physical ability is maintained)
- reduce the need for steroids
- reduce the number of hospital visits for treatment of MS
- reduce T1 and T2 (burden of disease) MRI brain lesions

When it should not be used:
REBIF should not be used if:

- You have a known hypersensitivity to any component of the formulation,
- You are pregnant.

What the medicinal ingredient is:
Interferon beta-1a.

What the important nonmedicinal ingredients are:
Mannitol, benzyl alcohol, poloxamer-188, methionine

For a full listing of nonmedicinal ingredients see Part 1 of the product monograph.

What dosage forms it comes in:
REBIF is available as a solution (liquid) in a pre-filled syringe, for subcutaneous injection.

REBIF in pre-filled syringe is available in:

- 22 μg/0.5 mL (light green packaging, contains 3 syringes)
- 44 μg/0.5 mL (dark green packaging, contains 3 syringes)
- Initiation Pack designed for the first 4 weeks of treatment (yellow packaging, contains six syringes of 8.8 μg/0.2 mL and six syringes of 22 μg/0.5 mL).

WARNINGS AND PRECAUTIONS

BEFORE you use REBIF talk to your doctor or pharmacist if:

- You are pregnant, are thinking of becoming pregnant or if you are breast-feeding
- You have cardiac disease, severe renal failure or severe decrease in the development of blood cells
- You have a pre-existing seizure disorder.
- You have depression or suicidal thoughts

INTERACTIONS WITH THIS MEDICATION

No known drug interactions.

PROPER USE OF THIS MEDICATION

Usual dose:
The recommended dose is 44 μg given three times per week by subcutaneous injection. Your physician may reduce your dose to 22 μg three times per week if you are not able to tolerate the higher dose.

In order to reduce the likelihood of adverse events when beginning treatment, your doctor may titrate your dose gradually over the first four weeks up to the recommended dose of 44 μg three times per week. A dose of 8.8 μg three times weekly may be given for the first two weeks, followed by a dose of 22 μg three times weekly for the next two weeks. The full dose of 44 μg three times weekly would then be administered from week 5 onwards. To assist with your titration, the REBIF Initiation Pack is available.

Missed dose:
If you missed one dose of REBIF, continue to inject from the day of the next scheduled dose. You should not take a double dose to make up for the missed dose.

Overdosage:
If you have accidentally injected too much REBIF, do not panic. Simply contact your physician or healthcare professional for further instructions.

Administration:
When using REBIF always follow the basic principles of injection:

- Maintain sterile conditions
- Check medication
- Check expiry date
- Check dosage and instructions
- Rotate injection sites

The Six Steps of REBIF Subcutaneous Injection of Prefilled Syringes

Important: Store all injection materials and your REBIF out of the reach of children at all times.

STEP 1: Cleanse.

Before you start, wash your hands well with soap and water. It is important that your hands and the items you use be as clean as possible. Needles should not touch any surface except alcohol-cleaned skin; keep them capped prior to use. Make sure you use a new syringe each time you inject to avoid contamination. Dispose of all syringes in a puncture-resistant the disposal container

STEP 2: Assembly of injection materials
Find a clean area and lay out everything you will need (alcohol swabs, pre-filled syringe, disposal container). The injection can be given any where you feel comfortable. If you use your kitchen, ensure that all medicines and needles are kept well away from food.

STEP 3: Selecting and preparing the injection site

REBIF is injected just under the skin, in the layer of subcutaneous tissue. For your own comfort, you should avoid injecting into the same area too often. There are many possible injection sites on your body (e.g., arms, thighs, buttocks, abdomen) - refer to the diagram following these instruction or in your patient diary. It is difficult to self-inject into the back of the arm, you will likely require assistance if you choose this site. It is a good idea to plan an injection site rotation schedule and note it in a diary.

Note: Do not inject in any area in which you feel lumps, firm knots or pain. Consult your doctor or healthcare professional about any such abnormalities you find.
Use an alcohol swab to clean the skin at the selected injection site. Let the skin dry completely (15 to 20 seconds) to avoid possible burning, then discard the alcohol swab.

Optional: Autoinjector
If you have been given an autoinjector, you should follow the detailed instructions that are supplied with the unit. It is recommended that the REBIF syringe be used with the autoinjector. Many patients find that using the autoinjector, the treatment is easier to administer.

STEP 4: Preparing the REBIF injection

Remove the REBIF syringe from the blister pack by peeling back the paper covering from the arrowed end, and lifting the syringe by the barrel. DO NOT ATTEMPT TO PRESS THE SYRINGE OUT THROUGH THE PAPER FROM BELOW: this may damage the needle. Keep the needle cap on.

Carefully inspect the contents of the syringe. The liquid should be clear to slightly yellow. **Do not use if the liquid is cloudy, discoloured, or contains particles.** Do not worry if there are small bubbles remaining in the solution, because injecting them subcutaneously (that is, just under the surface of the skin) will do no harm.

STEP 5: Injecting REBIF subcutaneously

Your doctor or nurse will have already advised you where to inject (e.g., abdomen, front of thigh, back of arm, buttock). Refer to the injection sites diagram (keeping a diary of injection sites as they are used is recommended). Follow the detailed instructions below each time you inject REBIF pre-filled syringes. If you have questions about injecting REBIF, contact your healthcare professional or call Multiple Support Program at 1-888-MS-REBIF (1-888-677-3243).

Note: Your first REBIF injection should be done under the supervision of your doctor or an appropriately qualified healthcare professional.

Carefully remove the cap from the needle as follows:

- Hold the syringe vertically with the needle cap pointing upwards.
- Hold the syringe with the 4 fingers of the dominant hand (the one you write with) curled round the barrel and use the thumbnail to loosen the needle cap by lifting from under the lip of the needle cap.
- Lift the needle cap completely off the needle with a continuous vertical motion, so as not to bend the needle or touch the point.

Note: If the needle is visually bent upon removal of the cap, DO NOT ATTEMPT TO STRAIGHTEN, as doing so could result in contamination and/or a painful injection. If the needle is bent, dispose of it and use a new pre-filled syringe for your injection.

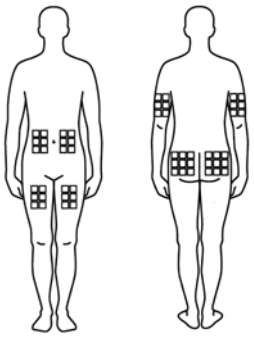
- Hold the syringe like a pencil or dart.
- With your other hand, gently pinch the skin around the injection site to lift it up a bit.
- Resting your wrist on the skin near the site, use a quick, firm motion to insert the needle straight into the skin at a 90° angle.
- Inject REBIF by gently pushing the plunger all the way down. Take as much time as you need to inject all of the solution.
- Remove the needle from the skin and gently massage the injection site with a dry cotton ball or gauze.

- Discard the used syringe, needle cap and cotton ball or gauze (if used) in the disposal unit.

STEP 6: Disposal of used items

Once you have finished your injection, immediately discard the needle in the disposal container provided. When the disposal container is full, consult your clinic for the safe disposal of its contents. They should not be disposed of in household garbage.

Possible Sites for Injection of REBIF



Additional advice:
It is important that you are familiar with the correct injection technique as outlined in these instructions before beginning your treatment with REBIF.

If the injection site bleeds afterwards, firmly press a cotton ball or gauze over the injection site immediately after removing the needle. This usually stops any further bleeding.

Local skin reactions are less likely to occur if you vary the injection site. If they do occur, they usually will disappear within a few days. In the meantime, icing the area may help reduce irritation. Swelling and irritation at the injection site may also be reduced by gently massaging the area for five minutes after the injection has been given. If a generalized rash develops, you should always report it to your doctor or nurse. Bruises may also occasionally occur at the injection site -- even when the injection has been given correctly -- but they will disappear.

Finally, remember that every treatment is individualized. REBIF has been carefully selected for you by your doctor according to your own specific needs. It is very important that you keep your appointments and follow your doctor's instructions, particularly with regard to the amount and frequency of the medication you are taking.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, REBIF can have side effects. The most common side effects are flu-like symptoms and injection site reactions. These symptoms are generally mild, are more common at the start of the treatment, and decrease with continued use. If any of these undesirable effects are severe or persist, you should contact your health care team.

In some cases, your physician may prescribe you a pain reliever (acetaminophen or ibuprofen) or may temporarily change your dose. You should not stop or alter the medication without your doctor's advice.

Should you develop multiple lesions and/or experience any break in the skin, which may be associated with swelling or drainage of fluid from the injection site, you should consult your physician, as a decision may be required to discontinue REBIF until healing has occurred

Other less common adverse events reported in association with interferon beta include diarrhea, loss of appetite, vomiting, inflammation of the liver, sleeping difficulty, dizziness, nervousness, itching, rash, nettle-rash, hair loss, dilatation of the blood vessels and palpitation.

Certain laboratory tests may change: the number of white blood cells or platelets may decrease and liver function tests may be disturbed. These changes are generally not noticed by the patient (no symptoms), are usually reversible and mild, and most often do not require particular treatment.

Interferons may cause your thyroid gland to 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.

Although uncommon, there is a potential risk of liver injury. As a safety precaution, your doctors will monitor your liver function with regular laboratory testing. If you notice any symptoms such as loss of appetite with malaise, fatigue, nausea, vomiting, abdominal pain, dark urine, please contact your doctor.

As with all interferons, female patients are recommended to take adequate contraception, as it is not known if interferons interfere with oral contraceptives, or if it interferes with the fetus. Please speak to your doctor if you are pregnant or are planning on becoming pregnant.

Depression, thoughts or attempt of suicide may occur in patients with multiple sclerosis. If you have any of these feelings, please contact your physician immediately. If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Common	Flu-like symptoms (headache, fever, chills, muscle aches, fatigue, nausea)	√		
	Injection site reactions [redness, swelling, discolouration, inflammation, pain, skin breakdown, and tissue destruction (necrosis)]	√		
Uncommon	Liver injury (symptoms: loss of appetite, nausea, vomiting, fatigue, abdominal pain, dark urine)		√	
	Depression		√	

This is not a complete list of side effects. For any unexpected effects while taking REBIF, contact your doctor or pharmacist.

HOW TO STORE IT

REBIF syringes should be stored refrigerated at 2°-8°C. REBIF syringes may be stored for a limited period of time at room temperature (up to 25°C), for up to 1 month. Do not freeze.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Report Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to:
    Canada Vigilance Program
    Health Canada
    Postal Locator 0701D
    Ottawa, Ontario
    K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Website at: www.healthcanada.gc.ca/medeffect

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be obtained by contacting the sponsor, EMD Serono, A Division of EMD Inc., Canada.

This leaflet was prepared by EMD Serono, A Division of EMD Inc., Canada, Mississauga, Ontario, Canada L5K 2N6

If you have any questions, call the Multiple Support Program at 1-888-MS-REBIF (1-888-677-3243).

Last revised: December 2010.

PART III: CONSUMER INFORMATION

REBIF® RebiDose™
(Interferon beta-1a)
Solution for injection in pre-filled pens

This leaflet is part III of a three-part "Product Monograph" published when REBIF was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about REBIF. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
Your doctor has prescribed REBIF (interferon beta-1a) treatment for your relapsing forms of Multiple Sclerosis (MS). Interferons belong to a family of proteins, which occurs naturally in the body, and help regulate the body's immune system, slowing the progression of disease.

As with any prescription medication, there are things you need to know about your treatment and what to expect from it. The following is important patient information about administering REBIF, and where to get more information should you have questions.

This information relates only to the use of REBIF in the treatment of relapsing forms of Multiple Sclerosis. If you have been prescribed any MS treatment other than REBIF, or if you have been prescribed REBIF for the treatment of any other condition, these instructions will not apply.

In clinical trials using a placebo comparator, REBIF has been demonstrated to:

- reduce the number of relapses
- reduce the severity of relapses
- slow disability progression (prolonging the time physical ability is maintained)
- reduce the need for steroids
- reduce the number of hospital visits for treatment of MS
- reduce T1 and T2 (burden of disease) MRI brain lesions

When it should not be used:
REBIF should not be used if:

- You have a known hypersensitivity to any component of the formulation,
- You are pregnant.

What the medicinal ingredient is:
Interferon beta-1a.

What the important nonmedicinal ingredients are:
Mannitol, benzyl alcohol, poloxamer-188, methionine

For a full listing of nonmedicinal ingredients see Part 1 of the product monograph.

What dosage forms it comes in:
Rebif®RebiDose™ is available as a solution (liquid) in a pre-filled pen, for subcutaneous injection.

Rebif®RebiDose™ pre-filled pen is available in:

- 22 μg/0.5 mL (light green packaging, contains 12 syringes)
- 44 μg/0.5 mL (dark green packaging, contains 12 syringes)
- Initiation Pack designed for the first 4 weeks of treatment (yellow packaging, contains six pens of 8.8 μg/0.2 mL and six pens of 22 μg/0.5 mL).

WARNINGS AND PRECAUTIONS

BEFORE you use REBIF talk to your doctor or pharmacist if:

- You are pregnant, are thinking of becoming pregnant or if you are breast-feeding
- You have cardiac disease, severe renal failure or severe decrease in the development of blood cells
- You have a pre-existing seizure disorder.
- You have depression or suicidal thoughts

INTERACTIONS WITH THIS MEDICATION

No known drug interactions.

PROPER USE OF THIS MEDICATION

Usual dose:
The recommended dose is 44 μg given three times per week by subcutaneous injection. Your physician may reduce your dose to 22 μg three times per week if you are not able to tolerate the higher dose.

In order to reduce the likelihood of adverse events when beginning treatment, your doctor may titrate your dose gradually over the first four weeks up to the recommended dose of 44 μg three times per week. A dose of 8.8 μg three times weekly may be given for the first two weeks, followed by a dose of 22 μg three times weekly for the next two weeks. The full dose of 44 μg three times weekly would then be administered from week 5 onwards. To assist with your titration, the REBIF Initiation Pack is available.

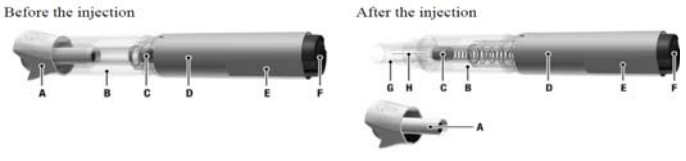
Missed dose:
If you missed one dose of REBIF, continue to inject from the day of the next scheduled dose. You should not take a double dose to make up for the missed dose.

Overdosage:
If you have accidentally injected too much REBIF, do not panic. Simply contact your physician or healthcare professional for further instructions.

Administration:
When using REBIF always follow the basic principles of injection:

- Maintain sterile conditions
- Check medication
- Check expiry date
- Check dosage and instructions
- Rotate injection sites

Below is a diagram that shows what the Rebif®RebiDose™ pre-filled pen looks like:



A. Cap
B. Transparent control area
C. Plunger
D. Label
E. Main body
F. Button
G. Safety guard
H. Needle

The Four Steps of REBIF Subcutaneous Injection of Rebif®RebiDose™ Pre-filled Pens

Important: Store all injection materials and your REBIF out of the reach of children at all times.

STEP 1: Cleansing and Assembly of injection materials

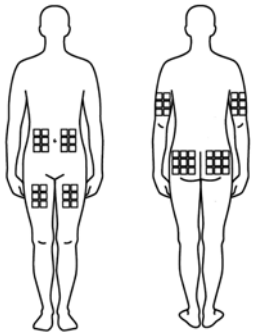
Wash your hands thoroughly with soap and water. Remove the pre-filled pen by peeling back the plastic covering. Check the appearance of REBIF through the transparent control area. It must be clear to opalescent, without particles and without any visible signs of deterioration. If there are particles 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 label (as indicated by "EXP"). You can also check the expiry date on the pen's outer box. Do not use the pre-filled pen if the expiry date has passed.

STEP 2: Selecting and preparing the injection site

REBIF is injected just under the skin, in the layer of subcutaneous tissue. For your own comfort, you should avoid injecting into the same area too often. There are many possible injection sites on your body (e.g., arms, thighs, buttocks, abdomen) - refer to the diagram following these instructions or in your patient diary. It is difficult to self-inject into the back of the arm, so you will likely require assistance if you choose this site. It is a good idea to plan an injection site rotation schedule and note it in a diary.

Note: Do not inject in any area in which you feel lumps, firm knots or pain. Consult your doctor or healthcare professional about any such abnormalities you find.
Use an alcohol swab to clean the skin at the selected injection site. Let the skin dry completely (15 to 20 seconds) to avoid possible burning, then discard the alcohol swab.

Possible Sites for Injection of Rebif® RebiDose™ pre-filled pen



STEP 3: How to inject with the Rebif®RebiDose™ pre-filled pen

Do not remove the cap until you are ready to administer the injection.

Hold the Rebif®RebiDose™ pre-filled pen by the main body and use your other hand to remove the cap.

Hold the Rebif®RebiDose™ pre-filled pen at a right angle (90 degrees) to the injection site. Push the pen down 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 the Rebif®RebiDose™ pre-filled pen pressed against the skin for at least 10 seconds in order to deliver the full medicinal product. It is not necessary to keep the button pressed down with your thumb after the injection has begun.

Remove the Rebif®RebiDose™ pre-filled pen from the injection site. The safety guard automatically surrounds the needle and locks into place to protect you from the needle.

Look through the transparent control area to make sure that the plunger has moved to the button as indicated in the figure. Visually check that there is no liquid left. If there is liquid left, not all the medicinal product has been injected and you should consult your doctor or nurse for assistance.

In case of any difficulties while using the Rebif®RebiDose™ pre-filled pen, please contact your doctor or nurse or call Multiple Support Program at 1-888-MS-REBIF (1-888-677-3243) for assistance.

STEP 4: Disposal of used items

Rebif®RebiDose™, solution for injection in a pre-filled pen is for single use only and should never be reused. Never put the needle cap back on the used Rebif®RebiDose™ pre-filled pen. Once you have finished your injection, immediately discard the Rebif®RebiDose™ pre-filled pen in an appropriate disposal unit. To avoid any injury, never insert your fingers in the opening of the safety guard covering the needle.

Additional advice:
It is important that you are familiar with the correct injection technique as outlined in these instructions before beginning your treatment with REBIF.

If the injection site bleeds afterwards, firmly press a cotton ball or gauze over the injection site immediately after removing the needle. This usually stops any further bleeding.

Local skin reactions are less likely to occur if you vary the injection site. If they do occur, they usually will disappear within a few days. In the meantime, icing the area may help reduce irritation. Swelling and irritation at the injection site may also be reduced by gently massaging the area for five minutes after the injection has been given. If a generalized rash develops, you should always report it to your doctor or nurse. Bruises may also occasionally occur at the injection site -- even when the injection has been given correctly -- but they will disappear.

Finally, remember that every treatment is individualized. REBIF has been carefully selected for you by your doctor according to your own specific needs. It is very important that you keep your appointments and follow your doctor's instructions, particularly with regard to the amount and frequency of the medication you are taking.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, REBIF can have side effects. The most common side effects are flu-like symptoms and injection site reactions. These symptoms are generally mild, are more common at the start of the treatment, and decrease with continued use. If any of these undesirable effects are severe or persist, you should contact your health care team.

In some cases, your physician may prescribe you a pain reliever (acetaminophen or ibuprofen) or may temporarily change your dose. You should not stop or alter the medication without your doctor's advice.

Should you develop multiple lesions and/or experience any break in the skin, which may be associated with swelling or drainage of fluid from the injection site, you should consult your physician, as a decision may be required to discontinue REBIF until healing has occurred

Other less common adverse events reported in association with interferon beta include diarrhea, loss of appetite, vomiting, inflammation of the liver, sleeping difficulty, dizziness, nervousness, itching, rash, nettle-rash, hair loss, dilatation of the blood vessels and palpitation.

Certain laboratory tests may change: the number of white blood cells or platelets may decrease and liver function tests may be disturbed. These changes are generally not noticed by the patient (no symptoms), are usually reversible and mild, and most often do not require particular treatment.

Interferons may cause your thyroid gland to 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.

Although uncommon, there is a potential risk of liver injury. As a safety precaution, your doctors will monitor your liver function with regular laboratory testing. If you notice any symptoms such as loss of appetite with malaise, fatigue, nausea, vomiting, abdominal pain, dark urine, please contact your doctor.

As with all interferons, female patients are recommended to take adequate contraception, as it is not known if interferons interfere with oral contraceptives, or if it interferes with the fetus. Please speak to your doctor if you are pregnant or are planning on becoming pregnant.

Depression, thoughts or attempt of suicide may occur in patients with multiple sclerosis. If you have any of these feelings, please contact your physician immediately. If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM			
Symptom / effect	Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
	Only if severe	In all cases	

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Common	Flu-like symptoms (headache, fever, chills, muscle aches, fatigue, nausea)	√		
	Injection site reactions [redness, swelling, discolouration, inflammation, pain, skin breakdown, and tissue destruction (necrosis)]	√		
Uncommon	Liver injury (symptoms: loss of appetite, nausea, vomiting, fatigue, abdominal pain, dark urine)		√	
	Depression		√	

This is not a complete list of side effects. For any unexpected effects while taking REBIF, contact your doctor or pharmacist.

HOW TO STORE IT

Rebif®RebiDose™ pre-filled pens should be stored refrigerated at 2°-8°C. Rebif®RebiDose™ pre-filled pens may be stored for a limited period of time at room temperature (up to 25°C), for up to 1 month. Do not freeze.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Report Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to:
    Canada Vigilance Program
    Health Canada
    Postal Locator 0701D
    Ottawa, Ontario
    K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Website at: www.healthcanada.gc.ca/medeffect

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be obtained by contacting the sponsor, EMD Serono, a Division of EMD Inc., Canada

This leaflet was prepared by EMD Serono, a Division of EMD Inc., Canada Mississauga, Ontario, Canada L5K 2N6

If you have any questions, call the Multiple Support Program at 1-888-MS-REBIF (1-888-677-3243).

PART III: CONSUMER INFORMATION

REBIF®
(Interferon beta-1a)

Solution for injection in pre-filled cartridges

This leaflet is part III of a three-part "Product Monograph" published when REBIF was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about REBIF. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
Your doctor has prescribed REBIF (interferon beta-1a) treatment for your relapsing forms of Multiple Sclerosis (MS). Interferons belong to a family of proteins, which occurs naturally in the body, and help regulate the body's immune system, slowing the progression of disease.

As with any prescription medication, there are things you need to know about your treatment and what to expect from it. The following is important patient information about administering REBIF, and where to get more information should you have questions.

This information relates only to the use of REBIF in the treatment of relapsing forms of Multiple Sclerosis. If you have been prescribed any MS treatment other than REBIF, or if you have been prescribed REBIF for the treatment of any other condition, these instructions will not apply.

In clinical trials using a placebo comparator, REBIF has been demonstrated to:

- reduce the number of relapses
- reduce the severity of relapses
- slow disability progression (prolonging the time physical ability is maintained)
- reduce the need for steroids
- reduce the number of hospital visits for treatment of MS
- reduce T1 and T2 (burden of disease) MRI brain lesions

When it should not be used:
REBIF should not be used if:

- You have a known hypersensitivity to any component of the formulation,
- You are pregnant.

What the medicinal ingredient is:
Interferon beta-1a.

What the important nonmedicinal ingredients are:
Mannitol, benzyl alcohol, poloxamer-188, methionine

For a full listing of nonmedicinal ingredients see Part 1 of the product monograph.

What dosage forms it comes in:
REBIF is available as a solution (liquid) in a pre-filled multi-dose cartridge, for subcutaneous injection.

REBIF in pre-filled cartridge is available as:

- 3 doses of 22 µg/0.5 mL in one cartridge (66 µg/1.5 mL). One box, light green packaging, contains 4 cartridges)
- 3 doses of 44 µg/0.5 mL in one cartridge (132µg /1.5mL). One box, dark green packaging, contains 4 cartridges)
- Initiation Pack, designed for the first 4 weeks of treatment. One box, yellow packaging, contains 2 cartridges of 132µg/1.5 mL.

WARNINGS AND PRECAUTIONS

BEFORE you use REBIF talk to your doctor or pharmacist if:

- You are pregnant, are thinking of becoming pregnant or if you are breast-feeding
- You have cardiac disease, severe renal failure or severe decrease in the development of blood cells
- You have a pre-existing seizure disorder.
- You have depression or suicidal thoughts

INTERACTIONS WITH THIS MEDICATION

No known drug interactions.

PROPER USE OF THIS MEDICATION

Usual dose:
The recommended dose is 44 µg given three times per week by subcutaneous injection. Your physician may reduce your dose to 22 µg three times per week if you are not able to tolerate the higher dose.

In order to reduce the likelihood of adverse events when beginning treatment, your doctor may titrate your dose gradually over the first four weeks up to the recommended dose of 44 µg three times per week. A dose of 8.8 µg three times weekly may be given for the first two weeks, followed by a dose of 22 µg three times weekly for the next two weeks. The full dose of 44 µg three times weekly would then be administered from week 5 onwards. To assist with your titration, the REBIF Initiation Pack is available.

Missed dose:
If you missed one dose of REBIF, continue to inject from the day of the next scheduled dose. You should not take a double dose to make up for the missed dose.

Overdosage:
If you have accidentally injected too much REBIF, do not panic. Simply contact your physician or healthcare professional for further instructions.

Administration:
When using REBIF always follow the basic principles of injection:

- Maintain sterile conditions
- Check medication
- Check expiry date
- Check dosage and instructions
- Rotate injection sites

The REBIF pre-filled cartridge is ready to be used with the RebiSmart™ autoinjection device. For instructions on how to load the cartridge into the RebiSmart™ autoinjection device and inject the solution please read the instructions provided with the RebiSmart™ autoinjection device.

Important: Store all injection materials and your REBIF out of the reach of children at all times.

STEP 1: Cleanse
Before you start, wash your hands well with soap and water. It is important that your hands and the items you use be as clean as possible. Needles should not touch any surface except alcohol-cleaned skin; keep them capped prior to use.

STEP 2: Assembly of injection materials
Find a clean area and lay out everything you will need (alcohol swabs, pre-filled cartridge, RebiSmart™ autoinjector device, disposal container). The injection can be given anywhere you feel comfortable. If you use your kitchen, ensure that all medicines and needles are kept well away from food.

STEP 3: Selecting and preparing the injection site
REBIF is injected just under the skin, in the layer of subcutaneous tissue. For your own comfort, you should avoid injecting into the same area too often. There are many possible injection sites on your body (e.g., arms, thighs, buttocks, abdomen) - refer to the diagram following these instruction or in your patient diary. It is difficult to self-inject into the back of the arm, you will likely require assistance if you choose this site. It is a good idea to plan an injection site rotation schedule and note it in a diary.

Note: Do not inject in any area in which you feel lumps, firm knots or pain. Consult your doctor or healthcare professional about any such abnormalities you find.

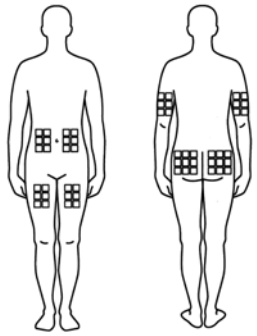
Use an alcohol swab to clean the skin at the selected injection site. Let the skin dry completely (15 to 20 seconds) to avoid possible burning, then discard the alcohol swab.

Carefully inspect the contents of the cartridge. The liquid should be clear to slightly yellow. **Do not use if the liquid is cloudy, discoloured, or contains particles.**

STEP 4: Injecting REBIF subcutaneously
Your doctor or nurse will have already advised you where to inject (e.g., abdomen, front of thigh, back of arm, buttock). Refer to the injection sites diagram (keeping a diary of injection sites as they are used is recommended). Follow the detailed instructions below each time you inject REBIF pre-filled cartridges. If you have questions about injecting REBIF, contact your healthcare professional or call Multiple Support Program at 1-888-MS-REBIF (1-888-677-3243).

Note: Your first REBIF injection should be done under the supervision of your doctor or an appropriately qualified healthcare professional. After receiving adequate training, you, a family member, friend or carer can use REBIF cartridges with the Rebismart™ autoinjector device to administer the medicine at home.

Possible Sites for Injection of 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 minimize 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 cartridge from the blister pack by peeling back the plastic covering.
- To place the cartridge in the device and perform the injection follow the instructions in the instruction manual provided with the RebiSmart™ autoinjector device. The manufacturer's instructions for using the device must be followed carefully for loading the cartridge, attaching the injection needle and administering REBIF.

- Ensure that the injection settings always correspond to the dose in the cartridge inserted in the RebiSmart™ autoinjector device.
- Before the injections 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.
- Place the RebiSmart™ device at a right angle (90°) against the skin
- Press the injection button.
- Wait for the injection to be completed.
- Remove the RebiSmart™ from the injection site.
- Remove and discard the needle according to the RebiSmart™ instruction manual.
- Gently massage the injection site with a dry cotton ball or gauze.

Full comprehensive instructions are provided in the instruction manual that is provided with the RebiSmart™ autoinjector device.

STEP 5: Disposal of used items
Once you have finished your injection, immediately discard the needle in the disposal container provided. When the disposal container is full, consult your clinic for the safe disposal of its contents. They should not be disposed of in household garbage.

Additional advice:
It is important that you are familiar with the correct injection technique as outlined in the instructions before beginning your treatment with REBIF.
If the injection site bleeds afterwards, firmly press a cotton ball or gauze over the injection site immediately after removing the needle. This usually stops any further bleeding.

Local skin reactions are less likely to occur if you vary the injection site. If they do occur, they usually will disappear within a few days. In the meantime, icing the area may help reduce irritation. Swelling and irritation at the injection site may also be reduced by gently massaging the area for five minutes after the injection has been given. If a generalized rash develops, you should always report it to your doctor or nurse. Bruises may also occasionally occur at the injection site -- even when the injection has been given correctly -- but they will disappear.

Finally, remember that every treatment is individualized. REBIF has been carefully selected for you by your doctor according to your own specific needs. It is very important that you keep your appointments and follow your doctor's instructions, particularly with regard to the amount and frequency of the medication you are taking.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, REBIF can have side effects. The most common side effects are flu-like symptoms and injection site reactions. These symptoms are generally mild, are more common at the start of the treatment, and decrease with continued use. If any of these undesirable effects are severe or persist, you should contact your health care team.

In some cases, your physician may prescribe you a pain reliever (acetaminophen or ibuprofen) or may temporarily change your dose. You should not stop or alter the medication without your doctor's advice.

Should you develop multiple lesions and/or experience any break in the skin, which may be associated with swelling or drainage of fluid from the injection site, you should consult your physician, as a decision may be required to discontinue REBIF until healing has occurred

Other less common adverse events reported in association with interferon beta include diarrhea, loss of appetite, vomiting, inflammation of the liver, sleeping difficulty, dizziness, nervousness, itching, rash, nettle-rash, hair loss, dilatation of the blood vessels and palpitation.

Certain laboratory tests may change: the number of white blood cells or platelets may decrease and liver function tests may be disturbed. These changes are generally not noticed by the patient (no symptoms), are usually reversible and mild, and most often do not require particular treatment.

Interferons may cause your thyroid gland to 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.

Although uncommon, there is a potential risk of liver injury. As a safety precaution, your doctors will monitor your liver function with regular laboratory testing. If you notice any symptoms such as loss of appetite with malaise, fatigue, nausea, vomiting, abdominal pain, dark urine, please contact your doctor.

As with all interferons, female patients are recommended to take adequate contraception, as it is not known if interferons interfere with oral contraceptives, or if it interferes with the fetus. Please speak to your doctor if you are pregnant or are planning on becoming pregnant.

Depression, thoughts or attempt of suicide may occur in patients with multiple sclerosis. If you have any of these feelings, please contact your physician immediately. If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM		
Symptom / effect	Talk with your doctor or pharmacist	Stop taking drug and

		Only if severe	In all cases	
Common	Flu-like symptoms (headache, fever, chills, muscle aches, fatigue, nausea)	√		
	Injection site reactions [redness, swelling, discolouration, inflammation, pain, skin breakdown, and tissue destruction (necrosis)]	√		
Uncommon	Liver injury (symptoms: loss of appetite, nausea, vomiting, fatigue, abdominal pain, dark urine)		√	
	Depression		√	

This is not a complete list of side effects. For any unexpected effects while taking REBIF, contact your doctor or pharmacist.

HOW TO STORE IT

REBIF cartridges should be stored refrigerated at 2°-8°C. REBIF cartridges may be stored for a limited period of time at room temperature (up to 25°C), for up to 1 month. Do not freeze.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Report Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to:
    Canada Vigilance Program
    Health Canada
    Postal Locator 0701D
    Ottawa, Ontario
    K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Website at: www.healthcanada.gc.ca/medeffect

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be obtained by contacting the sponsor, EMD Serono, A Division of EMD Inc., Canada.

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If you have any questions, call the Multiple Support Program at 1-888-MS-REBIF (1-888-677-3243).

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