AUSTRALIAN PRODUCT INFORMATION

REBIF® (interferon beta-1a)

1. NAME OF THE MEDICINE

Interferon beta-1a

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

REBIF is registered in two strengths of 22 microgram/0.5 mL (6 MIU) and 44 microgram/0.5 mL (12 MIU) of interferon beta-1a (rch) in pre-filled syringes for single dose use (0.5 mL) and in cartridges for multidose use (1.5 mL). There is also a pre-filled syringe presentation which includes a RebiDose® single use autoinjector (0.5 mL).
REBIF also contains mannitol, poloxamer, methionine, water for injections and benzyl alcohol. Sodium hydroxide and acetic acid are used for pH adjustment.
For the full list of excipients, see Section 6.1 List of excipients

3. PHARMACEUTICAL FORM

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

4. CLINICAL PARTICULARS
4.1. THERAPEUTIC INDICATIONS

REBIF is indicated for the treatment of:

- Patients with a single demyelinating event in the central nervous system with an active inflammatory process, if alternative diagnoses have been excluded, and if they are determined to be at high risk of developing clinically definite multiple sclerosis. High risk can be inferred from cerebral MRI with 2 or more lesions suggestive of demyelination.
- Ambulatory patients with multiple sclerosis who have experienced two or more relapses within the last 2 years.

REBIF therapy should not be initiated in secondary progressive MS patients who no longer experience relapses.

4.2. DOSE AND METHOD OF ADMINISTRATION

Treatment should be initiated under supervision of a physician experienced in the treatment of multiple sclerosis.
When first starting treatment with REBIF, it is recommended that the dose be gradually increased in order to allow tachyphylaxis to develop thus reducing the risk of adverse reactions. It is recommended that 20% of the total dose be administered during the first two weeks of therapy, 50% of the total dose be administered in weeks three and four, and the full dose from the fifth week onwards.
Prior to injection and for an additional 24 hours after each injection, an antipyretic analgesic is advised to decrease flu-like symptoms associated with REBIF administration.

Dosage

First Demyelinating Event
The recommended dose for patients who have experienced a first demyelinating event is 44 micrograms (12 MIU) REBIF given three times per week by subcutaneous injection.
Upon conversion to relapsing multiple sclerosis these patients must be treated according to the recommended dosage for relapsing multiple sclerosis.

Relapsing Multiple Sclerosis
The recommended dose for patients with relapsing multiple sclerosis is 44 microgram (12 MIU) REBIF given three times per week by subcutaneous injection. REBIF 22 microgram (6 MIU) given three times per week by subcutaneous injection is recommended for patients who cannot tolerate the higher dose.

Please refer to Section 4.4 Special Warnings and Precautions for Use regarding regular liver function test monitoring of patients.

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

Paediatric population
There is limited experience with REBIF in children under 12 years of age with multiple sclerosis.

No formal clinical trials or pharmacokinetic studies of REBIF have been conducted in children or adolescents. However, limited published data suggest that the safety profile in adolescents from 12 to 16 years of age receiving REBIF 22 micrograms subcutaneous three times per week is similar to that seen in adults.

Method of Administration

Allow REBIF solution to reach room temperature before administration. The solution should not be administered if it contains particles and is not clear.

REBIF cartridges intended for multidose use in one patient only must be used with RebiSmart® provided separately. Only validated needle sizes as specified in the Instructions for Use supplied with the RebiSmart device should be used. Refer to the Instructions for Use provided with RebiSmart. Cartridges should be discarded within 21 days after first use.

4.3. CONTRAINDICATIONS

REBIF is contraindicated in patients with a known hypersensitivity to natural or recombinant interferon beta, or to any other component of the formulation (listed under Section 2 Qualitative and Quantitative Composition).

REBIF is contraindicated in women who are or plan to become pregnant while on therapy, patients with severe depressive disorders and/or suicidal ideation, and in epileptic patients with seizures not adequately controlled by treatment.

4.4. SPECIAL WARNINGS AND PRECAUTIONS FOR USE

General

Patients should be informed of the most common adverse reactions associated with REBIF administration, including symptoms of the flu-like syndrome. These symptoms tend to be most prominent at the initiation of therapy and decrease in frequency and severity with continued treatment.

REBIF should be used under the supervision of a physician. The first injection should be performed under the supervision of an appropriately qualified healthcare professional.

Caution must be used and close monitoring considered when administering REBIF to patients with severe renal and hepatic failure, patients with severe myelosuppression and depressive patients. There are currently no data available on the use of REBIF in patients with severe hepatic or renal impairment or with myelosuppression.

Only sparse safety and efficacy data are available from non-ambulatory patients with multiple sclerosis.

Thrombotic microangiopathy

Cases of thrombotic microangiopathy, manifested as thrombotic thrombocytopenic purpura (TTP) or haemolytic uraemic syndrome (HUS) have been reported, including fatal cases.

Monitoring of early symptoms in all patients e.g. new onset hypertension, impaired renal function and thrombocytopenia is recommended. Prompt treatment of TTP/HUS is required and discontinuation of treatment with REBIF is recommended.

Depression and Suicidal Ideation

REBIF should be administered with caution to patients with previous or current depressive disorders in particular to those with antecedents of suicidal ideation. Depression and suicidal ideation are known to occur at an increased frequency in the multiple sclerosis population and in association with interferon use.

Patients treated with REBIF must be advised to immediately report any symptoms of depression and/or suicidal ideation to their prescribing physician. Patients exhibiting depression must be monitored closely during therapy with REBIF and treated appropriately. Cessation of therapy with REBIF must be considered.

Hepatic Dysfunction and Injury

Interferon therapy is frequently associated with asymptomatic elevations of hepatic transaminases (particularly ALT). In clinical trials with REBIF, the majority of these elevations are below 2.5 times the upper limit of normal [ULN] with 1 3% of patients developing elevations above 5 times ULN. They are reversible with dose reduction or discontinuation of therapy but may resolve while therapy continues. Serum ALT levels must be monitored prior to the start of therapy, at months 1, 3 and 6 on therapy and periodically thereafter in the absence of clinical symptoms. 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 with REBIF must be considered if ALT rises above 5 times the ULN and gradually re-escalated when enzyme levels have normalised. Treatment with REBIF must be stopped if icterus or other clinical symptoms of liver dysfunction appear (see also Section 4.8 Adverse Effects (Undesirable Effects)).

Beta-interferons including REBIF, have a potential for causing severe liver injury, including acute hepatic failure. The mechanism for the rare symptomatic hepatic dysfunction is not known. No specific risk factors have been identified.

Patients should be informed of the symptoms suggesting liver dysfunction, such as loss of appetite accompanied by other symptoms such as malaise, fatigue, nausea, vomiting, abdominal pain, dark urine, jaundice or pruritis. They should be advised to consult with a physician immediately if such symptoms arise.

Seizure Disorder
Caution must be exercised when administering REBIF to patients with pre existing seizure disorders (see also Section 4.5 Interactions With Other Medicines and Other Forms of Interactions). For patients without a pre existing seizure disorder who develop seizures during therapy with REBIF, an aetiological basis should be established and appropriate anti-convulsant therapy instituted prior to resuming REBIF treatment.

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

Injection Site Necrosis
Injection site necrosis has been reported in patients using REBIF. To minimise the risk patients must be advised to:

- use an aseptic injection technique
- rotate the injection sites with each dose

The procedure for self-administration by the patient should be reviewed periodically especially if injection site reactions have occurred. If the patient experiences any break in the skin, which may be associated with swelling or drainage of fluid from the injection site, the patient must be advised to consult with their physician before continuing injections with REBIF. If the patient has multiple lesions, REBIF must be discontinued until healing has occurred. Patients with single lesions may continue provided that the necrosis is not too extensive.

Immune Reactions (including hypersensitivity, autoimmunity, immunogenicity)
Anaphylaxis has been reported as a rare complication of REBIF use. Other allergic reactions have included skin rash, angio-oedema, 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
In a controlled clinical study, between 14% and 23% of patients developed neutralising antibodies against REBIF by the end of 4 years of therapy, most developing in the first 12 to 18 months.

Development of neutralising antibodies (NAb) has been associated with a reduced benefit, as evaluated by MRI parameters and clinical relapse rate. The full significance of NAb development in individual cases remains uncertain. Neutralising antibodies are cross-reactive to different forms of interferon beta.

Treatment decisions should be based on the complete clinical assessment of efficacy by the clinician in view of available data regarding NAb. A poor clinical course associated with the presence of persistent NAb should prompt reconsideration of interferon therapy.

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

Effects on 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, liver enzyme monitoring, complete and differential white blood cell counts, platelet counts and blood chemistries, are recommended during REBIF therapy. Blood cell counts are recommended at regular intervals (1, 3 and 6 months) following introduction of REBIF therapy and then periodically thereafter in the absence of clinical symptoms.

Thyroid disorder
As with other interferons, patients being treated with REBIF may occasionally develop new or worsening thyroid abnormalities. Thyroid function testing is recommended at baseline and if abnormal, every 6-12 months following initiation of therapy. If normal, routine testing is not needed but testing must be performed if clinical findings of thyroid dysfunction appear (see also Section 4.8 Adverse Effects (Undesirable Effects)).

Paediatric Use
There is limited experience with REBIF in children under 12 years of age with multiple sclerosis.

No formal clinical trials or pharmacokinetic studies of REBIF have been conducted in children or adolescents. However, limited published data suggest that the safety profile in adolescents from 12 to 16 years of age receiving REBIF 22 micrograms subcutaneous three times per week is similar to that seen in adults.

Use in the Elderly
No dedicated studies have been conducted in elderly patients.

4.5. INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

No formal drug interaction studies relevant to approved indications have been conducted with REBIF in humans.

Clinical trial experience indicates that patients with multiple sclerosis can receive concomitant therapy with REBIF and corticosteroid or ACTH treatment during relapses. Antidepressant and oral contraceptive therapy were co-administered in the clinical trial with no increase in adverse effects.

However, interferons have been reported in the literature to reduce the activity of hepatic cytochrome P450-dependent enzymes in humans and animals. Exploratory results from a study in 8 normal volunteers on the effect of REBIF on the CYP450 system showed an effect on

CYP1A2 only, however this study was of limited power. The effect of interferon beta on the CYP450 system suggests a down-regulation of CYP1A1 and CYP1A2 in rats and of CYP1A1, CYP2B1 and CYP3A and total hepatic cytochrome P450 in mice. Caution should be exercised when administering REBIF in combination with medicinal products that have a narrow therapeutic index and/or are dependent on the hepatic cytochrome P450 system for clearance, for example:

- antiepileptics, which may include phenytoin, carbamazepine, sodium valproate, benzodiazepines (such as clonazepam); and
- some classes of antidepressants, which may include MAOI, SSRIs, tricyclic antidepressants, etc.

As with all interferon products, proper monitoring of patients is required if REBIF is given in combination with myelosuppressive agents.

Immune response to influenza vaccine is maintained in patients with multiple sclerosis receiving REBIF.

4.6. FERTILITY, PREGNANCY AND LACTATION

Effects on Fertility
The effects of REBIF on fertility have not been investigated. However, in monkeys, exposure to interferon beta-1a at more than 18 times the maximum likely clinical exposure (based on AUC), had no effect on the menstrual cycle or serum oestradiol levels in females; or sperm function, motility, count, morphology or serum testosterone levels in males.

Use in Pregnancy
Initiation of treatment with REBIF is contraindicated during pregnancy (Category D).

There are no studies of REBIF in pregnant women. At high doses in monkeys, abortifacient effects were observed with other interferons. When administered to pregnant monkeys during the period of organogenesis, interferon beta-1a was not teratogenic. However, the results of this study may have been compromised by the production of low levels of antibodies to interferon beta-1a in the test monkeys.

Fertile women receiving REBIF must take appropriate contraceptive measures. Patients planning for pregnancy and those becoming pregnant should be informed of the potential hazards of interferons to the foetus and REBIF should be discontinued.

Use in Lactation
It is not known whether interferon beta-1a is excreted in human milk. Because of the potential for serious adverse reactions in breastfed infants, a decision should be made either to discontinue breastfeeding or to discontinue REBIF therapy.

4.7. EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

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

4.8. ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Summary of the safety profile

The highest incidence of adverse reactions associated with REBIF therapy is related to flu like syndrome. Flu-like symptoms tend to be most prominent at the initiation of therapy and decrease in frequency with continued treatment. Approximately 70% of patients treated with REBIF can expect to experience the typical interferon-related flu-like syndrome within the first six months after starting treatment. Prior to injection and for an additional 24 hours after each injection, an antipyretic analgesic is advised to decrease flu-like symptoms associated with REBIF. Approximately 30% of patients will also experience reactions at the injection site, predominantly mild inflammation or erythema.

Asymptomatic increases in laboratory parameters of hepatic function and decreases in blood cells are also common. This includes decreases in white blood cell counts (leucopenia, lymphopenia, granulocytopenia), red cells and thrombocyte counts and alterations in liver function tests such as elevated ALT and AST (see also Section 4.4 Special Warnings and Precautions for Use). These effects are usually mild and reversible.

Tachyphylaxis with respect to most side effects is well recognised.

Injection site reactions are commonly encountered and are usually mild and reversible. Rare cases of skin ulceration/necrosis at the site of injection have been reported with long term REBIF treatment (see also Section 4.4 Special Warnings and Precautions for Use).

Occasional thyroid dysfunction, most often presenting as hypothyroidism or hyperthyroidism, and generally transient and mild, may occur during the first year of treatment, particularly in patients with pre-existing thyroiditis (see also Section 4.4 Special Warnings and Precautions for Use).

In case of severe or persistent adverse reactions, the dose of REBIF may be temporarily lowered or interrupted or the treatment discontinued, at the discretion of the physician.

Clinical Trials

PRISMS and SPECTRIMS Studies

A pooled analysis of the adverse events reported at a cut-off of 10% active vs. placebo in the PRISMS and SPECTRIMS clinical studies with the original formulation during the 2 first years of placebo-controlled treatment.

Table 1

System Organ Class Preferred Term	Placebo Subjects (n=392) n (%)	REBIF 22 mcg/tiw (n=398) n (%)	REBIF 44 mcg/tiw (n=388) n (%)
General disorders and administration site conditions			
Influenza like illness	155 (39.5)	156 (39.2)	166 (42.8)
Injection site erythema	52 (13.3)	205 (51.5)	205 (52.8)
Fatigue	128 (32.7)	137 (34.4)	163 (42.0)
Injection site reaction	25 (6.4)	99 (24.9)	128 (33.0)
Pyrexia	61 (15.6)	81 (20.4)	98 (25.3)
Injection site pain	64 (16.3)	82 (20.6)	91 (23.5)

System Organ Class Preferred Term	Placebo Subjects (n=392) n (%)	REBIF 22 mcg/tiw (n=398) n (%)	REBIF 44 mcg/tiw (n=388) n (%)
Chills	26 (6.6)	37 (9.3)	48 (12.4)
Injection site inflammation	6 (1.5)	40 (10.1)	50 (12.9)
Injection site haematoma	43 (11.0)	20 (5.0)	27 (7.0)
Infections and infestations			
Nasopharyngitis	117 (29.8)	105 (26.4)	94 (24.2)
Upper respiratory tract infection	107 (27.3)	97 (24.4)	83 (21.4)
Urinary tract infection	75 (19.1)	89 (22.4)	73 (18.8)
Influenza	76 (19.4)	79 (19.8)	61 (15.7)
Rhinitis	78 (19.9)	76 (19.1)	58 (14.9)
Cystitis	44 (11.2)	37 (9.3)	27 (7.0)
Nervous system disorders			
Headache	237 (60.5)	233 (58.5)	261 (67.3)
Dizziness	63(16.1)	49 (12.3)	59 (15.2)
Paraesthesia	49 (12.5)	40 (10.1)	37 (9.5)
Musculoskeletal and connective tissue disorders			
Back pain	72 (18.4)	77 (19.3)	78 (20.1)
Pain in extremity	77 (19.6)	63 (15.8)	64 (16.5)
Myalgia	46 (11.7)	72 (18.1)	69 (17.8)
Arthralgia	61 (15.6)	60 (15.1)	65 (16.8)
Muscular weakness	50 (12.8)	44 (11.1)	45 (11.6)
Muscle spasms	28 (7.1)	25 (6.3)	39 (10.1)
Gastrointestinal disorders			
Nausea	103 (26.3)	108 (27.1)	87 (22.4)
Diarrhoea	59 (15.1)	68 (17.1)	62 (16.0)
Constipation	48 (12.2)	42 (10.6)	33 (8.5)
Vomiting	42 (10.7)	40 (10.1)	39 (10.1)
Psychiatric disorders			
Depression	96 (24.5)	86 (21.6)	98 (25.3)
Insomnia	69 (17.6)	69 (17.3)	64 (16.5)
Investigations			
Alanine aminotransferase increased	19 (4.8)	76 (19.1)	101 (26.0)
Lymphocyte count decreased	32 (8.2)	45 (11.3)	56 (14.4)
Aspartate aminotransferase increased	12 (3.1)	41 (10.3)	62 (16.0)
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain	112 (28.6)	93 (23.4)	79 (20.4)
Cough	63 (16.1)	51 (12.8)	50 (12.9)
Blood and lymphatic system disorders			
Lymphopenia	19 (4.8)	36 (9.0)	54 (13.9)
Leukopenia	5 (1.3)	29 (7.3)	44 (11.3)

<u>REBIF HSA-free Formulation</u>

No new or unexpected treatment emergent adverse events (TEAEs) were observed in the multicentre, single arm, open-label REBIF HSA-free formulation Cohort (Study 25632) compared to a Historical Cohort.

The Historical Cohort consisted of patients from three phase III clinical trials (PRISMS Study GF6789, SPECTRIMS Study GF6954 and EVIDENCE Study GF21125) who were administered identical dosing of interferon beta-1a (44 mcg tiw) during the 96 week period,

and for the purposes of these comparisons, the Historical Cohort TEAE data to week 96 of treatment was recorded in MedDRA version 8.0.

Table 2 compares the REBIF HSA-free formulation Cohort with that of the Historical Cohort based upon pre-specified MedDRA common AEs known to be associated with interferon beta-1a.

Table 2

MedDRA preferred term	**Adverse Events Incidence Rate**	
	REBIF HSA-free formulation Cohort (n=260)	**Historical Cohort (n=727)**
Cytopenia	13.5%	13.0% to 39.7%
Flu-like syndrome	71.5%	49.0% to 69.0%
Hepatic disorders	14.2%	18.6% to 38.0%
Hypersensitivity reactions	5.8%	5.6% to 12.0%
Injection site reactions	30.8%	85.3% to 92.4%
Depression and suicidal ideation	6.5%	22.7% to 36.3%
Skin rashes	6.2%	16.5% to 25.5%
Thyroid disorders	4.2%	4.9 to 8.7%

Subjects in the REBIF HSA-free formulation Cohort experienced similar or lower rates of incidence in the eight pre-specified AE groups compared to the Historical Cohort with the exception of "flu-like syndrome".

Study 27025: REFLEX

Study 27025 was a two year controlled study conducted to evaluate the efficacy, safety, and immunogenicity of REBIF (HSA-free formulation) in subjects with a first clinical demyelinating event at high risk of converting to MS. The safety analysis was performed on the double-blind (DB) safety population (including all subjects who received at least one DB study treatment injection [either active or placebo], whether randomized or not) and on the open label (OL) safety population (including all subjects from the DB study population who received at least one OL study treatment injection with REBIF 44 mcg three times a week (tiw) after having converted the Clinically Definite Multiple Sclerosis (CDMS).

Table 3 presents treatment-emerging adverse events that were reported in 1% or more of patients in the double-blind treatment period of Study 27025. The adverse events are listed by MedDRA (Version 13.0) System Organ Class.

Table 3 Incidence of Most Common Related Treatment-Emergent Adverse Events[(a)] During the DB Treatment Period by MedDRA Preferred Term

System Organ Class	**Preferred Term (subjects with most common events)**	**Placebo (n=171) n (%)**	**REBIF 44 mcg ow (n=173) n (%)**	**REBIF 44 mcg tiw (n=171) n (%)**
Blood and lymphatic system disorders	Neutropenia	1 (0.6)	5 (2.9)	13 (7.6)
	Leukopenia	1 (0.6)	4 (2.3)	7 (4.1)
	Thrombocytopenia	0	0	5 (2.9)
	Lymphopenia	0	1 (0.6)	3 (1.8)
	Lymphadenopathy	0	2 (1.2)	0
Ear and labyrinth disorders	Vertigo	2 (1.2)	3 (1.7)	2 (1.2)
Eye disorders	Eye pain	2 (1.2)	0	1 (0.6)
Gastrointestinal disorders	Vomiting	0	3 (1.7)	0
General disorders and administration site conditions	Influenza like illness	34 (19.9)	121 (69.9)	92 (53.8)
	Injection site erythema	3 (1.8)	33 (19.1)	49 (28.7)

System Organ Class	Preferred Term (subjects with most common events)	Placebo (n=171) n (%)	REBIF 44 mcg ow (n=173) n (%)	REBIF 44 mcg tiw (n=171) n (%)
	Pyrexia	6 (3.5)	16 (9.2)	5 (2.9)
	Injection site pain	6 (3.5)	4 (2.3)	8 (4.7)
	Fatigue	5 (2.9)	2 (1.2)	8 (4.7)
	Injection site haematoma	3 (1.8)	5 (2.9)	7 (4.1)
	Asthenia	4 (2.3)	6 (3.5)	4 (2.3)
	Chills	2 (1.2)	7 (4.0)	5 (2.9)
	Injection site oedema	0	1 (0.6)	2 (1.2)
	Injection site rash	0	0	3 (1.8)
	Malaise	0	0	2 (1.2)
Infections and infestations	Upper respiratory tract infection	6 (3.5)	2 (1.2)	6 (3.5)
	Nasopharyngitis	5 (2.9)	1 (0.6)	1 (0.6)
	Pharyngitis	1 (0.6)	3 (1.7)	0
	Oral herpes	2 (1.2)	0	1 (0.6)
	Injection site infection	0	0	2 (1.2)
	Urinary tract infection	2 (1.2)	0	0
Investigations	Alanine aminotransferase increased	3 (1.8)	9 (5.2)	13 (7.6)
	Aspartate aminotransferase increased	1 (0.6)	8 (4.6)	9 (5.3)
	Body temperature increased	0	4 (2.3)	0
	Blood creatine phosphokinase increased	2 (1.2)	1 (0.6)	0
	Hepatic enzyme increased	0	0	2 (1.2)
Metabolism and nutrition disorders	Decreased appetite	0	0	2 (1.2)
Musculoskeletal and connective tissue disorders	Myalgia	3 (1.8)	8 (4.6)	10 (5.8)
	Arthralgia	1 (0.6)	5 (2.9)	1 (0.6)
	Pain in extremity	3 (1.8)	1 (0.6)	1 (0.6)
	Muscle spasms	2 (1.2)	0	1 (0.6)
	Musculoskeletal stiffness	0	2 (1.2)	1 (0.6)
Nervous system disorders	Headache	14 (8.2)	14 (8.1)	21 (12.3)
	Paraesthesia	6 (3.5)	1 (0.6)	0
	Tremor	1 (0.6)	1 (0.6)	2 (1.2)
	Hypoaesthesia	0	0	2 (1.2)
Psychiatric disorders	Depression	5 (2.9)	6 (3.5)	8 (4.7)
	Insomnia	2 (1.2)	4 (2.3)	4 (2.3)
	Anxiety	1 (0.6)	2 (1.2)	1 (0.6)
Respiratory, thoracic and mediastinal disorders	Oropharyngeal pain	2 (1.2)	1 (0.6)	0
Skin and subcutaneous tissue disorders	Alopecia	2 (1.2)	1 (0.6)	1 (0.6)
	Dermatitis allergic	0	1 (0.6)	2 (1.2)
	Erythema	1 (0.6)	0	2 (1.2)
	Hypoaesthesia facial	0	0	2 (1.2)

[(a)] Only TEAEs included that are possibly or probably related to study drug

List of adverse reactions
Adverse reactions are listed below by frequency of occurrence and by MedDRA System Organ Class.

The following definitions apply to the frequency terminology:

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

Adverse reactions, as identified in clinical trials, are presented by body system and by class of frequency (in excess of placebo).

Blood and the lymphatic system disorders

Very common: Neutropenia, lymphopenia, leukopenia, thrombocytopenia, anaemia

Endocrine disorders

Uncommon: Thyroid dysfunction most often presenting as hypothyroidism or hyperthyroidism

Hepatobiliary disorders

Very common: Asymptomatic transaminase increase

Common: Severe elevations of transaminase

Psychiatric disorders

Common: Depression

Nervous system disorders

Very common: Headache

Skin and subcutaneous tissue disorders

Common: Pruritus, rash, erythematous rash, maculopapular rash

Musculoskeletal and connective disorders

Common: Myalgia, arthralgia

General disorders and administration site conditions

Very common: Injection site inflammation, injection site reactions (e.g. swelling, bruising, redness), influenza-like symptoms

Common: Injection site pain, fatigue, rigors, fever

Uncommon: Injection site necrosis, injection site abscess

Post-Marketing Data

Adverse reactions identified during post-marketing surveillance:

Immune system disorders

Rare:	Anaphylactic reactions

Blood and lymphatic system disorders

Rare:	Thrombotic microangiopathy including thrombotic thrombocytopenic purpura/haemolytic uraemic syndrome, pancytopenia
Frequency not known:	Haemolytic anaemia

Nervous system disorders

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

Eye disorders

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

Hepatobiliary disorders

Uncommon:	Hepatitis with or without icterus
Rare:	Hepatic failure, autoimmune hepatitis

Renal disorders

Frequency not known:	Nephrotic syndrome

Skin and subcutaneous tissue disorders

Uncommon:	Urticaria
Rare:	Quincke's oedema (angio-oedema), erythema multiforme, Stevens-Johnson syndrome

Musculosketal and connective tissue disorder

Rare:	Drug-induced lupus erythematosus

General disorders and administration site conditions

Uncommon:	Injection site infections, which could be severe, increased sweating
Rare:	Injection site cellulitis, which could be severe

Reporting suspected adverse reactions
Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9. OVERDOSE

A few cases of overdose have been reported, and the only adverse event observed in one case was flu-like syndrome. However, in case of overdosage, patients should be hospitalised for observation and appropriate supportive treatment should be given.

For information on the management of overdose, contact the Poison Information Centre on 13 11 26 (Australia) or 0800 764 744 (New Zealand).

5. PHARMACOLOGICAL PROPERTIES

5.1. PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Immunostimulants, Interferons ATC code: L03AB07

Interferons are a group of naturally occurring proteins that are produced by eukaryotic cells in response to viral infection and other biological inducers. Interferon beta, one member of this family, is produced by various cell types including fibroblasts and macrophages. Natural interferon beta and interferon beta-1a are glycosylated with each containing a single N-linked complex carbohydrate moiety.

Mechanism of action

Interferons are cytokines that mediate immunomodulatory, antiviral and antiproliferative activities in response to viral infection and other biological inducers. Interferon beta exerts its biological effects by binding to specific receptors on the surface of human cells. This binding initiates a complex cascade of intracellular events that leads to the expression of numerous interferon-induced gene products and markers, including 2',5'-oligoadenylate synthetase, beta 2-microglobulin and neopterin. These products have been measured in the serum and cellular fractions of blood collected from volunteers.

However, the relationship of these markers to any beneficial therapeutic effect of REBIF in multiple sclerosis patients is not clear. The precise mechanism of action of REBIF in multiple sclerosis is still under investigation. REBIF has not been studied in primary progressive disease and should not be administered to such patients.

Clinical trials

PRISMS STUDY (Prevention of Relapses and Disability by Interferon beta-1a in Relapsing-Remitting Multiple Sclerosis)

A total of 560 patients diagnosed with clinically definite or laboratory-supported relapsing-remitting multiple sclerosis, Expanded Disability Status Scale (EDSS) 0-5 with at least a 1-year history before study entry, were randomised to one of 3 treatments (placebo, REBIF 22 mcg (6 MIU) three times a week (tiw), or REBIF 44 mcg (12 MIU) tiw) in a ratio of 1:1:1. About 90% of patients completed the 2 years of treatment and entered the extension phase and 79% remained in the study to the end of year 4. The patients originally randomised to 22 and 44 mcg tiw groups continued their treatment (years 1-4). Prior to the start of the extension phase (years 3-4), all patients from the original placebo group were re-randomised to receive, in blinded fashion, either REBIF 22 mcg (n=85) or REBIF 44 mcg (n=87) tiw. The patients re-randomised from placebo (year 1-2) to treatment (years 3-4) on either REBIF 22 mcg tiw or REBIF 44 mcg tiw are referred to as placebo/REBIF 22 mcg tiw or placebo/REBIF 44 mcg tiw, respectively.

The withdrawal rate due to adverse events for patients randomised to REBIF 22 mcg and REBIF 44 mcg, from years 1-4, were 8 (4.2%) and 18 (9.8%), respectively.

Results of PRISMS study
Effect on exacerbations

REBIF 22 mcg tiw and 44 mcg tiw had a significant effect during Year 1 and Year 2 on the primary outcome measure by reducing relapse count compared to placebo. The relapse rate reduction continued during years 3 and 4 of therapy. REBIF 22 mcg tiw and 44 mcg tiw had a significant effect in delaying relapses (median time to 1st exacerbation 7.6 and 9.6 months, respectively compared to 4.5 months with placebo [years 1-2], and median time to 2nd exacerbation 23.1 and 31.7 months compared to 14.8 months for placebo/treatment group [years 1-4], respectively).

Table 4 Effect on Exacerbations: Summary - Intention to Treat (ITT)

Exacerbation	Placebo/REBIF 22 mcg tiw **or** Placebo/REBIF 44 mcg tiw	REBIF 22 mcg tiw	REBIF 44 mcg tiw	p-value
Exacerbation rate (years 1-4)	1.02	0.80	0.72	REBIF 44 *vs* placebo=0.0001 REBIF 22 *vs* placebo=0.0001 REBIF 44 *vs* REBIF 22=0.0693
Proportion exacerbation free (year 4)	6.67%	14.36%	18.99%	REBIF 44 *vs* placebo=0.0002 REBIF 22 *vs* placebo=0.0158 REBIF 44 *vs* REBIF 22=0.1596
Time (months) to 1st exacerbation (years 1-2)	4.5	7.6	9.6	REBIF 44 *vs* placebo<0.0001 REBIF 22 *vs* placebo=0.0008
Time (months) to 2nd exacerbation (years 1-4)	14.8	23.1	31.7	REBIF 44 *vs* placebo=0.0001 REBIF 22 *vs* placebo=0.0058 REBIF 44 *vs* REBIF 22=0.0460

Effect on time to first progression in disability

Analysis of the intent-to-treat (ITT) group shows that REBIF 44 mcg tiw significantly prolonged time to progression compared to placebo/REBIF. This prolongation is 18 months for REBIF 44 mcg tiw compared to placebo (p=0.0474) and 12 months for REBIF 22 mcg tiw compared to placebo (p=0.2893), for the 40th percentile (median not reached). The time to first progression was in favour of 44 mcg tiw compared to 22 mcg tiw (p=0.3333).

The reductions in the rate of Expanded Disability Status Scale (EDSS) change for 44 mcg tiw were 29% (p=0.005) compared to placebo, 23% (p=0.030) compared to 22 mcg tiw, and 8% (ns) for 22 mcg tiw compared to placebo. The reduction rate of EDSS changes was measured by the average number (a Poisson regression model) of EDSS changes per patient, per year. An EDSS change was defined as a one point change in the EDSS scale (or 0.5 point change above EDSS 5.5) occurring during the study.

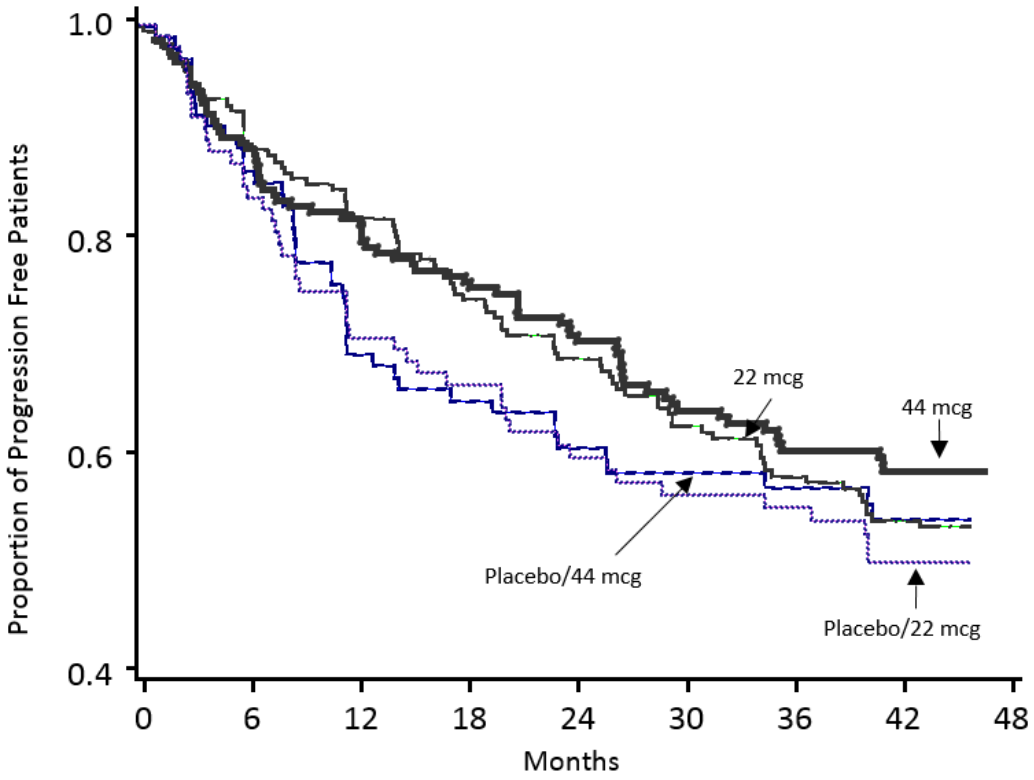
Table 5 Number of confirmed EDSS changes during years 1-4: ITT

	Estimated confirmed annual progression rate†		
Time Period (years)	Placebo (n=187)	REBIF 22 mcg tiw (n=189)	REBIF 44 mcg tiw (n=184)
1-4	0.24	0.22	0.17
	Treatment comparison		p-value†
1-4	REBIF 44 mcg *vs* placebo REBIF 22 mcg *vs* placebo REBIF 44 mcg *vs* REBIF 22 mcg		0.0048 0.5227 0.0295

†The estimated rate for years 1-4 is from a Poisson Regression model with effects for treatment and centre (treatment-by-centre interaction p=0.06)

The prolongation of time to confirmed progression in disability is illustrated by the Kaplan-Meier curves by treatment group shown below (Figure 1). The curves demonstrate the effect of total cumulative doses of REBIF on progression in disability over 4 years. The best outcome is for patients receiving 44 mcg tiw for the entire study duration.

Figure 1 Time to Confirmed Progression in Disability: Kaplan-Meier Curves by Treatment Group



Effect on multiple sclerosis pathology as detected by MRI scans

The MRI data show a highly significant effect of interferon therapy on burden of disease (BOD) and MRI activity measures compared to placebo groups and a dose effect favouring patients treated with 44 mcg tiw vs 22 mcg tiw after 4 years (p=0.009 and p<0.0001 respectively). There is an overall net reduction in BOD of 6.2% over 4 years in patients treated with 44 mcg tiw, and patients originally treated with the high dose of REBIF retain an overall significant benefit on BOD (p=0.003) and T2 activity measure (p<0.0001) compared to patients treated with placebo/REBIF 44 mcg tiw.

Table 6 Percent change in burden of disease during years 1-4

		Treatment Groups			
Time Period (years)	Statistic	Placebo/REBIF 22 mcg tiw	Placebo/REBIF 44 mcg tiw	REBIF 22 mcg tiw	REBIF 44 mcg tiw
1-4	N	57	49	117	111
	Median	9.7	7.2	3.4	-6.2
	Treatment Comparison			p-value	
1-4	REBIF 44 *vs* Placebo/REBIF 44			0.0027	
	REBIF 22 *vs* Placebo/REBIF 22			0.1125	
	REBIF 44 *vs* REBIF 22			0.0089	

Table 7 Median of mean number of T2 active lesions per patient per scan during years 1-4

		Treatment Groups			
Time Period (years)	Statistic	Placebo/REBIF 22 mcg tiw	Placebo/REBIF 44 mcg tiw	REBIF 22 mcg tiw	REBIF 44 mcg tiw
1-4	N	90	92	180	180
	Median	2.0	2.7	1.3	0.5
	Treatment Comparison			p-value	
1-4	REBIF 44 *vs* Placebo/REBIF 44			< 0.0001	
	REBIF 22 *vs* Placebo/REBIF 22			0.0009	
	REBIF 44 *vs* REBIF 22			< 0.0001	

Conclusion

These data demonstrate a continued benefit of REBIF therapy up to 4 years and provide further evidence of a dose-effect relationship in the treatment of multiple sclerosis with interferon beta-1a. In the initial two year study, REBIF 44 mcg had a statistically significant benefit over REBIF 22 mcg for the MRI endpoints (number of active T2 lesions and percentage of T2 active scans per patient). However, in the extension phase (years 3-4) REBIF 44 mcg demonstrated statistically significant benefits for a greater number of parameters. The parameters include: exacerbation rate (years 3-4 only), time to second exacerbation (years 1-4), the number of steroid courses (years 1-4 and years 3-4), time to confirmed progression in disability (years 3-4), number of confirmed EDSS changes (years 1-4) and mean Integrated Disability Status Score (IDSS) for years 3-4, burden of disease (years 1-4), number of active T2 lesions (years 1-4 and years 3-4) and percentage of T2 active scans per patient (years 1-4 and years 3-4). A trend was observed for REBIF 44 mcg over REBIF 22 mcg for: exacerbation (years 1-4), number of confirmed EDSS changes (years 3-4) and patients not reaching EDSS 6.0 (year 4). Finally, patients treated early (randomised to REBIF 22 or 44 mcg from years 1-4) attained more benefit at 4 years than those delaying treatment until the start of year 3 (placebo/REBIF groups).

High Disability Group (EDSS 3.5)

Additional analyses were performed in the group of patients with baseline EDSS>3.5 who are at higher risk of evolving into the phase of disease characterised by steady progression of disability (sometimes referred to as “Transitional MS”). Progression in this group of patients is of particular concern, as progression involves development of difficulty in ambulation.

Efficacy parameters were analysed for the cohort of patients with baseline EDSS>3.5. The low number of patients in this cohort during the extension phase limits the comparisons for this group. Both doses significantly reduced exacerbation count compared to placebo ($p<0.0001$), however only REBIF 44 mcg tiw was statistically beneficial compared to placebo for time to 1st confirmed EDSS progression and number of confirmed EDSS changes.

SPECTRIMS STUDY (Secondary Progressive Efficacy Clinical Trial of Recombinant Interferon beta-1a in Multiple Sclerosis)

A total of 618 patients (229 men and 389 women) aged 19-56 years with secondary progressive MS (EDSS 3-6.5) were randomised to receive REBIF 22 mcg, 44 mcg, or matching placebo as SC injections tiw for 3 years. A total of 506 patients (82%) completed the 3-year study treatment. The proportions of patients completing the study were similar in the placebo (90.7%), REBIF 22 mcg (93.3%), and REBIF 44 mcg (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

Primary Endpoint

The primary efficacy endpoint was the effect of treatment on the time to first confirmed progression of disability with the main comparison being between REBIF 44 mcg tiw and placebo. Time to progression of disability was prospectively defined as the time to at least 1.0 point progression on the EDSS, or a deterioration of 0.5 point if the baseline EDSS was ≥5.5, confirmed at two consecutive visits three months apart. The time to progression (primary outcome) was not significantly affected by treatment compared to placebo. The hazard ratio for progression was 0.83 (95% CI [0.65, 1.07]; p=0.146), for 44 mcg tiw (high dose) and 0.88 (95% CI [0.69, 1.22]; p=0.305) for 22 mcg (low dose).

Figure 2 Time to confirmed progression in disability: All patients

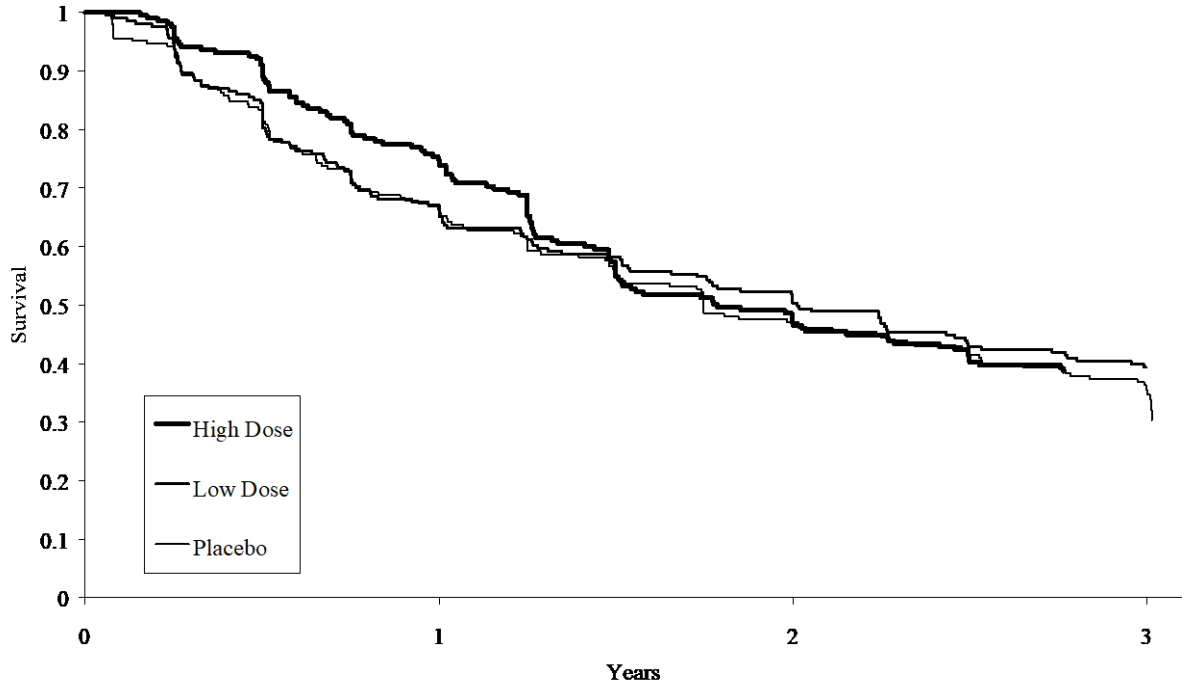
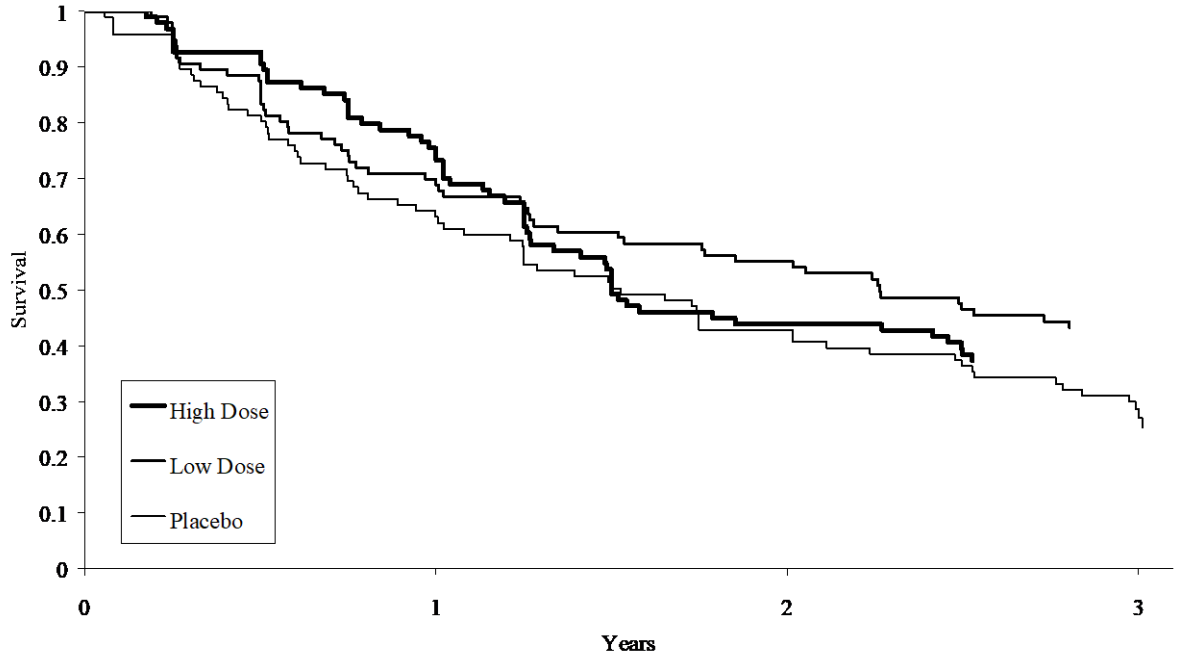


Figure 3 Patients with relapses



Secondary Endpoints

The three secondary endpoints were relapse rate, T2 active lesion count and the change in T2 burden of disease (BOD).

Table 8 Secondary endpoints results

	Placebo tiw	REBIF 22 mcg tiw	REBIF 44 mcg tiw	P value 22 mcg tiw *vs* placebo	P value 44 mcg tiw *vs* placebo
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
% Change in BOD (median)	+10.0	-0.5	-1.3	<0.001	<0.001

Both doses of REBIF had 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 high and low dose groups respectively ($p<0.001$ for both doses compared to placebo).

Subgroup Analyses

A retrospective analysis was performed to examine the differential effects of treatment based on whether or not patients had relapses during the 2 years before entry to the study. These results obtained a posteriori should be interpreted cautiously.

Primary Endpoints

The analysis indicated that the benefit for the combined treatment group, compared to placebo was greater for relapsing patients (n=293) as opposed to non-relapsing patients (n=325), p=0.055 and p=0.934, respectively. Among patients with pre-study relapses, those who received REBIF 44 and 22 mcg tiw, were less likely to progress to disability than those on placebo (hazard ratio 0.76 for 44 mcg and 0.71 for 22 mcg). Among patients without pre-study relapses, treated patients were as likely to progress as placebo patients (hazard ratio 0.95 for REBIF 44 mcg and 1.10 for REBIF 22 mcg). The corresponding odds ratios for progressing in the treated relapsing and non-relapsing patients were 0.52 (95% CI [0.29, 0.93]; p=0.027) and 1.07 (95% CI [0.64, 1.78]; p=0.802), respectively.

Secondary Endpoints

The comparison of relapsing vs non-relapsing patients revealed differences in both baseline MRI characteristics and on-study behaviour and treatment response. The relapsing group achieved greater treatment benefit on the MRI measures (77 vs 48% reduction in T2 activity, and 34% greater reduction in BOD change). In summary, treatment was more effective on the secondary outcomes for patients with pre-study relapses compared to the non-relapsing patients.

Table 9 Summary of on-study behaviour of relapsing vs non-relapsing patients

	Relapsing Pre-study			Non-relapsing Pre-study		
Dose of REBIF	REBIF 44 mcg tiw	REBIF 22 mcg tiw	Placebo	REBIF 44 mcg tiw	REBIF 22 mcg tiw	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

A treatment by sex interaction was seen for the primary outcome measure in which women had a significant benefit on therapy whereas men did not. Exploration of study data could not identify a reason for this interaction nor has such an interaction been previously reported in the literature. A treatment by sex interaction was not seen on relapse count but was noted on the MRI outcome measures. For the MRI measures, women had significant benefit compared to placebo at both doses while men experienced significant benefit on 44 mcg tiw only.

Study 25632 (REBIF HSA-free formulation)

In a multi-national, single-arm, open-label study, patients with a relapsing form of MS received HSA-free formulation of REBIF 44 mcg three times a week. The primary objective of the study was to compare the antigenicity of the FBS-free/HSA-free interferon beta-1a (REBIF) formulation to historical data. The data reported here represent the results following 96 weeks of treatment. Patients with a relapsing form of MS according to the McDonald criteria, an EDSS<6.0 and no prior interferon beta therapy were enrolled.

All 260 enrolled subjects received REBIF HSA-free formulation, 207 subjects (79.6%) completed treatment and 224 subjects (86.2%) completed the trial. Demographic characteristics were similar to previous REBIF trials: median age of 34.0 years, 71.5% of subjects were female. The vast majority of subjects (253 subjects or 97.3%) had relapsing-remitting MS (RRMS), 6 (2.3%) had secondary progressive MS (SPMS) with superimposed relapses and one (0.4%) had progressive relapsing MS (PRMS). The median time since first attack was 5.45 years. EDSS scores at screening ranged from 0 to 6.5, with a median of 2.0.

The trial primary endpoint was the proportion of subjects with neutralising antibodies (NAb positive) at Week 96, using LOCF for missing values. At Week 96 or last assessment, 45 subjects (17.4%) were NAb positive (95% CI: 13.0% 22.5%). The proportion of NAb positive HSA-free formulation cohort subjects was lower than that observed in recent clinical studies performed with REBIF.

One hundred and thirty eight subjects (53.3%) were relapse-free at Week 96 (95% CI: 47.0%, 59.5%). Median time to first relapse (Kaplan-Meier estimator) was not reached, as more than 50% of subjects were relapse-free (or censored) at Week 96/early termination; the first quartile

(Q1) was 45.0 weeks. Among subjects with known relapse status at Week 96/early termination, the estimated relapse rate per subject was 0.70 (95% CI: 0.48, 1.13) over 96 weeks. Overall, 95 subjects or 36.7% had experienced at least one relapse by Week 96/early termination. The mean number of relapses per subject was 0.70. EDSS scores showed very little change over the 2 years of the trial: median changes from baseline were zero at all time points examined. Overall, the results in this study were consistent with past experience with the original formulation of REBIF.

Study 27025 (REFLEX) - Single clinical event suggestive of multiple sclerosis

One 2-year controlled clinical trial with REBIF was performed in patients with a single clinical event at risk of conversion to multiple sclerosis (i.e. with at least two clinically silent lesions on the T2-weighted MRI scan, with a size of at least 3 mm, at least one of which is ovoid or periventricular or infratentorial). Patients with monofocal or multifocal onset of the disease were included (i.e. patients with clinical evidence for involvement of a single or at least two locations, respectively, of the central nervous system). Patients recruited into the REFLEX study were not strictly/explicitly stratified by the degree of their clinical symptoms/manifestations, as assessed by the investigating clinician, into mild, moderate or severe. Any disease other than MS that could better explain signs and symptoms of the patient had to be excluded.

Patients were randomised in a double-blind (DB) manner to either REBIF 44 mcg given three times per week, REBIF 44 mcg once weekly, or placebo. Upon conversion to clinically definite multiple sclerosis (CDMS) patients switched to the recommended dosage of REBIF 44 mcg three times per week in an open label manner, while maintaining blinding as to initial randomisation.

Table 10 Efficacy results from Study 27025 (REFLEX)

Parameter Statistics	**Treatment**			**Treatment Comparison**	
	Placebo (n=171)	**REBIF 44 mcg qw* (n=175)**	**REBIF 44 mcg tiw** (n=171)**	**REBIF 44 mcg tiw versus Placebo**	**REBIF 44 mcg qw versus Placebo**
Time to McDonald (2005) Conversion (Primary Endpoint)					
Number of events	144	129	106		
KM Estimate [(a)] at 24 months	85.8%	75.5%	62.5%		
Median Time (days)	97	182	310		
Hazard Ratio [95% CI] [(b)]				0.49 [0.38;0.64]	0.69 [0.54;0.87]
Log-rank p-value [(c)]				<0.001	0.008
Time to CDMS Conversion					
Number of events	60	37	33		
KM Estimate [(a)] at 24 months	37.5%	21.6%	20.6%		
Hazard Ratio [95% CI] [(b)]				0.48 [0.31;0.73]	0.53 [0.35;0.79]
Log-rank p-value [(c)]				<0.001	0.002

Parameter Statistics	Treatment			Treatment Comparison	
	Placebo (n=171)	REBIF 44 mcg qw* (n=175)	REBIF 44 mcg tiw** (n=171)	REBIF 44 mcg tiw versus Placebo	REBIF 44 mcg qw versus Placebo
Mean Combined Unique Active (CUA) Lesions per Subject per Scan During the DB Period					
Least Square Means (SE) (d)	2.58 (0.30)	0.95 (0.11)	0.50 (0.06)		
Rate Ratio [95% CI] (d)				0.19 [0.14;0.26]	0.37 [0.27;0.50]
Non-parametric ANOVA p-value (e)				<0.001	<0.001

* qw – once a week
** tiw – three times per week

(a) Kaplan-Meier estimate of the cumulative probability of developing McDonald MS (or CDMS) over 2 years
(b) Multivariate Cox's proportional hazards model with treatment and randomisation stratification factors as covariates
(c) Stratified Chi-square log-rank test controlling for randomisation stratification factors
(d) Negative binomial model with treatment and randomisation stratification factors (f) as covariates and log number of scans as an offset variable
(e) 2-sided stratified non-parametric ANOVA model on ranked data with effects for treatment group and the randomisation stratification factors
(f) Randomisation stratification factors: age (<30 years, ≥30 years), classification of first clinical demyelinating event (monofocal, multifocal), steroid use at first clinical demyelinating event (yes, no), and presence of Gd Enhancing Lesions at baseline (yes, no).

In the placebo-controlled phase, both REBIF 44 mcg given three times per week and REBIF 44 mcg given once per week delayed the progression from the first clinical event to MS according to the McDonald (2005) criteria and to CDMS in a statistically significant and clinically meaningful manner versus placebo.

The treatment effect of REBIF 44 mcg given three times per week was superior to the treatment effect of REBIF 44 mcg given once per week in delaying the progression from the first clinical event to MS according to the McDonald (2005) criteria and in reducing the number of combined unique active (CUA) lesions. Treatment with REBIF 44 mcg given three times per week resulted in a 51% reduction of risk of conversion to McDonald MS compared to placebo (Hazard Ratio = 0.49, 95% CI [0.38, 0.64], p-value < 0.001, primary endpoint). The absolute risk reduction at 24 Months for McDonald conversion based on KM estimates between placebo and Rebif 44mcg tiw was 23.3% and the relative risk reduction at 24 Months was 27.2%.

Treatment with REBIF 44 mcg tiw resulted in a 52% relative reduction of risk of conversion to CDMS compared to placebo (Hazard Ratio = 0.48, 95% CI [0.31, 0.73], p-value < 0.001). The absolute risk reduction at 24 Months for CDMS conversion based on KM estimates was 16.9% and the relative risk reduction at 24 Months was 45.1%.

Subgroup Analysis

Subsequent to the availability of revised McDonald (2010) criteria, a post hoc subgroup analysis was performed whereby subjects of Study 27025 (REFLEX) were re-categorised according to the new diagnostic criteria. Over one third of patients randomised had MS at baseline according to McDonald (2010) criteria. Compared with placebo, REBIF 44 mcg given three times per week significantly reduced the risk of MS according to McDonald (2005) and of CDMS at 2 years, irrespective of the McDonald (2010) status at baseline.

5.2. PHARMACOKINETIC PROPERTIES

The pharmacokinetic and pharmacodynamic profiles of the REBIF HSA-free formulation were investigated in phase I study 25827, a double-blind, randomised, 2 period, crossover study in which 41 healthy subjects received single 44 microgram doses of REBIF (containing Human Serum Albumin (HSA)) and the REBIF HSA-free formulation. The geometric mean C_{max} (17.1 IU/mL) and AUC (54.0 IU·h/mL) of the current formulation were approximately 70% higher than that of the previous formulation (10.2 IU/mL and 31.9 IU·h/mL, respectively). The median T_{max} was 0.25 h (vs 0.33 h for the previous formulation). There was high inter-patient variability in the pharmacokinetics of interferon beta-1a with both formulations. Bioequivalence was not demonstrated for PK parameters. However, in this study, both REBIF HSA and REBIF HSA-free formulations were shown to be bioequivalent on the basis of two markers of biological activity, neopterin and β-2 microglobulin.

The raw neopterin responses measured for REBIF HSA and REBIF HSA-free formulations were similar. Median t_{max} was 24 hours after dosing for both formulations. Mean (± sd) C_{max} was 42 ± 21 nmol/L for REBIF HSA-free formulation, and 40 ± 19 nmol/L for REBIF HSA formulation. Mean AUC_{last} were 3882 ± 1804 nmol·h/L for REBIF HSA-free formulation and 3581 ± 1475 nmol·h/L for the REBIF HSA formulation.

The β-2 microglobulin responses of REBIF HSA and REBIF HSA-free formulations were similar. For both formulations the median t_{max} was 48 hours after administration. Mean C_{max} was 3017 ± 597ng/mL for REBIF HSA-free formulation, and 2970 ± 646 ng/mL for REBIF HSA formulation. Mean AUC_{last} were 401 ± 67 µg·h/mL and 392 ± 70 µg·h/mL for the REBIF HSA-free and REBIF HSA formulations, respectively.

The following data were obtained from an earlier REBIF formulation, now replaced with the REBIF Human Serum Albumin (HSA)-free formulation.

In a phase I study, 28 healthy volunteers were injected with increasing (22, 44 and 66 micrograms) intravenous (IV) injections, single 66 micrograms IV, subcutaneous (SC), and intramuscular (IM) injections, and repeated SC injections. The pharmacokinetic analysis showed that after intravenous injection, interferon beta followed a tri-exponential pattern of decay, with three half-lives of 3 minutes, 41 minutes and 21.5 hours. Initial volume of distribution was 5 L, volume of distribution at steady state was 380 L and clearance was 33-55 L/h.

After SC and IM administration, median absolute bioavailability was similar regardless of route, at 27% and 30% respectively. The mean absorption time of interferon beta following administration of REBIF by the SC and IM routes was approximately 7 hours. Following SC administration, absorption appeared to be the rate-limiting step for elimination. This led to an apparent terminal half-life of (median) 66 hours following multiple dosing with REBIF every other day. An accumulation ratio of 2.4 was noted on the fourth dose (near steady state).

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

Special populations

No studies have been conducted to evaluate the pharmacokinetics of REBIF in elderly or paediatric MS patients, or in subjects with renal or hepatic impairment.

However, limited published data suggest that the safety profile in adolescents from 12 to 16 years of age receiving REBIF 22 micrograms subcutaneous three times per week is similar to that seen in adults.

5.3. PRECLINICAL SAFETY DATA

Carcinogenicity

The carcinogenic potential of REBIF has not been investigated in animals or humans.

Genotoxicity

Interferon beta-1a appeared to not be genotoxic when tested in in vitro and in vivo assays for gene mutation and chromosomal damage.

6. PHARMACEUTICAL PARTICULARS

6.1. LIST OF EXCIPIENTS

Mannitol, poloxamer, methionine, water for injections and benzyl alcohol.
Sodium hydroxide and acetic acid are used for pH adjustment.

6.2. INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3. SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the

Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging. Do not use after the expiry date.

6.4. SPECIAL PRECAUTIONS FOR STORAGE

REBIF should be stored at 2°C to 8°C (Refrigerate. Do not freeze) in the original packaging to protect it from light. Should refrigeration be temporarily unavailable, REBIF can be stored at or below 25ºC for up to 14 days, then put back in the refrigerator and used before the expiry date.

6.5. NATURE AND CONTENTS OF CONTAINER

REBIF is registered in two strengths of 22 microgram/0.5 mL (6 MIU) and 44 microgram/0.5mL (12 MIU) of interferon beta-1a (rch). REBIF 22 microgram/0.5 mL (6 MIU) is not currently supplied.

REBIF 44 microgram/0.5 mL is supplied in the following presentations:

- pre-filled syringe for single dose use (0.5 mL)
- pre-filled syringe in a RebiDose single use autoinjector (0.5 mL)
- cartridge for multidose use (1.5 mL).

REBIF pre-filled syringe (Glass Type I Clear)

REBIF is available in packs of 12 pre-filled syringes (44 microgram/0.5 mL), ready for use. REBIF pre-filled syringe is for single use in one patient only. Contains no antimicrobial agent. Use once only and discard any residue. REBIF pre-filled syringe may also be administered with a suitable autoinjector (Rebiject II®).

REBIF pre-filled syringe (Glass Type I Clear) in a RebiDose single use autoinjector

REBIF is available in packs of 12 pre-filled syringes (44 microgram/0.5 mL), each pre-assembled in a disposable RebiDose autoinjector and ready for use. REBIF pre-filled syringe in RebiDose single use autoinjector is for use in one patient only. Contains no antimicrobial agent. Use once only and discard any residue.

REBIF multidose cartridge (Glass Type I Clear)

REBIF is available in packs of 4 cartridges (132 microgram/1.5 mL) for multidose use in one patient only.

REBIF cartridge must be administered with a reusable autoinjection device, RebiSmart. The autoinjection device containing a cartridge of REBIF must be stored in the device storage box at 2°C to 8°C (Refrigerate. Do not freeze). Should refrigeration be temporarily unavailable, it can be stored at or below 25ºC for up to 14 days. Cartridges should be discarded within 21 days after first use.

6.6. SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7. PHYSICOCHEMICAL PROPERTIES

Chemical structure

REBIF (interferon beta-1a (rch)) is composed of the native amino acid sequence of natural human interferon beta. Because it is produced in mammalian cells (Chinese Hamster Ovary), it is glycosylated as is the natural protein. Interferon beta-1a has 166 amino acids and an approximate molecular weight of 22,500 daltons.

The specific activity of REBIF is approximately 0.27 million international units (MIU) of antiviral activity per microgram interferon beta-1a.

CAS number

145258-61-3

7. MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 (Prescription Only Medicine)

8. SPONSOR

Supplied in Australia by:
Merck Healthcare Pty Ltd
Suite 1, Level 1, Building B
11 Talavera Road
Macquarie Park NSW 2113

9. DATE OF FIRST APPROVAL

Pre-filled syringe: 5 December 2008
Pre-filled syringe autoinjector: 21 October 2010
Multidose cartridge: 21 January 2010

10. DATE OF REVISION

10 August 2020

Summary table of changes

Section changed	Summary of new information
4.8	Adding "Frequency not known: Haemolytic anaemia" under *Blood and lymphatic system disorders*, *POST-MARKETING* DATA per the request from the TGA