Professional Information

SCHEDULING STATUS

S4

1. NAME OF MEDICINE

Rebif 22 injection

Rebif 44 injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Rebif 22 contains interferon beta-1a 22 micrograms (6 MIU*) per 0,5 ml per pre-filled syringe or pre-filled pen.

Rebif 44 contains interferon beta-1a 44 micrograms (12 MIU*) per 0,5 ml per pre-filled syringe or pre-filled pen.

*Million International Units, measured by cytopathic effect (CPE) bioassay against the in-house interferon beta-1a standard which is calibrated against the current international NIH standard (GB-23-902-531)

**produced in Chinese hamster ovary cells (CHO-K1) by recombinant DNA technology.

Excipient with known effect: 2.5 mg benzyl alcohol

For full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Solution for injection in pre-filled syringe or pre-filled pen.

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Rebif is indicated for the treatment of ambulatory patients with relapsing remitting multiple sclerosis (MS) characterised by at least 2 recurrent attacks of neurological dysfunction (relapses) over the preceding 2-

year period. Rebif decreases the frequency and severity of relapses over 2 years and slows the progression of disability.

Rebif is also indicated in patients who have experienced a first clinical episode and have MRI features consistent with multiple sclerosis.

Rebif has not yet been investigated in patients with progressive multiple sclerosis and should be discontinued in patients who develop progressive multiple sclerosis.

4.2 Posology and method of administration

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 reactions, it is recommended that 8,8 micrograms be administered by subcutaneous injection three times per week during the initial 2 weeks of therapy.
Thereafter, 22 micrograms be administered by subcutaneous injection three times per week in weeks 3 and 4, and the total of the 44 micrograms strength be administered by subcutaneous injection three times per week 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.

For the first four weeks of initiating treatment it is recommended that Rebif in pre-filled syringes be used, as Rebif pre-filled pen is not a suitable presentation for dose initiation.

First clinical episode

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

Relapsing multiple sclerosis

The recommended posology of Rebif is 44 micrograms given three times per week by subcutaneous injection. Rebif 22 micrograms, also given three times per week by subcutaneous injection, is recommended for patients who cannot tolerate the higher dose in view of the treating specialist.

Paediatric population

There is no experience with Rebif in children under 16 years of age with multiple sclerosis, and therefore Rebif should not be used in this population.

At the present time, it is not known for how long patients should be treated. Safety and efficacy with Rebif have not been demonstrated beyond 4 years in randomised prospective controlled studies. However, published data suggest that efficacy is maintained beyond 4 years.
Long-term post-marketing surveillance does not show emergence of new onset adverse reactions beyond the first few years of treatment. It is recommended that patients should be evaluated at least every second year in the 4-year period after initiation of treatment with Rebif and the treating physician should then make a decision for longer-term treatment on an individual basis.

Mode of administration

REBIJECT (Pre-filled syringe)

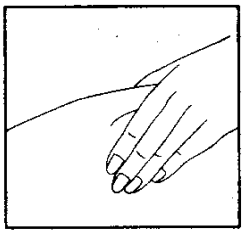
The solution for injection in a pre-filled syringe is ready for use. It may also be administered with a suitable autoinjector. Instructions for use of the specific autoinjector are supplied with the device.

Subcutaneous (under the skin) self-administration

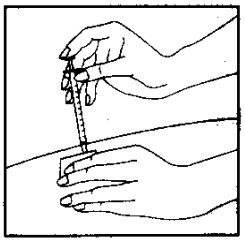
- Choose an injection site. Your doctor will advise you on the possible injection sites (good sites include the upper thighs and the lower abdomen). Hold the syringe like a pencil or dart. It is recommended that you keep track of and rotate your injection sites, so that one area is not injected too frequently.

NOTE: Do not use any areas in which you feel lumps, firm knots, or pain. Talk to you doctor or healthcare professional about anything you find.

- Wash your hands thoroughly with soap and water.
- Remove the Rebif syringe from the blister pack by peeling back the plastic covering.
- Use an alcohol wipe to clean the skin at the injection site. Let the skin dry. If a bit of alcohol is left on the skin, you may get a stinging sensation.
- Gently pinch the skin together around the site (to lift it up a bit).



- Resting your wrist on the skin near the site, stick the needle at a right angle straight into the skin with a quick firm motion.



- Inject the medicine by using a slow steady push (push the plunger all the way in until the syringe is empty).
- Hold a swab on the injection site. Remove the needle from the skin.
- Gently massage the injection site with a dry cotton ball or gauze.
- Dispose of all used items: once you have finished your injection, immediately discard the syringe in the appropriate disposal unit.

REBIDOSE (Pre-filled pen)

Rebif is intended for subcutaneous (under the skin) injection. The pre-filled pen is for single use. Only use it when the solution is clear to opalescent without particles or any other visible signs of deterioration.

The first injection(s) must be performed under the supervision of an appropriately qualified healthcare professional. After receiving adequate training, you, a family member, friend or carer can use Rebif pre-filled pen to administer the medicine at home.

Rebif is administered three times per week, and if possible:

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

Subcutaneous (under the skin) self-administration

Please refer to the booklet “RebiDose Instructions for use” included in the carton.

4.3 Contraindications

Rebif is contra-indicated in patients with a known hypersensitivity to natural or recombinant interferon beta, human serum albumin, or any other component of the formulation.

Rebif is contra-indicated in patients with severe depressive disorders and/or suicidal ideation, and in epileptic patients with a history of seizures not adequately controlled by treatment (see Warnings and Special Precautions, and Undesirable effects).

Hyper- or hypothyroidism.

Rebif should not be prescribed for children under the age of 16 years.

4.4 Special warnings and precautions for use

Patients should be informed of the most common adverse events associated with Rebif administration, including symptoms of the flu-like syndrome (see Undesirable effects). These symptoms tend to be most prominent at the initiation of therapy and decrease in frequency and severity with continued treatment.

Thrombotic microangiopathy

Cases of thrombotic microangiopathy, manifested as thrombotic thrombocytopenic purpura (TTP) or haemolytic uraemic syndrome (HUS), have been reported, including fatal cases. Events were reported at various time points during treatment and may occur after several years of treatment with Rebif. Monitoring of early symptoms, 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.

Pulmonary Arterial Hypertension

Cases of pulmonary arterial hypertension (PAH) have been reported with interferon alfa and beta products. Patients developing suspicious symptoms (e.g., dyspnoea, fatigue) should be assessed for PAH.

Depression and suicidal ideation

Rebif should be administered with caution to patients with previous or current depressive disorders, in particular to those with antecedent of suicidal ideation

Depression and suicidal ideation are known to occur in increased frequency in the multiple sclerosis population and in association with interferon use. Patients treated with Rebif should be advised to immediately report any symptoms of depression and/or suicidal ideation to their prescribing physician. Patients exhibiting depression should be closely monitored during therapy with Rebif and treated appropriately. Cessation of therapy with interferon beta-1a should be considered.

Seizure disorders

Caution should be exercised when administering Rebif to patients with pre-existing seizure disorders. 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, should be closely monitored for worsening of their clinical condition during initiation of therapy with Rebif. Symptoms of the flu-like syndrome associated with Rebif therapy may prove stressful to patients with cardiac conditions.

Injection site necrosis

Injection site necrosis (ISN) has been reported in patients using Rebif (see Undesirable effects). To minimise the risk of injection site necrosis patients should be advised to:

- Use an aseptic injection technique
- Rotate the injection site 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 should be advised to consult with their physician before continuing with injections of Rebif. If the patient has multiple lesions, Rebif should be discontinued until healing has occurred. Patients with single lesions may continue provided that necrosis is not too extensive.

Hepatic dysfunction

In clinical trials with Rebif, asymptomatic elevations of hepatic transaminases (particularly alanine aminotransferase (ALT)) were common and 1 – 3 % of patients developed elevations of transaminases above 5 times the upper limit of normal (ULN). Dose reduction with Rebif should be considered if ALT rises above 5 times the ULN and gradually re-escalated when enzyme levels have normalised. 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). Serum ALT levels should 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. Treatment with Rebif should be stopped if icterus or other clinical symptoms or liver dysfunction appear (see Undesirable effects). Rebif, like other interferons beta, has 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.

Laboratory abnormalities

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

Thyroid disorders

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

Severe renal or hepatic failure and severe myelosuppression

Caution should be used and close monitoring considered when administering Rebif to patients with severe renal and hepatic failure and to patients with severe myelosuppression.

Neutralising antibodies

Serum neutralising antibodies against interferon beta-1a may develop. The precise incidence of antibodies is as yet uncertain. Clinical data suggest that after 24 to 48 months of treatment of Rebif 44 micrograms approximately 28 % of patients develop persistent serum antibodies to interferon beta-1a.
The presence of antibodies has been shown to attenuate the pharmacodynamic response to interferon beta-1a (beta-2 microglobulin and neopterin).
These patients had a significantly higher incidence of relapses than patients without neutralising antibodies and had more progressive disability than patients without neutralising antibodies. MRI changes in these patients approached those of the placebo/Rebif group.
The clinical significance of the induction of antibodies has not been fully elucidated but may be associated with reduced efficacy. If a patient responds poorly to therapy with Rebif, and has neutralising antibodies, the treating physician should reassess the benefit/risk ratio of continued Rebif therapy.

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

Sodium content

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, i.e. essentially “sodium-free”.

4.5 Interaction with other medicines and other forms of interaction

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. anti-epileptics and some classes of antidepressants.
Due to its potential to cause neutropenia and lymphopenia, proper monitoring of patients is required if Rebif is given in combination with myelosuppressive agents.

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

4.6 Fertility, pregnancy and lactation

A large amount of data (more than 1000 pregnancy outcomes) from pregnancy registries and post-marketing experience indicates no adverse effect on pregnancy or infant outcomes, after exposure to interferon beta before conception and/or during pregnancy.

A prospective European interferon beta pregnancy registry contained 948 known pregnancy outcomes with 573 exposed during the 1st trimester, and limited data in 2nd and 3rd trimester. The reported overall rate of congenital malformations in live births and of spontaneous abortions was in line with the rates observed both in the general population and in MS patients not receiving any treatment.

In a retrospective register-based study, data from 3054 pregnancy outcomes from women with MS were analysed.
No evidence was found of an increased risk of serious adverse pregnancy outcomes, including spontaneous abortions and major congenital anomalies, after exposure to interferon beta before and/or during pregnancy compared to the women with MS that were unexposed to any MS disease modifying drug within the study. Further it was found that interferon-beta exposure does not affect the mean birth weight and risk of preterm birth.

A comprehensive review of literature on published data supports the findings of the two studies.

Interferon beta can be used during pregnancy if clinically needed.

Breastfeeding

Limited information available on the transfer of interferon beta-1a into breast milk suggests that levels of interferon beta-1a excreted in human milk are negligible. No harmful effects in breastfed infants of women treated with interferon beta-1a have been reported.

The benefit and potential risk of breastfeeding should be considered along with the mother's medical need for interferon beta-1a therapy.

Fertility

The effects of Rebif on fertility have not been investigated.

4.7 Effects of ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

The highest incidence of adverse reactions associated with Rebif therapy is related to flu-like syndrome. Flu-like symptoms tend to be most prominent at the initiation of therapy and decrease in frequency with continued treatment. Depending on the formulation, up to approximately 70 % of patients treated with Rebif can expect to experience the typical interferon flu-like syndrome within the first six months after starting treatment. Similarly, approximately 30 % of patients or more, depending on the formulation, will also experience reactions at the injection site, predominantly mild inflammation or erythema.
Asymptomatic increases in laboratory parameters of hepatic function and decreases in white blood cells are also common.
The majority of adverse reactions observed with interferon beta-1a are usually mild and reversible and respond well to dose reductions. In the case of severe or persistent undesirable effects, the dose of Rebif may be temporarily lowered or interrupted, at the discretion of the physician.

List of adverse reactions

The adverse reactions reported below are classified according to the frequency of occurrence as follows: Very common ≥1/10; Common ≥1/100, < 1/10; Uncommon ≥1/1000, < 1/100; Rare ≥1/10 000, < 1/1000; Very rare <1/10 000; Frequency not known (cannot be estimated from the available data)

The adverse reactions presented have been identified from clinical studies, as well as from port-marketing reports (an asterisk (*) indicates the adverse reactions identified during post-marketing surveillance).

Blood and the lymphatic system disorders

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

Rare: Thrombotic microangiopathy including thrombotic thrombocytopenic purpura/haemolytic uraemic syndrome*, pancytopenia*

Endocrine disorders

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

Gastrointestinal disorders:

Common: Diarrhoea, vomiting, nausea

Immune system disorders

Rare: Anaphylactic reactions*

Hepatobiliary disorders

Very common: Asymptomatic transaminase increase

Common: Severe elevations in transaminases

Uncommon: Hepatitis with or without jaundice*

Rare: Hepatic failure*, autoimmune hepatitis*

Psychiatric disorders

Common: Depression, insomnia, suicide attempt

Very rare: Depersonalisation

Nervous system disorders

Very common: Headache

Uncommon: Seizures*

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

Eye disorders

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

Skin and subcutaneous tissue disorders

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

Uncommon: Urticaria*

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

Very rare: Hair loss

Musculoskeletal and connective disorders

Common: Myalgia, arthralgia

Rare: Drug-induced lupus erythematosus*

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, severe injection site infections*, increased sweating*

Rare: Severe injection site cellulitis*

The following side effects are known to occur with interferons as a class, but the incidence of occurrence with Rebif is not known.

Nervous system disorders

Dizziness

Metabolism and nutrition disorders

Anorexia

Cardiac disorders

Palpitation

Arrhythmia

Psychiatric disorders

Anxiety

Vascular disorders

Vasodilation

Respiratory, thoracic and mediastinal disorders

Pulmonary arterial hypertension

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "6.04 Adverse Drug Reactions Reporting Form", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

The symptoms of overdosage are not known. The patient should be hospitalised for observation and appropriate supportive treatment given.

5. PHARMACOLOGICAL PROPERTIES

A 34 Other

5.1 Pharmacodynamic properties

Pharmacotherapeutic Group: Immunostimulants, interferons, ATC: L03 AB07

Interferons (IFNs) are a group of endogenous glycoproteins endowed with immunomodulatory, antiviral and antiproliferative properties.

Interferon beta-1a is composed of the native amino acid sequence of natural human interferon beta. It is produced in mammalian cells (Chinese Hamster Ovary) and is therefore glycosylated like the natural protein.

The precise mechanism of action of interferon beta-1a in multiple sclerosis is still under investigation. Interferons exert several different types of biological effects including anti-viral, anti-proliferative, differentiative and immunomodulatory.

Relapsing-remitting multiple sclerosis

The safety and efficacy of action of interferon beta-1a has been evaluated in patients with relapsing-remitting multiple sclerosis at doses ranging from 11 – 44 micrograms (3 – 12 million IU), administered subcutaneously three times per week.

At licensed posology, interferon beta-1a has been demonstrated to decrease the incidence (approximately 30 % over 2 years) and severity of clinical relapses in patients with at least 2 exacerbations in the previous 2 years and with and EDSS of 0 – 5,0 at entry.

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

Single clinical event suggestive of multiple sclerosis

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

Patients were randomised in a double-blind manner to either Rebif 44 micrograms given three times per week, Rebif 44 micrograms once weekly, or placebo.

If a second clinical demyelinating event occurred confirming definite multiple sclerosis, patients switched to the recommended posology of Rebif 44 micrograms three times per week in an open label manner, while maintaining blinding as to initial randomisation. Efficacy results of Rebif 44 micrograms given three times per week compared to placebo from this study are as follows:

Parameter Statistics	Treatment		Treatment Comparison Rebif 44 µg tiw* versus Placebo		
	Placebo (n = 171)	Rebif 44 µg tiw* (n = 171)	Risk Reduction	Cox's Proportional Hazard Ratio [95 % CI]	Log-Rank p-value
McDonald (2005) Conversion					
No. of events	144	106	51 %	0,49 [0,38; 0,64]	< 0,001
KM Estimate	85,8 %	62,5 %			
CDMS Conversion					
No. of events	60	33	52 %	0,48 [0,31; 0,73]	< 0,001
KM Estimate	37,5 %	20,6 %			
Mean CUA Lesions per Subject per Scan During the Double Blind Period					
Least Square Means (SE)	2,58 (0,30)	0,50 (0,06)	81 %	0,19 [0,14; 0,26]	< 0,001
*tiw – three times per week					

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

5.2 Pharmacokinetic properties

In healthy volunteers after intravenous administration, interferon beta-1a exhibits a sharp multi-exponential decline, with serum levels proportional to the dose. The initial half-life is in the order of minutes and the terminal half-life is several hours, with the possible presence of a deep compartment. When administered by the subcutaneous or intramuscular routes, serum levels of interferon beta remain low, but are still measurable up to 12 to 24 hours post-dose. Subcutaneous and intramuscular administrations of interferon beta-1a produce equivalent exposure to interferon beta. Following a single 60 microgram dose, the maximum peak concentration, as measured by immunoassay, is around 6 to 10 IU/mL, occurring on average around 3 hours after the dose, regardless of the route of administration.

After subcutaneous administration at the same dose repeated every 48 hours for 4 doses, a modest accumulation occurs (about 2.5 x for AUC).

Regardless of the route of dosing, pronounced pharmacodynamic changes are associated with the administration of interferon beta-1a. After a single dose, intracellular and serum activity of 2-5A synthetase and serum concentrations of $beta_2$-microglobulin and neopterin increase within 24 hours, and start to decline within 2 days. Intramuscular and subcutaneous administrations produce fully superimposable responses. After repeated subcutaneous administration every 48 hours for 4 doses, these biological responses remain elevated, with no signs of accumulation or tolerance development.

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

5.3 Preclinical safety data

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

Rebif has not been investigated for carcinogenicity.

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Inactive components are mannitol, Poloxamer 188, L-methionine, benzyl alcohol, acetic acid, sodium hydroxide and water for injections

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 months

6.4 Special precautions for storage

Keep out of reach of children.

Store at 2 – 8 ºC (in a refrigerator) in the original container.

Do not freeze.

Should refrigeration be unavailable, Rebif can be stored below 25 °C for a period of up to 30 days.

Protect from light.

6.5 Nature and contents of container

REBIJECT: 0,5 ml of a clear, colourless solution for injection in a pre-filled 1 ml glass syringe with a stainless steel needle.

REBIDOSE: 0,5 ml of a clear, colourless solution for injection in a cartridge in a pre-filled pen.

REBIJECT:

A carton with three pre-filled syringes of Rebif 22 or a carton with twelve pre-filled syringes of Rebif 22.

A carton with twelve pre-filled syringes of Rebif 44.

REBIDOSE:

Pre-filled pen ready for use for self-administration.

Packs of one, three and twelve pre-filled pens.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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

For single use only.

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

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

7. HOLDER OF CERTIFICATE OF REGISTRATION

Merck (Pty) Ltd

1 Friesland Drive

Longmeadow Business Estate

Modderfontein, 1645

South Africa

8. REGISTRATION NUMBERS

Rebif 22: 34/34/0096

Rebif 44: 35/34/0188

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation:

Rebif 22: 24 July 2001

Rebif 44: 26 March 2002

10. DATE OF REVISION OF THE TEXT

26 July 2022