Rebif
Interferon beta 1-a

1. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each pre-filled syringe (0.5 ml) contains 22 micrograms (6 MIU) of interferon beta-1a.

Excipient with known effect: Contains 2.5 mg benzyl alcohol per dose of 0.5 mL.

For the full list of excipients, see section 5.1 List of Excipients.

2. PHARMACEUTICAL FORM
Solution for injection in pre-filled syringe.

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

3. CLINICAL PARTICULARS
3.1 Therapeutic indications
Rebif is indicated for the treatment of relapsing multiple sclerosis.

In clinical trials, this was characterised by two or more acute exacerbations in the previous two years (*see section 4.1 Pharmacodynamic properties*).

Efficacy has not been demonstrated in patients with secondary progressive multiple sclerosis without ongoing relapse activity (*see section 4.1 Pharmacodynamic properties*).

3.2 Posology and method of administration
Treatment should be initiated under supervision of a physician experienced in the treatment of the disease.

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

Posology
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 2 weeks of therapy, 50 % of the total dose be administered in weeks 3 and 4, and the full dose from the 5th week onwards.

Relapsing multiple sclerosis
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
No formal clinical trials or pharmacokinetic studies have been conducted in children or adolescents. However, a paediatric retrospective cohort study collected safety data with Rebif from medical records in children (n=52) and adolescents (n=255). The results of this study suggest that the safety profile in children (2 to 11 years old) and in adolescents (12 to 17 years old) receiving Rebif 22 micrograms or 44 micrograms subcutaneous three times per week is similar to that seen in adults.
The safety and efficacy of Rebif in children below 2 years of age have not yet been established. Rebif should not be used in this age group.

Method of administration

Prior to injection and for an additional 24 hours after each injection, an antipyretic analgesic is advised to decrease flu-like symptoms associated with Rebif administration.

At the present time, it is not known for how long patients should be treated. Safety and efficacy with Rebif have not been demonstrated beyond 4 years of treatment. It is recommended that patients should be evaluated at least every second year in the 4-year period after initiation of treatment with Rebif and a decision for longer term treatment should then be made on an individual basis by the treating physician.

3.3 Contraindications

- Hypersensitivity to natural or recombinant interferon-β, or to any excipients.
- Current severe depression and/or suicidal ideation (*see section 3.4 Special warnings and precautions for use and 3.8 Undesirable effects*).

3.4 Special warnings and precautions for use

General recommendations

Patients should be informed of the most frequent adverse reactions associated with interferon beta administration, including symptoms of the flu-like syndrome (*see section 3.8 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) including fatal cases have been reported with Rebif. Events were reported at various time points during treatment and may occur several weeks to several years after starting treatment with interferon beta products.

Early clinical features include trombocytopenia, new onset hypertension, fever, central nervous system symtoms (e.g confusion, paresis) and impaired renal functions. Laboratory findings suggestive of TMA include decreased platelet counts, increased serum lactate dehydrogenase (LDH) due to haemolysis and schistocytes (erythrocyte fragmentation) on a blood film. Therefore if clinical features of TMA are observed, further testing of blood platelet levels, serum LDH, blood films and renal function is recommended. If TMA is diagnosed, prompt treatment is required (considering plasma exchange) and immediate discontinuation of Rebif is recommended

Depression and suicidal ideation

Rebif should be administered with caution to patients with previous or current depressive disorders in particular to those with antecedents of suicidal ideation (*see section 3.3 Contraindications*). Depression and suicidal ideation are known to occur in increased frequency in the multiple sclerosis population and in association with interferon use. Patients treated with Rebif should be advised to immediately report any symptoms of depression and/or suicidal ideation to their prescribing physician. Patients exhibiting depression should be monitored closely during therapy with Rebif and treated appropriately. Cessation of therapy with Rebif should be considered (*see section 3.3 Contraindications and 3.8 Undesirable effects*).

Seizure disorders

Rebif should be administered with caution to patients with a history of seizures, to those receiving treatment with anti-epileptics, particularly if their epilepsy is not adequately controlled with anti-epileptics (*see section 3.5 Interaction with other medicinal products and other forms of interaction and 3.8 Undesirable effects*).

Cardiac disease

Patients with cardiac disease, such as angina, congestive heart failure or arrhythmia, should be closely monitored for worsening of their clinical condition during initiation of therapy with interferon beta-1a. Symptoms of the flu-like syndrome associated with interferon beta-1a therapy may prove stressful to patients with cardiac conditions.

Injection site necrosis

Injection site necrosis (ISN) has been reported in patients using Rebif (*see section 3.8 Undesirable effects*). To minimise the risk of injection site necrosis patients should be advised to:

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

The procedure for the self-administration by the patient should be reviewed periodically especially if injection site reactions have occurred.

If the patient experiences any break in the skin, which may be associated with swelling or drainage of fluid from the injection site, the patient should be advised to consult with their physician before continuing injections with Rebif. If the patient has multiple lesions, Rebif should be discontinued until healing has occurred. Patients with single lesions may continue provided that the necrosis is not too extensive.

Hepatic dysfunction

In clinical trials with Rebif, asymptomatic elevations of hepatic transaminases (particularly alanine aminotransferase (ALT)) were common and 1-3% of patients developed elevations of hepatic transaminases above 5 times the upper limit of normal (ULN). In the absence of clinical symptoms, serum ALT levels should be monitored prior to the start of therapy, at months 1, 3 and 6 on therapy and periodically thereafter. Dose reduction of Rebif should be considered if ALT rises above 5 times the ULN, and gradually re-escalated when enzyme levels have normalized. Rebif should be initiated with caution in patients with a history of significant liver disease, clinical evidence of active liver disease, alcohol abuse or increased serum ALT (>2.5 times ULN). Treatment with Rebif should be stopped if icterus or other clinical symptoms of liver dysfunction appear (*see section 3.8 Undesirable effects*).

Rebif, like other interferons beta, has a potential for causing severe liver injury including acute hepatic failure (*see section 3.8 Undesirable effects*). The majority of the cases of severe liver injury occurred within the first six months of treatment. The mechanism for the rare symptomatic hepatic dysfunction is not known. No specific risk factors have been identified.

Renal and urinary disorders

Nephrotic syndrome

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

Laboratory abnormalities

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

Thyroid disorders

Patients being treated with Rebif may occasionally develop new or worsening thyroid abnormalities. Thyroid function testing is recommended at baseline and if abnormal, every 6-12 months following initiation of therapy. If tests are normal at baseline, routine testing is not needed but should be performed if clinical findings of thyroid dysfunction appear (*see section 3.8 Undesirable effects*).

Severe renal or hepatic failure and severe myelosuppression

Caution should be used, and close monitoring considered when administering interferon beta-1a to patients with severe renal and hepatic failure and to patients with severe myelosuppression.

Neutralising antibodies
Serum neutralising antibodies against interferon beta-1a may develop. The precise incidence of antibodies is as yet uncertain. Clinical data suggest that after 24 to 48 months of treatment with Rebif 22 micrograms, approximately 24% of patients develop persistent serum antibodies to interferon beta-1a. The presence of antibodies has been shown to attenuate the pharmacodynamic response to interferon beta-1a (Beta-2 microglobulin and neopterin). Although the clinical significance of the induction of antibodies has not been fully elucidated, the development of neutralising antibodies is associated with reduced efficacy on clinical and MRI variables. If a patient responds poorly to therapy with Rebif, and has neutralising antibodies, the treating physician should reassess the benefit/risk ratio of continued Rebif therapy.

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

Other forms of multiple sclerosis
Only sparse safety and efficacy data are available from non-ambulatory patients with multiple sclerosis. Rebif has not yet been investigated in patients with primary progressive multiple sclerosis and should not be used in such patients.

Excipients
Sodium content
This medicinal product contains less than 1 mmol sodium (23 mg) per dose, i.e. it is essentially 'sodium-free'.

Benzyl alcohol
This medicinal product contains benzyl alcohol. Benzyl alcohol may cause allergic reactions.

Monitor patients less than 3 years of age for respiratory symptoms.

Advise patients who are pregnant or breastfeeding of the potential risk from excipient benzyl alcohol, which might accumulate over time and cause metabolic acidosis. Use with caution in patients with hepatic or renal impairment, because of the potential risk from excipient benzyl alcohol which might accumulate over time and cause metabolic acidosis.

3.5 Interaction with other medicinal products and other forms of interaction
No interaction studies have been performed with interferon beta-1a in humans.

Interferons have been reported to reduce the activity of hepatic cytochrome P450-dependent enzymes in humans and animals. Caution should be exercised when administering Rebif in combination with medicinal products that have a narrow therapeutic index and are largely dependent on the hepatic cytochrome P450 system for clearance, e.g. antiepileptics and some classes of antidepressants.

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

3.6 Fertility, pregnancy and lactation
Women of childbearing potential
Women of child-bearing potential should take appropriate contraceptive measures. If the patient becomes pregnant or plans to become pregnant while taking Rebif she should be informed of the potential hazards and discontinuation of therapy should be considered (*see section 4.3 Preclinical Safety Data*). In patients with a high relapse rate before treatment has started, the risk of a severe relapse following discontinuation of Rebif in the event of pregnancy should be weighed against a possible increased risk of spontaneous abortion.

Pregnancy
A large amount of data (more than 1,000 pregnancy outcomes) from registries and post-marketing experience indicates no increased risk of major congenital anomalies after pre-conception exposure to interferon beta or such exposure during the first trimester of pregnancy. However, the duration of exposure during the first trimester is uncertain, because data were collected when interferon beta use was contraindicated during pregnancy, and treatment likely interrupted when the pregnancy was detected and/or confirmed. Experience with exposure during the second and third trimester is very limited.

Based on animal data (*see section 4.3 Preclinical Safety Data*) there is a possibly increased risk for spontaneous abortion. The risk of spontaneous abortions in pregnant women exposed to interferon beta cannot adequately be evaluated based on the currently available data, but the data do not suggest an increased risk so far.

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

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

Rebif can be used during breast-feeding.

Fertility
The effects of Rebif on fertility have not been investigated.

3.7 Effects on ability to drive and use machines
Central nervous system-related adverse events associated with the use of interferon beta (e.g. dizziness) might influence the patient's ability to drive or use machines (*see section 3.8 Undesirable effects*).

3.8 Undesirable effects
Summary of the safety profile
The highest incidence of adverse reactions associated with Rebif therapy is related to flu-like syndrome. Flu-like symptoms tend to be most prominent at the initiation of therapy and decrease in frequency with continued treatment. Approximately 70% of patients treated with Rebif can expect to experience the typical interferon flu-like syndrome within the first six months after starting treatment. Approximately 30% of patients will also experience reactions at the injection site, predominantly mild inflammation or erythema. Asymptomatic increases in laboratory parameters of hepatic function and decreases in white blood cells are also common.

The majority of adverse reactions observed with interferon beta-1a are usually mild and reversible, and respond well to dose reductions. In case of severe or persistent undesirable effects, the dose of Rebif may be temporarily lowered or interrupted, at the discretion of the physician.

List of adverse reactions
The adverse reactions presented have been identified from clinical studies as well as from post-marketing reports *(an asterisk [*] indicates adverse reactions identified during post-marketing surveillance)*. The following definitions apply to the frequency terminology used hereafter: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), frequency not known (cannot be estimated from the available data).

Blood and lymphatic system disorders
Very common: Neutropenia, lymphopenia, leucopenia, thrombocytopenia, anaemia
Rare: Thrombotic microangiopathy including thrombotic thrombocytopenic purpura/ Haemolytic uremic syndrome*, pancytopenia*

Endocrine Disorders

Uncommon: Thyroid dysfunction most often presenting as hypothyroidism or hyperthyroidism

Immune system disorder
Rare: Anaphylactic reactions*

Hepatobiliary disorders
Verry common: Asymptomatic transaminase increase
Common: Severe elevations in transaminases
Uncommon: Hepatitis with or without icterus*
Rare: Hepatic Failure* (*see section 3.4 Special warnings and precautions for use*), autoimmune hepatitis*.

Psychiatric disorders
Common: Depression, insomnia
Rare: Suicide attempt*

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

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

Vascular disorders
Uncommon: Thromboembolic events*.

Respiratory, thoracic and mediastinal disorders
Uncommon: Dyspnoea*

Gastrointestinal disorders
Common: Diarrhoea, vomiting, nausea

Skin and subcutaneous tissue disorders
Common: Pruritus, rash, erythematous rash, maculo-papular rash, alopecia*
Uncommon: Urticaria*
Rare: Quicke's oedema (angio-oedema)* erythema multiforme*, erythema multiforme-like skin reactions*, Stevens Johnson syndrome*.

Musculoskeletal and connective disorders
Common: Myalgia, arthralgia
Rare: Drug-induced lupus erythematosus*.

Renal and urinary disorders
Rare: Nephrotic syndrome*, glomerulosclerosis* (*see section 3.4 Special Warnings and precautions for use*).

General disorders and administratisite conditions
Very common: Injection site inflammation, injection site reaction, influenza-like symptoms.
Common: Injection site pain, fatigue, rigors, fever
Uncommon: Injection site necrosis, injection site mass, injection site abscess, injection site infections*, increased sweating*
Rare: Injection site cellulitis*

*Adverse reactions identified during post marketing surveillance

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

Class effects
The administration of interferons has been associated with anorexia, dizziness, anxiety, arrhythmias, vasodilation and palpitation, menorrhagia and metrorrhagia.

An increased formation of auto-antibodies may occur during treatment with interferon beta.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions.

3.9 Overdose
In case of overdose, patients should be hospitalised for observation and appropriate supportive treatment should be given.

4. PHARMACOLOGICAL PROPERTIES
4.1 Pharmacodynamic properties
Pharmacotherapeutic group: Immunostimulants, Interferons, ATC code: L03AB07.

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

Rebif (interferon beta-1a) shares the same amino acid sequence with endogenous human interferon beta. It is produced in mammalian cells (Chinese hamster ovary) and is therefore glycosylated like the natural protein.

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

Biological response markers (e.g., 2',5'-OAS activity, neopterin and beta-2-microglobulin) are induced by interferon beta-1a following subcutaneous doses administered to healty volunteer subjects. Time to peak concentrations following a single subcutaneous injections were 24 to 48 hour for neopterin, beta-2-microglobulin and 2'5'OAS, 12 hours for MX1 and 24 hours for OAS1 and OAS2 gene expression. Peak of similar height and time were observed for most of these markers after firts and sixth administrations.

The precise mechanism of action of Rebif in multiple sclerosis is still under investigation.

Relapsing-remitting multiple sclerosis
The safety and efficacy of Rebif has been evaluated in patients with relapsing-remitting multiple sclerosis at doses ranging from 11 to 44 micrograms (3-12 million IU), administered subcutaneously three times per week. At licensed posology, Rebif 22 micrograms has been demonstrated to decrease the incidence (approximately 30% over 2 years) and severity of clinical relapses in patients with at least 2 exacerbations in the previous 2 years and with an EDSS of 0-5.0 at entry. The proportion of patients with disability progression, as defined by at least one point increase in EDSS confirmed three months later, was reduced from 39% (placebo) to 30% (Rebif 22 micrograms). Over 4 years, the reduction in the mean exacerbation

rate was 22% in patients treated with Rebif 22 micrograms, group compared with a group of patients treated with placebo for 2 years and then Rebif 22 for 2 years.

Secondary progressive multiple sclerosis
In a 3-year study in patients with secondary progressive multiple sclerosis (EDSS 3-6.5) with evidence of clinical progression in the preceding two years and who had not experienced relapses in the preceding 8 weeks, Rebif had no significant effect on progression of disability, but relapse rate was reduced by approximately 30%. If the patient population was divided into 2 subgroups (those with and those without relapses in the 2-year period prior to study entry), there was no effect on disability in patients without relapses, but in patients with relapses, the proportion with progression in disability at the end of the study was reduced from 70% (placebo)to 57% (Rebif 22 microgram and Rebif 44 microgram). These results obtained in a subgroup of patients a posteriori should be interpreted cautiously.

Primary progressive multiple sclerosis
Rebif has not yet been investigated in patients with primary progressive multiple sclerosis, and should not be used in these patients.

4.2 Pharmacokinetic properties
Absorption
In healthy volunteers after intravenous administration, interferon beta-1a exhibits a sharp multi-exponential decline, with serum levels proportional to the dose. Subcutaneous and intramuscular administrations of Rebif produce equivalent exposure to interferon beta.

Distribution
Following repeated subcutaneous injections of 22 and 44 micrograms doses of Rebif maximum concentrations were typically observed after 8 hours, but this was highly variable.

Elimination
After repeated subcutaneous doses in healthy volunteers, the main PK parameters (AUC_{tau} and C_{max}) increased proportional to the increased in dose from 22 micrograms to 44 micrograms. The estimated apparent half-life is 50 to 60 hours, which is in line with the accumulation observed after multiple dosing.

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

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

Rebif has not been investigated for carcinogenicity.

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

5. PHARMACEUTICAL PARTICULARS
5.1 List of excipients
Mannitol
Poloxamer 188
L-methionine
Benzyl alcohol
Sodium acetate
Acetic acid for pH adjustment
Sodium hydroxide for pH adjustment
Water for injections

5.2 Incompatibilities
Not applicable.

5.3 Shelf life
The expiry date is indicated in the packaging.

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

5.5 Nature and contents of container
One ml type I glass syringe, with a stainless steel needle, containing 0.5 ml solution.

Rebif 22 micrograms is available as a package of 3 syringes.

Not all pack sizes may be marketed.

5.6 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 product or waste material should be disposed of in accordance with local requirements.

5.7 Package Quantities and Registration Number
Rebif®, Box, 3 pre-filled syringes @ 22 mcg (0.5 ml) Reg. No. DKI0980500843A1

HARUS DENGAN RESEP DOKTER
On Medical Prescription Only

Manufactured by
Merck Serono S.p.A.,
Via delle Magnolie 15 (loc. Frazione Zona Industriale)
70026 Modugno (BA), Italy

Imported by
PT Merck Tbk.
Jakarta, Indonesia

PI based on CCDS v11.0
DW/jt/28May2021

Update approval: XX XX XXXX

INFORMASI UNTUK PASIEN

REBIF® 22 mikrogram
Interferon beta-1a

Larutan untuk injeksi dalam *pre-filled syringe*

Baca seluruh petunjuk ini dengan hati-hati sebelum Anda mulai menggunakan obat, karena petunjuk ini berisi informasi yang penting untuk Anda.
- Simpan lembar petunjuk ini. Anda mungkin akan memerlukannya kembali.
- Jika Anda memiliki pertanyaan lebih lanjut, harap menghubungi kepada dokter, apoteker atau perawat Anda.
- Obat ini diresepkan hanya untuk Anda. Jangan diberikan kepada orang lain karena dapat membahayakan orang tersebut meskipun terdapat gejala yang sama pada orang tersebut.
- Jika Anda mengalami efek samping hubungi dokter, apoteker, atau perawat Anda. Ini termasuk kemungkinan efek samping yang tidak terdapat dalam informasi produk. Lihat bagian 4.

Petunjuk ini terdiri dari informasi sebagai berikut:

1. Apa itu Rebif dan apa kegunaannya?
Rebif termasuk ke dalam golongan obat-obatan yang dikenal sebagai interferon. Interferon merupakan zat alami yang mengirimkan pesan antar sel. Interferon diproduksi oleh tubuh dan memainkan peran penting dalam sistem kekebalan tubuh. Melalui mekanisme yang tidak sepenuhnya dipahami, interferon membantu membatasi kerusakan sistem saraf pusat yang diasosiasikan dengan *multiple sclerosis*.

Rebif adalah protein larut yang sangat murni yang mirip dengan beta interferon alami yang diproduksi dalam tubuh manusia.

Rebif digunakan untuk pengobatan *multiple sclerosis.* Rebif telah terbukti mengurangi frekuensi dan keparahan kekambuhan serta memperlambat perkembangan disabilitas.

2. Apa yang perlu Anda ketahui sebelum Anda menggunakan Rebif
Jangan gunakan Rebif
- jika Anda alergi terhadap beta interferon alami atau rekombinan atau salah satu dari bahan lain dari obat ini (tercantum dalam bagian 6).
- jika Anda sangat depresi saat ini dan/atau memiliki keinginan untuk bunuh diri.

Peringatan dan tindakan pencegahan
Bicarakan dengan dokter, apoteker atau perawat Anda sebelum menggunakan Rebif.
- Rebif hanya boleh digunakan dengan pengawasan dokter Anda.
- Sebelum pengobatan dengan Rebif, baca dengan seksama dan ikuti saran yang diberikan pada bagian “Bagaimana cara menggunakan Rebif” untuk meminimalkan risiko nekrosis di tempat suntikan (kerusakan kulit dan kerusakan jaringan) yang telah dilaporkan pada pasien yang diobati dengan Rebif. Jika Anda mengalami reaksi lokal yang mengganggu, hubungi dokter Anda.
- Bicarakan dengan dokter atau apoteker Anda sebelum menggunakan Rebif jika Anda memiliki alergi (hipersensitivitas) terhadap obat lain.

- Pembekuan darah di pembuluh darah kecil dapat terjadi selama pengobatan Anda. Bekuan darah ini bisa mempengaruhi ginjal Anda. Ini mungkin dapat terjadi beberapa minggu hingga beberapa tahun setelah memulai Rebif. Dokter Anda mungkin ingin memeriksa tekanan darah Anda, darah (jumlah trombosit) dan fungsi ginjal Anda.

Beritahu dokter Anda jika Anda memiliki penyakit
- sumsum tulang,
- ginjal,
- hati,
- jantung,
- tiroid,
- atau jika Anda pernah mengalami depresi,
- atau jika Anda memiliki riwayat kejang epilepsi,

sehingga dokter dapat memantau pengobatan Anda dan hal memperburuk kondisi ini.

Obat-obatan lainnya dan Rebif
Beritahu dokter atau apoteker Anda jika Anda sedang menggunakan, baru-baru ini telah menggunakan atau mungkin menggunakan obat lain. Khususnya Anda harus memberi tahu dokter jika Anda menggunakan antiepilepsi atau antidepresan.

Kehamilan dan menyusui
Jika Anda sedang hamil, berpikir Anda mungkin hamil atau berencana untuk memiliki bayi, hubungi dokter atau apoteker Anda untuk meminta saran sebelum menggunakan obat ini.

Tidak ada efek yang membahayakan pada bayi yang disusui oleh Ibu yang mendapat Interferon beta-1a. Rebif dapat digunakan selama menyusui.

Mengemudi dan menggunakan mesin
Efek dari penyakit itu sendiri atau pengobatannya dapat mempengaruhi kemampuan Anda untuk mengemudi atau menggunakan mesin.

Anda harus membicarakan hal ini dengan dokter Anda jika Anda khawatir.

Rebif mengandung sodium dan benzyl alcohol
Obat ini mengandung 2,5 mg benzyl alkohol per dosis. Benzyl alcohol dapat menyebabkan reaksi alergi.

Benzyl alcohol telah dikaitkan dengan risiko efek samping yang berat termasuk masalah pernapasan (yang dikenal dengan "*gasping syndrome*") pada anak-anak.

Jangan gunakan selama lebih dari seminggu pada anak-anak (kurang dari 3 tahun), kecuali jika disarankan oleh dokter atau apoteker Anda.

Hubungi dokter atau apoteker Anda untuk meminta saran jika Anda sedang hamil atau menyusui, atau jika Anda memiliki masalah gangguan hati atau ginjal. Hal ini dikarenakan, konsistensi benzyl alcohol yang tinggi dapat menumpuk dalam tubuh Anda dan dapat menyebabkan efek samping (yang dikenal dengan asidosis metabolik).

3. Bagaimana cara menggunakan Rebif

Selalu gunakan obat ini persis seperti yang disarankan oleh dokter Anda. Konfirmasi kembali dengan dokter Anda jika Anda tidak yakin.

Dosis
Dosis umum adalah 44 mikrogram (12 juta IU) diberikan tiga kali per minggu. Dokter anda telah meresepkan dosis yang lebih rendah yaitu 22 mikrogram (6 juta IU) diberikan tiga kali per minggu untuk Anda. Dosis ini dianjurkan untuk pasien yang tidak dapat mentoleransi dosis yang lebih tinggi.

Rebif harus diberikan tiga kali per minggu, dan jika mungkin:
- pada tiga hari yang sama setiap minggu (setidaknya dengan jeda 48 jam per dosis, misalnya, Senin, Rabu, Jumat)
- pada waktu yang sama (sebaiknya di malam hari).

Penggunaan pada anak-anak dan remaja (usia 2 hingga 17 tahun)
Tidak ada studi klinis formal yang dilakukan pada anak-anak atau remaja. Namun ada beberapa data klinis yang tersedia yang menunjukkan bahwa profil keamanan pada anak-anak dan remaja yang menerima Rebif 22 mikrogram atau Rebif 44 mikrogram tiga kali per minggu hampir sama dengan yang profil keamanan yang terlihat pada orang dewasa.

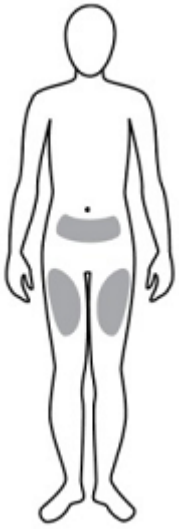
Penggunaan pada anak-anak (di bawah 2 tahun)
Rebif tidak disarankan untuk digunakan pada anak-anak di bawah usia 2 tahun.

Cara pemberian
Rebif ditujukan untuk suntikan subkutan (di bawah kulit).

Suntikan pertama harus dilakukan di bawah pengawasan profesional kesehatan yang memenuhi syarat. Setelah mendapatkan pelatihan yang memadai, Anda, anggota keluarga, teman atau pengasuh dapat menggunakan suntikan Rebif untuk memberikan obat di rumah. Rebif juga dapat diberikan dengan injektor otomatis yang sesuai.

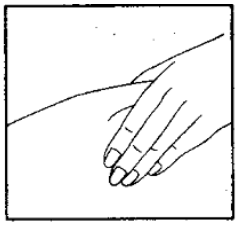
Untuk pemberian Rebif, harap baca petunjuk berikut dengan seksama:
Obat ini untuk sekali pakai. Hanya larutan yang jernih hingga opalescent tanpa partikel dan tanpa terlihat tanda-tanda kerusakan yang dapat digunakan.

Cara menyuntikkan Rebif

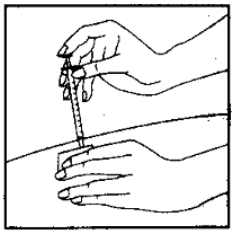


- Pilih tempat penyuntikan. Dokter Anda akan memberi tahu Anda kemungkinan tempat penyuntikan (tempat penyuntikan yang baik meliputi paha atas dan perut bagian bawah). Pegang jarum suntik seperti pensil atau panah. Disarankan agar Anda memantau dan mengganti tempat penyuntikan Anda secara berkala, sehingga satu area tidak terlalu sering disuntik untuk meminimalkan risiko nekrosis pada tempat penyuntikan.

  CATATAN: jangan gunakan area dimana Anda merasakan ada benjolan, tonjolan keras, atau terasa nyeri; diskusikan dengan dokter atau profesional kesehatan Anda tentang apa pun yang Anda temukan.
- Cuci tangan Anda dengan sabun dan air.
- Lepaskan jarum suntik Rebif dari kemasan blister dengan mengelupas penutup plastik.
- Sebelum penyuntikan, gunakan pembersih alkohol untuk membersihkan kulit di tempat penyuntikan. Biarkan kulit kering. Jika sedikit alkohol tersisa di kulit, Anda mungkin merasakan sensasi menyengat.



- Cubit kulit di sekitar tempat penyuntikan dengan lembut (untuk mengangkatnya sedikit).
- Letakkan pergelangan tangan Anda pada kulit di dekat tempat penyuntikan, suntikan jarum pada sudut yang tepat langsung ke dalam kulit dengan gerakan yang cepat dan kuat.
- Suntikkan obat dengan dorongan yang pelan dan stabil (tekan *plunger* sampai *syringe* kosong).
- Pegang kapas beralkohol pada tempat suntikan. Cabut jarum dari kulit.



- Pijat lembut tempat suntikan dengan bola kapas kering atau kain kasa.
- Buang semua barang yang telah digunakan: begitu Anda selesai menyuntikkan, segera buang *syringe* di tempat pembuangan yang sesuai.

Jika Anda menggunakan Rebif lebih dari yang seharusnya
Jika terjadi overdosis, segera hubungi dokter Anda.

Jika Anda lupa menggunakan Rebif
Jika Anda melewatkan satu dosis, teruskan suntikkan pada dosis hari berikutnya sesuai yang dijadwalkan. Jangan gunakan dosis dua kali lipat untuk mengganti dosis yang terlupakan.

Jika Anda berhenti menggunakan Rebif
Efek Rebif mungkin tidak segera terlihat. Oleh karena itu, Anda tidak boleh berhenti menggunakan Rebif, Anda harus terus menggunakannya secara teratur untuk mencapai hasil yang diinginkan. Jika Anda tidak yakin tentang manfaatnya, silakan berkonsultasi dengan dokter Anda.

Anda tidak boleh menghentikan pengobatan tanpa terlebih dahulu menghubungi dokter Anda.

Jika Anda memiliki pertanyaan lebih lanjut tentang penggunaan obat ini, tanyakan kepada dokter, apoteker atau perawat Anda.

4. Kemungkinan efek samping

Seperti semua obat-obatan, obat ini dapat menyebabkan efek samping, meskipun tidak semua orang akan mengalaminya.

Beritahu dokter Anda segera dan berhenti menggunakan Rebif jika Anda mengalami salah satu dari efek samping yang serius berikut ini:

- **Reaksi alergi (hipersensitivitas) yang serius**. Jika, segera setelah pemberian Rebif, Anda mengalami kesulitan bernapas yang tiba-tiba, yang mungkin timbul dalam kaitannya dengan pembengkakan wajah, bibir, lidah atau tenggorokan, ruam jelatang, gatal di seluruh tubuh, dan perasaan lemas atau pingsan, segera hubungi dokter Anda atau cari pertolongan medis darurat. Reaksi-reaksi ini jarang terjadi (dapat terjadi pada hingga 1 dari 1.000 orang).
- Beritahu dokter Anda segera jika Anda mengalami salah satu kemungkinan gejala **gangguan hati** berikut: penyakit kuning (kulit atau bagian putih mata menguning), gatal-gatal yang menyebar luas, kehilangan nafsu makan disertai mual dan muntah dan kulit mudah memar. Masalah hati yang parah dapat dikaitkan dengan gejala-gejala tambahan, misalnya kesulitan berkonsentrasi, kantuk dan kebingungan.

- **Depresi** sering terjadi (dapat terjadi pada hingga 1 dari 10 orang) pada pasien dengan *multiple sclerosis* yang sedang dalam pengobatan. Jika Anda merasa **depresi atau berpikir untuk bunuh diri**, segera laporkan ke dokter Anda.

Bicarakan dengan dokter Anda jika Anda mengalami salah satu efek samping berikut:

- **Gejala mirip flu**, seperti sakit kepala, demam, menggigil, nyeri otot dan sendi, kelelahan dan mual *sering terjadi* (dapat terjadi pada lebih dari 1 dari 10 orang).

  Gejala-gejala ini biasanya ringan, lebih sering terjadi pada awal pengobatan dan berkurang dengan penggunaan terus-menerus.

  Untuk membantu mengurangi gejala-gejala ini, dokter Anda mungkin menyarankan Anda untuk meminum obat penghilang rasa sakit dan pereda demam sebelum menyuntikan dosis Rebif dan 24 jam setelah setiap suntikan.

- **Reaksi di tempat penyuntikan** termasuk kemerahan, pembengkakan, perubahan warna, peradangan, nyeri dan kerusakan kulit *sering terjadi*.

  Frekuensi terjadinya reaksi di tempat penyuntikan biasanya akan menurun seiring dengan waktu.

  Kehancuran jaringan (nekrosis), abses dan gumpalan massa di tempat penyuntikan jarang terjadi (dapat terjadi pada hingga 1 dari 100 orang).

  Lihat rekomendasi di bagian "Peringatan dan tindakan pencegahan" untuk meminimalkan risiko reaksi di tempat penyuntikan.

  Tempat penyuntikan dapat terinfeksi (*jarang*); kulit akan menjadi bengkak yang terasa sakit dan keras dan seluruh area mungkin akan terasa sangat sakit. Jika Anda mengalami gejala-gejala ini, hubungi dokter Anda untuk meminta saran.

- **Tes laboratorium** tertentu dapat berubah. Perubahan ini umumnya tidak diperhatikan oleh pasien (tidak ada gejala), biasanya reversibel dan ringan, dan biasanya tidak memerlukan pengobatan khusus.

  Jumlah sel darah merah, sel darah putih atau trombosit dapat berkurang baik sendiri-sendiri (*sering*) atau semua pada satu waktu sekaligus (*sangat jarang*). Kemungkinan gejala akibat dari perubahan ini bisa berupa kelelahan, berkurangnya kemampuan untuk melawan infeksi, memar atau pendarahan yang tidak dapat dijelaskan.

  Tes fungsi hati mungkin terganggu (*sering*). Peradangan hati juga telah dilaporkan (*jarang*). Jika Anda mengalami gejala yang menunjukkan gangguan hati, seperti kehilangan nafsu makan disertai dengan gejala lain seperti mual, muntah, sakit kuning, silakan hubungi dokter Anda segera (lihat di atas “Beritahu dokter Anda segera ...”).

- **Disfungsi tiroid** *jarang terjadi*. Kelenjar tiroid dapat berfungsi secara berlebihan, atau secara tidak memadai. Perubahan-perubahan dalam aktivitas tiroid ini hampir selalu tidak dirasakan oleh pasien sebagai gejala; Namun dokter Anda mungkin akan merekomendasikan tes yang sesuai.

- **MS *pseudo-relapse*** (*frekuensi tidak diketahui*): Ada kemungkinan bahwa pada awal pengobatan Anda dengan Rebif, Anda mungkin mengalami gejala yang mirip dengan gejala kambuhnya *multiple sclerosis*. Misalnya, otot Anda mungkin terasa sangat tegang atau sangat lemah, menyebabkan Anda tidak bisa bergerak seperti yang Anda inginkan. Dalam beberapa kasus, gejala-gejala tersebut diasosiasikan dengan demam atau gejala mirip flu yang dijelaskan di atas. Jika Anda menyadari salah satu efek samping ini, konsultasikan dengan dokter Anda.

Kemungkinan efek samping lain meliputi:
Sangat sering terjadi (dapat terjadi pada lebih dari 1 dari 10 orang):
- Sakit kepala

Sering terjadi (dapat terjadi pada hingga 1 dari 10 orang):
- Insomnia (kesulitan tidur)
- Diare, mual, muntah
- Gatal, ruam (erupsi kulit)
- Nyeri otot dan sendi
- Kelelahan, demam, menggigil
- Rambut rontok

Jarang (dapat terjadi pada hingga 1 dari 100 orang):
- Urtikaria
- Kejang epilepsi
- Peradangan hati (hepatitis)
- Kesulitan bernapas
- Pembekuan darah seperti trombosis vena dalam
- Gangguan retina (belakang mata) seperti peradangan atau pembekuan darah dengan gangguan penglihatan sebagai konsekuensi (gangguan penglihatan, hilangnya penglihatan)
- Meningkatnya keringat

Sangat Jarang (dapat terjadi pada hingga 1 dari 1.000 orang):
- Percobaan bunuh diri
- Reaksi kulit serius - sebagian dengan lesi mukosa
- Pembekuan darah di pembuluh darah kecil yang dapat memengaruhi ginjal Anda (purpura thrombocytopenic trombotik atau sindrom uremik hemolitik). Gejala mungkin termasuk memar-memar yang meningkat, perdarahan, demam, kelemahan ekstrim, sakit kepala, pusing atau pening. Dokter Anda mungkin menemukan perubahan dalam darah Anda dan fungsi ginjal Anda.
- Lupus eritematosus yang diinduksi oleh obat: efek samping dari penggunaan Rebif jangka panjang. Gejalanya mungkin termasuk nyeri otot, nyeri sendi dan bengkak, dan ruam. Anda mungkin juga mengalami gejala-gejala lain seperti demam, penurunan berat badan, dan kelelahan. Biasanya gejala hilang dalam satu atau dua minggu setelah pengobatan dihentikan.
- Masalah ginjal termasuk luka yang dapat mengurangi fungsi ginjal Anda. Jika Anda mengalami beberapa atau semua gejala ini:
  - air kencing berbusa
  - kelelahan
  - bengkak, terutama di pergelangan kaki dan kelopak mata, dan berat badan.

  Beritahu dokter Anda karena mungkin ada tanda-tanda kemungkinan masalah ginjal.

Efek samping berikut dilaporkan untuk interferon beta (frekuensi tidak diketahui)
- Pusing
- Gugup
- Kehilangan selera makan
- Dilatasi pembuluh darah dan palpitasi
- Kelainan dan/atau perubahan aliran menstruasi.
- Hipertensi arteri pulmonal - penyakit penyempitan pembuluh darah parah di paru-paru yang menyebabkan tekanan darah tinggi di pembuluh darah yang membawa darah dari jantung ke paru-paru. Hipertensi arteri pulmonal telah terlihat pada berbagai titik waktu selama pengobatan, termasuk beberapa tahun setelah memulai pengobatan dengan Rebif.

Anda tidak boleh menghentikan atau mengubah pengobatan tanpa saran dari dokter Anda.

Anak-anak dan remaja
Efek samping pada anak-anak dan remaja hampir sama dengan yang diamati pada orang dewasa.

Pelaporan efek samping
Jika Anda mengalami efek samping, bicarakan dengan dokter, apoteker, atau perawat Anda. Ini termasuk kemungkinan efek samping yang tidak terdapat dalam informasi produk ini.

5. Bagaimana menyimpan Rebif

Jauhkan obat ini dari pandangan dan jangkauan anak-anak.

Jangan gunakan obat ini setelah tanggal kedaluwarsa yang tercantum pada label di bagian EXP.

Simpan dalam lemari pendingin (2°C - 8°C).

Jangan dibekukan. (Untuk mencegah pembekuan yang tidak disengaja, jangan ditempatkan di dekat kompartemen *freezer*).

Untuk tujuan penggunaan rawat jalan, Anda dapat mengeluarkan Rebif dari lemari pendingin dan menyimpannya pada suhu di bawah 25°C selama satu periode hingga 14 hari. Rebif harus dikembalikan ke lemari pendingin dan digunakan sebelum tanggal kedaluwarsa.

Simpan dalam kemasan asli untuk melindunginya dari cahaya.

Jangan gunakan obat ini jika Anda melihat tanda-tanda kerusakan seperti jika larutan tidak lagi jernih atau jika terdapat partikel.

Jangan membuang obat apa pun melalui air limbah atau limbah rumah tangga. Tanyakan apoteker Anda bagaimana membuang obat-obatan yang tidak lagi Anda gunakan. Langkah-langkah ini akan membantu melindungi lingkungan.

6. Isi kemasan dan informasi lainnya

Apa kandungan Rebif

- Rebif mengandung zat aktif~~nya adalah~~ interferon beta-1a. Setiap ~~jarum suntik~~ *syringe* mengandung 22 mikrogram setara dengan 6 juta Unit Internasional (IU) interferon beta-1a.
- Bahan lainnya adalah mannitol, poloxamer 188, methionine, benzyl alcohol, sodium acetate, acetic acid, sodium hydroxide dan air untuk injeksi.

Seperti apa tampilan Rebif dan isi kemasan
Rebif tersedia sebagai larutan untuk injeksi dalam *pre-filled syringe* dengan jarum untuk penyuntikan sendiri. Larutan Rebif jernih hingga *opalescent. Pre-filled syringe* siap digunakan dan berisi 0,5 mL larutan.

Rebif tersedia dalam kemasan 3 *pre-filled syringes.*

Kemasan dan Nomor Izin Edar

Rebif®, Dus, 3 *pre-filled syringes* @ 22 mcg (0.5 mL) Reg. No. DKI0980500843A1

HARUS DENGAN RESEP DOKTER

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