Merck Serono

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Rebif® 22 micrograms 44 micrograms

solution for injection in pre-filled syringe

Interferon beta-1a

COMPOSITION

Rebif 22 micrograms solution for injection in pre-filled syringe:

Each pre-filled syringe contains 22 micrograms of interferon beta-1a in 0.5 ml solution corresponding to 6 million International Units (IU).

Rebif 44 micrograms solution for injection in pre-filled syringe:

Each pre-filled syringe contains 44 micrograms of interferon beta-1a in 0.5 ml solution corresponding to 12 million International Units (IU).

Excipients: mannitol, poloxamer 188, L-methionine, benzyl alcohol, sodium acetate, acetic acid for pH adjustment, sodium hydroxide for pH adjustment, water for injections.

PROPERTIES

Interferon beta-1a, the active ingredient in Rebif, is similar to the natural interferon beta that is produced in the human body.

Mechanism of action

Interferons are natural substances produced by the body that transmit messages between cells. They play an essential role in the immune system and help to limit the damage of the central nervous system associated with multiple sclerosis (MS). Rebif has been shown to reduce the number and the severity of relapses of multiple sclerosis and to slow the progression of disability.

Pharmacodynamic properties

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 super imposable responses.

Biological response markers are induced by interferon beta-1a. following subcutaneous doses administered to healthy volunteer subjects and to patients with multiple sclerosis

Time to peak concentrations following a single subcutaneous injection were 24 to 48 hours fro neopterin, beta-2-microglobulin and 2'5'OAS, 12 hours for MXI and 24 hours for OASI and OAS2 gene expression. Peaks of similar height and time were observed for most of these markers after first and sixth administration

Administration of Rebif 22 micrograms three times per week (tiw) inhibited mitogen-induced release of pro-inflammatory cytokines (IFN-γ, IL-1, IL-6, TNF-α and TNF-β) by peripheral blood mononuclear cells that, on average, was near double that observed with Rebif administered once per week (qw) at either 22 or 66 micrograms.

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. The initial half-life is in the order of minutes and the terminal half-life is several hours.

When administered by the subcutaneous or intramuscular routes, serum levels of interferon beta remain low, but are still measurable up to 12-24 hours post-dose. Subcutaneous and intramuscular administration of Rebif produce equivalent exposure to interferon beta.

Distribution

Following repeated subcutaneous injections of 22 and 44 microgram doses of Rebif maximum concentrations were observed after 3-8 hours

Elimination

After repeated subcutaneous doses in healthy volunteers, the main PK parameters (AUCtau and Cmax) increased proportional to the increase in dose from 22 microgram to 44 microgram. 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.

Clinical efficacy

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 high 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). 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. Upon conversion to clinically definite multiple sclerosis (CDMS) 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. Both Rebif 44 micrograms given three times per week and Rebif 44 micrograms given once per week delayed the progression from the first clinical event to multiple sclerosis according to the McDonald (2005) criteria and to CDMS in a statistically significant and clinically meaningful manner compared to placebo.

The treatment effect of Rebif 44 microgram given three times per week was superior to the treatment effect of Rebif 44 micrograms given once per week in delaying the progression from the first clinical event to multiple sclerosis according to the McDonald (2005) criteria.

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 the recommended 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 Expanded Disability Status Scale (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, 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 micrograms or Rebif 44 micrograms for 2 years.

Secondary progressive multiple sclerosis

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

Non-clinical safety

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. Based on observations with other alpha and beta interferons, an increased risk of abortions cannot be excluded.

INDICATION

Rebif is indicated for the treatment of

- patients with relapsing forms of multiple sclerosis,
- patients who have experienced a single clinical event likely to be a first sign of multiple sclerosis and have Magnetic Resonance Imaging (MRI) features consistent with multiple sclerosis.

CONTRAINDICATIONS

Do not use Rebif if you are allergic (hypersensitive) to natural or recombinant interferon beta or any of the other ingredients of Rebif (see 'COMPOSITION').

Pregnancy, nursing mothers & pediatric use:

Don't administer injections with benzyl alcohol to neonates, infants, pregnant women or nursing mothers. Benzyl alcohol has been associated with serious adverse events & death, particularly in pediatric patients. Injections preservative free should be used in these populations.

Pregnancy

Do not initiate treatment with Rebif if you are pregnant. There is limited information on the use of interferon beta-1a in pregnancy, but there may be an increased risk of spontaneous abortion.

While taking Rebif, you must use effective methods of contraception if you are a woman of child bearing potential. If you become pregnant or plan to become pregnant while using Rebif ask your doctor for advice.

Use of interferon beta-1a before establishment of pregnancy is not associated with increased risk of adverse pregnancy outcome. Patients planning for pregnancy and those becoming pregnant must be informed of the potential hazards of interferons to the foetus, i.e. potential increased risk of early miscarriage, and discontinuation of therapy should be considered. In patients with a high relapse rate before treatment started, the risk of disease reactivation following discontinuation of Rebif in the event of pregnancy must be weighed carefully.

Nursing mothers

Prior to taking the medicine, please inform your doctor if you are breast-feeding.

It is not known whether Rebif is excreted in human milk. Because of the potential for serious adverse reactions in breast-fed infants, your doctor will decide whether to stop breast-feeding or Rebif therapy.

SPECIAL WARNINGS AND PRECAUTIONS

This product contains benzyl alcohol which is potentially toxic when administered locally to neural tissue.

This product is contra-indicated for use in premature infants because the formulation contains benzyl alcohol.

Before treatment with Rebif, **read carefully and follow the advice given under 'DOSAGE AND ADMINISTRATION' in order to minimise the risk of skin breakdown and tissue destruction at the injection site (injection site necrosis)**. If you experience troubling local reactions, contact your doctor.

Please also read carefully the information under 'ADVERSE REACTIONS' to understand which are the most common unwanted effects and in which situations you may need to contact a doctor immediately.

Inform your doctor

- if you have a **disease of the liver, heart, thyroid, bone marrow**, or
- if you have experienced **depression**, or
- if you have any **history of epileptic seizures**,

so that he/she can closely monitor your treatment and any worsening of these conditions.

Thrombotic microangiopathy

Cases of thrombotic microangiopathy, manifested as thrombotic thrombocytopenic purpurea (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

Flu-like syndrome

Symptoms of the flu-like syndrome tend to be most prominent at the initiation of therapy and decrease in frequency and severity with continued treatment.

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. A relationship between the occurrence of depression, suicidal ideation or suicide attempts and the use of Rebif has not been established in subjects with multiple sclerosis. Depressive symptoms associated with Rebif may often be an atypical syndrome, occurring more frequently early in the course of treatment and not associated

with all of the usual clinical symptoms of depression: in particular, suicide ideation and suicide attempts are not more frequent in Rebif-treated patients. Depression and suicidal ideation are known to occur in increased frequency in the multiple sclerosis population. 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. If a patient develops depression, cessation of treatment with Rebif must be considered.

Cardiac disease

Patients with cardiac disease, such as angina, congestive heart failure or arrhythmia, must 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 has been reported in patients using Rebif. To minimise the risk of injection site necrosis patients must 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 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.

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 alanine-aminotransferase (ALT) levels must be monitored prior to the start of therapy, at months 1, 3 and 6 on therapy and periodically thereafter. Dose reduction of Rebif must 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). Treatment with Rebif must be stopped if icterus or other clinical symptoms of liver dysfunction appear. Rebif, like other interferons beta, has a potential for causing severe liver injury including acute hepatic failure. The mechanism for the rare symptomatic hepatic dysfunction is not known. No specific risk factors have been identified.

Seizure disorder

Caution must 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 must be established and appropriate anti-convulsant therapy instituted prior to resuming Rebif treatment.

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 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

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 must be performed if clinical findings of thyroid dysfunction appear.

Neutralising antibodies

The precise incidence of neutralising antibodies depends on several factors such as product formulation, dose, disease type, cut off titre, etc. The presence of antibodies has been shown to attenuate the pharmacodynamic response to the antiviral effect of Rebif (Beta 2 microglobulin and neopterin).

Although the clinical significance of the induction of antibodies has not been fully elucidated, the development of neutralising antibodies has been associated in some studies with reduced efficacy on clinical (relapses) and MRI variables. A NAb test alone cannot be used as the sole element on which to base therapeutic decision. A poor clinical course associated with the presence of persistent neutralising antibodies (NAb) should prompt reconsideration of interferon 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.

Effects on the ability to drive and use machines

Some adverse reactions of Rebif (e.g. dizziness) may affect your ability to concentrate and react and thus pose a risk when you are driving or using machines. If you experience such adverse reactions, speak to your doctor whether it is advisable for you to drive.

ADVERSE REACTIONS

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

For the adverse reactions described hereafter, the following definitions apply to the frequency terms used:

Very common	(may affect more than 1 in 10 people)
Common	(may affect up to 1 in 10 people)
Uncommon	(may affect up to 1 in 100 people)
Rare	(may affect up to 1 in 1,000 people)
Very rare	(may affect up to 1 in 10,000 people)
Frequency unknown	(cannot be estimated from the available data)

- Tell your doctor immediately and stop using Rebif if you experience any of the following serious adverse reactions:
- **Allergic (hypersensitivity) reactions, in rare cases severe allergic (anaphylactic) reactions.** If, immediately following Rebif administration you experience a sudden difficulty breathing, which may appear in association with swelling of face, lips, tongue or throat (angio-oedema), nettle rash (urticaria), itching all over the body, and a feeling of weakness or faintness, contact your doctor immediately or seek urgent medical attention.
- **Liver failure (rare) or liver inflammation (hepatitis) with or without jaundice (uncommon).** Inform your doctor immediately if you experience any of the following possible symptoms of a liver problem: jaundice (yellowing of the skin or of the whites of the eyes), widespread itching, loss of appetite accompanied by nausea and vomiting and easy bruising of the skin. Severe liver problems can be associated with additional signs, e.g. difficulty concentrating, sleepiness and confusion. The majority of the cases of severe liver problem occurred within the first six months of treatment. No specific risk factors have been identified.
- **Depression.** If you feel very depressed or develop thoughts of suicide, which is common under Rebif treatment, report it immediately to your doctor.

Flu-like symptoms

Headache, fever, chills, muscle and joint pain, fatigue and nausea are experienced by up to 70% of patients treated with Rebif within the first six months after starting treatment.

These symptoms are usually mild, are more common at the start of the treatment and decrease with continued use. To help reduce these symptoms your doctor may advise you to take a fever reducing painkiller before a dose of Rebif and then for 24 hours after each injection.

Injection site reactions

Redness, swelling, discoloration, inflammation, pain and skin breakdown are experienced by 30% of patients or more. The occurrence usually decreases over time.

Tissue destruction (necrosis), abscess and mass at injection site are uncommon (see recommendations in section "SPECIAL WARNINGS AND PRECAUTIONS" to minimise the risk of injection site reactions). It means that the injection site can become infected; the skin may become swollen tender and hard and the whole area could be very painful. If you experience any of these symptoms, contact your doctor for advice.

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Blood disorders

The number of red blood cells, white blood cells or platelets may decrease (anaemia, leukopenia, neutropenia, lymphopenia, or thrombocytopenia), which will be recognised in laboratory tests. These decreases in blood cells are very common, but are usually reversible and mild, and most often do not require particular treatment. A decrease in all cell lines at one time (pancytopenia) is rare. Possible symptoms resulting from these changes could include tiredness, reduced ability to fight infection, bruising or unexplained bleeding.

Thrombotic microangiopathy including thrombotic thrombocytopenic purpura/haemolytic uraemic syndrome, a disorder that may present with small blood clots, increased bruising, bleeding, decreased platelets, anaemia, extreme weakness, and renal disorders, is rare.

Thyroid disorders

The thyroid gland may function either excessively or insufficiently (thyroid dysfunction most often presenting as hypothyroidism or hyperthyroidism). These changes in the thyroid activity are almost always not felt by the patient as symptoms; however your doctor may recommend testing as appropriate. This adverse reaction is uncommon.

Nervous system disorders

Epileptic seizures are uncommon.

MS pseudo-relapses may occur at an unknown frequency at the beginning of your treatment with Rebif and you may experience transient neurological symptoms that resemble those of a multiple sclerosis relapse. For example, your muscles may feel very tense or very weak, preventing you from moving as you want (hypoesthesia, muscle spasm, paraesthesia, difficulty in walking, musculoskeletal stiffness). These symptoms may also mimic exacerbations of your illness.

Eye disorders

Disorders of the retina (back of the eye) are uncommon. They may present as inflammation or blood clots with consequent vision disorders which may lead to loss of vision (retinopathy, cotton wool spots, obstruction of retinal artery or vein).

Skin disorders

Itching or skin eruption (rash, erythematous rash, maculo-papular rash) are common. In rare cases patients may experience blistering or peeling of the skin, which may indicate a severe skin reaction (erythema multiforme, Stevens-Johnson syndrome). **If you experience these symptoms, please speak to a doctor immediately,** because these signs may have serious consequences including life-threatening conditions.

Musculoskeletal disorders

Muscle pain or joint pain are common.

Drug-induced lupus erythematosus is a rare adverse reaction of long-term use of Rebif. Symptoms may include muscle pain, joint pain and swelling, and rash. You may also experience other signs such as fever, weight loss, and fatigue. Usually symptoms disappear after treatment is stopped.

General disorders

Headache, fatigue, rigors or fever may commonly occur, while increased sweating is uncommon.

Investigations

Liver function tests may be disturbed. Increase in certain liver enzymes (transaminases) without further symptoms is very common. Severe elevations in transaminases are common.

Tell your doctor if you notice any of the adverse reactions listed above or any other unwanted or unexpected effects. To prevent serious reactions, speak to a doctor immediately if an adverse reaction is severe, occurred suddenly or gets worse rapidly.

INTERACTIONS

Please tell your doctor or pharmacist if you are using or have recently used any other medicines, including medicines obtained without a prescription.

Formal hepatic drug metabolism studies with Rebif in humans have not been conducted. In short term studies Rebif was not found to alter the cytochrome P-450 oxidase-mediated drug metabolism.

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 adrenocorticotropic hormone (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 influenza vaccine is maintained in patients with multiple sclerosis receiving Rebif.

DOSAGE AND ADMINISTRATION

Always use Rebif exactly as your doctor has told you. Check with your doctor if you are not sure.

A doctor experienced in the treatment of multiple sclerosis will initiate your treatment with Rebif.

Dosage

When first starting treatment with Rebif, the dose should be gradually escalated in order to allow tachyphylaxis to develop, thus reducing adverse reactions. Your doctor will advise you accordingly.

It is recommended that 8.8 micrograms (e.g. 0.1ml of the 44 micrograms syringe or 0.2ml of the 22 micrograms syringe) be given three times per week during the first 2 weeks of therapy. Thereafter, 22 micrograms (e.g. 0.25ml of the 44 micrograms syringe or 0.5ml of the 22 micrograms syringe) be given three times per week in weeks 3 and 4, and the total of the 44 micrograms syringe be given from the fifth week onwards.

Patients who have experienced a single clinical event

The recommended dose is 44 micrograms (12 million IU) given three times per week for adults and adolescents from 16 years of age.

Patients with multiple sclerosis

The recommended dose is 44 micrograms (12 million IU) given three times per week for adults and adolescents from 16 years of age. Rebif 22 micrograms also given three times per week is recommended for patients who cannot tolerate the higher dose in view of the treating specialist.

Use in children and adolescents

No formal clinical trials or pharmacokinetic studies 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.

There is limited information on the use of interferon beta 1a in children under 12 years of age and therefore Rebif should not be used in this population.

Administration

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

Prior to injection and for an additional 24 hours after each injection, your doctor may advise you to take a fever-reducing painkiller (antipyretic analgesic) to reduce flu-like symptoms associated with Rebif administration.

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 syringes to administer the medicine at home. It may also be administered with a suitable auto-injector.

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).

How to inject Rebif

- Choose an injection site. Your doctor will advise you on the possible injection sites (good sites include the upper thighs and the lower abdomen). 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 in order to minimise the risk of injection site necrosis. NOTE: do not use any areas in which you feel lumps, firmknots, or pain; talk to your doctor or healthcare professionalabout 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.
- Before the injection 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 an appropriate disposal unit.

Duration of treatment

Your doctor will advise how long you can take Rebif. Do not stop treatment without contacting your doctor.

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 randomized 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 be evaluated at least every second year in the 4 year period after initiation of treatment with Rebif and that the treating physician then make a decision for longer-term treatment on an individual basis.

Missed dose

If you miss a dose, continue to inject from the day of the next scheduled dose. Do not take a double dose to make up for a forgotten dose.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

OVERDOSE

If you have used more Rebif than prescribed, contact your doctor immediately.

Patients who have administered an overdose should be hospitalised for observation and appropriate supportive treatment should be given.

STORAGE AND STABILITY

Keep medicines out of the reach of children.

Do not use Rebif after the expiry date which is stated on the label after EXP.

Store in a refrigerator from 2°C to 8°C. Do not freeze. To prevent accidental freezing, avoid placing near the freezer compartment.

For the purpose of ambulatory use, you may remove Rebif from the refrigerator and store it not above 25°C for one single period of up to 14 days. Rebif must then be returned to the refrigerator and used before the expiry date.

Store in the original package in order to protect from light.

PRESENTATIONS

Pre-filled syringe ready for use with a fixed needle for self-administration.

Packs of 1, 3 and 12 pre-filled syringes.

Not all pack sizes may be marketed.

Marketing Authorisation Holder In EU

Merck Serono Europe, Limited UK

Manufacturer

Merck Serono S.P.A, Bari Italy

DATE OF INFORMATION

28 October 2013

For further inquiries inside Egypt, Call 16935

This is a medicine

A medicine is a product which affects your health and its consumption, contrary to instructions, is dangerous for you.

Closely follow your doctor's prescription, the method of use and the instructions of the pharmacist who sold the product.

Your doctor and the pharmacist are experts in medicine, its benefits and risks.

Do not interrupt the period of treatment prescribed without your doctor's permission

Do not repeat the same prescription without consulting your doctor.

Keep medicines out of reach of children.

Council of Arab Health Ministers

Union of Arab Pharmacists