PATIENT PACKAGE INSERT IN ACCORDANCE WITH
THE PHARMACISTS' REGULATIONS (PREPARATIONS) – 1986
The medicine is dispensed with a doctor's prescription only

Rebif® 22 mcg
Rebif® 44 mcg
Solution for subcutaneous injection

Pre-filled syringe
Cartridge for insertion into an electronic syringe
The active ingredient:
Interferon beta-1a

Each pre-filled syringe of **Rebif® 22 mcg** including a needle, contains:
22 micrograms (6 million International Units [IU]) interferon beta-1a in 0.5 mL.
The preparation contains 2.5 mg benzyl alcohol.
Each pre-filled syringe of **Rebif® 44 mcg** including a needle, contains:
44 micrograms (12 million International Units [IU]) interferon beta-1a in 0.5 mL.
The preparation contains 2.5 mg benzyl alcohol.
Each cartridge of **Rebif® 22 mcg** inserted into an appropriate syringe, contains:
66 micrograms (18 million International Units [IU]) interferon beta-1a in 1.5 mL.
The preparation contains 7.5 mg benzyl alcohol.
Each cartridge of **Rebif® 44 mcg** inserted into an appropriate syringe, contains:
132 micrograms (36 million International Units [IU]) interferon beta-1a in 1.5 mL.
The preparation contains 7.5 mg benzyl alcohol.
Inactive ingredients: see section 6 and section 2 under "Important information about some of the ingredients of the medicine".

- **Read this leaflet carefully in its entirety before using the medicine.** This leaflet contains concise information about the medicine.
- Keep this leaflet at hand; you may need to read it again.
- If you have further questions, refer to the doctor or pharmacist.
- This medicine has been prescribed for the treatment of your ailment. Do not pass it on to others. It may harm them even if it seems to you that their medical condition is similar.
- Use the medicine properly.
- Consult the pharmacist if you need further information. Refer to the doctor if the signs of the disease (symptoms) worsen or are not improving.
- If you experience any side effects, refer to your doctor. This includes any possible side effect not included in this leaflet. See section 4.

1. WHAT IS THE MEDICINE INTENDED FOR

Rebif (interferon beta-1a) belongs to a group of preparations known as interferons. These are natural substances whose role is to transmit information between cells.
Interferons are produced by the body and play a central role in the immune system; they act through a mechanism that is not fully understood, and help to limit the damage to the central nervous system associated with multiple sclerosis. Rebif is a highly purified, soluble interferon-protein, produced by genetic engineering; it is similar to the natural interferon beta produced in the human body.
Rebif is used for the treatment of multiple sclerosis, reduces the frequency and the severity of attacks and slows the progression of the disease.
Rebif 44 mcg only is also approved for use in patients who have experienced a single clinical event which is the first sign of multiple sclerosis.
Therapeutic group: Immunostimulants – interferons.

2. BEFORE USING THE MEDICINE

Do not use Rebif if:

- you are sensitive (allergic) to the active ingredient, natural or recombinant interferon beta, or to any of the additional ingredients contained in the medicine (see section 6).
- you are severely depressed and/or have suicidal thoughts.

Special warnings regarding use of the medicine
Talk to your doctor, pharmacist or nurse before using Rebif.

- Only use Rebif under a doctor's supervision.
- Before use, read the leaflet carefully and follow the instructions for use in this leaflet, in order to minimize the risk of injection site necrosis (harm to skin and tissue), as has been reported in patients treated with Rebif. If you notice troubling local reactions, refer to a doctor.
- Before using Rebif, inform your doctor or pharmacist if you are allergic (hypersensitive) to any medicine.
- If you have, during the course of treatment, signs of thrombocytopenia, new onset hypertension, fever, central nervous system symptoms (e.g., confusion or paralysis) and impaired kidney function or laboratory findings such as: reduced platelet count, increased LDH, perform further tests of platelet levels, serum LDH and kidney function tests (all of these signs can be a clinical manifestation of TMA – thrombotic microangiopathy – formation of blood clots in small blood vessels during the course of treatment that could affect your kidneys). This might happen several months to several years after starting treatment with Rebif. If you develop signs of edema, proteinuria and kidney function problems, inform the doctor – especially if you are at high risk of developing kidney disease (these may be signs of nephrotic syndrome and kidney function disorders).
- Inform the doctor if you are suffering from diseases of the bone marrow, kidney, liver, thyroid, if you have had **depression or suicidal thoughts**, if you have history of epileptic seizures, if you are taking antiepileptics (especially if the epilepsy is uncontrolled), or if you have a heart disease (angina, heart failure or arrhythmias), so that the doctor will be sure to follow and monitor your treatment or exacerbation of these conditions.

Drug interactions
If you are taking, have recently taken or might take other medicines, including non-prescription medicines and nutritional supplements, tell the doctor or pharmacist. In particular, inform the doctor if you are using antidepressants or antiepileptics.
Pregnancy and breastfeeding
If you are pregnant, think you may be pregnant or are planning to become pregnant, ask the doctor or pharmacist before taking the medicine.
No harmful effect on the breastfeeding baby is expected. Rebif can be used during breastfeeding.
Driving and use of machines
Use of the medicine or your medical condition may influence your ability to drive or operate machines. In case of concern, consult with the doctor.
Important information about some of the ingredients of the medicine
This medicine contains less than 1 mmol sodium (23 mg) per dose; this is considered "sodium-free".
This medicine contains 2.5 mg benzyl alcohol per dose. Benzyl alcohol may cause allergic reactions.
Benzyl alcohol has been linked with the risk of severe side effects including breathing problems (called "gasping syndrome") in young children.
Do not use for more than one week in young children (under 3 years old), unless advised by the doctor or pharmacist.
Refer to the doctor or pharmacist if you have a liver or kidney disease or if you are pregnant or breastfeeding. This is because large amounts of benzyl alcohol can build-up in your body and may cause side effects (called "metabolic acidosis").

3. HOW TO USE THE MEDICINE

The medicine in the pre-filled syringe is for single use.
The medicine in the cartridge is for multidose use.
Always use the preparation according to the doctor's instructions. Check with doctor or pharmacist if you are uncertain about the dosage and treatment regimen.
The dosage and the treatment regimen will be determined by the doctor only.
The usual dosage is generally:
Patients who have experienced a single clinical sign
The recommended dose is 44 micrograms (12 million IU), administered 3 times per week.
Patients with multiple sclerosis
The recommended dose is 44 micrograms (12 million IU), administered 3 times per week.
A reduced dose of 22 micrograms (6 million IU), administered 3 times per week, is recommended in patients who cannot tolerate the higher dose.
Inject Rebif three times per week, if possible:

- On the same three days of the week (at intervals of at least 48 hours, for example: Sunday, Tuesday, Thursday)
- At the same time (preferably in the evening)

Do not exceed the recommended dose.
Use in children and adolescents (ages 2-17 years)
No official clinical trials have been conducted in children and adolescents. Yet, there are clinical data that indicate that the safety profile in children and adolescents receiving Rebif 22 mcg or Rebif 44 mcg three times per week is similar to that of adults.
Use in children (under two years of age)
Rebif is not recommended for use in children under two years of age.
Instructions for use:

- Rebif is intended for subcutaneous injection.
- Administration of the first injection should be in the presence of a healthcare professional.
- After you, a family member, friend or your caregiver has received proper training regarding use of the Rebif syringe or cartridge, which has to be inserted into the appropriate syringe, injection of the preparation can be performed at home.

Rebif is presented as:

- **a syringe** filled with the solution, ready for injection; a needle intended for subcutaneous (under the skin) self-injection is attached to the syringe. This syringe is intended for single-use. It may also be used with auto-injector (Rebiject).
- **a cartridge** that has to be inserted into a device that is an electronic syringe called RebiSmart, designated for the cartridge, for subcutaneous self-injection.
- Consult your doctor regarding the Rebif form most suitable for you.

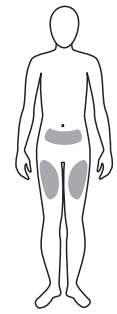
Instructions for use of Rebif, read the following instructions for use carefully:

1. **Rebif cartridge – read the full instructions for use provided with the electronic RebiSmart syringe; follow these instructions carefully**
2. **Rebif pre-filled syringe – the instructions are provided below in this leaflet**

Before injecting

- Wash your hands thoroughly with water and soap.
- Take the Rebif syringe or cartridge out of its package by peeling away the plastic cover.
- Check (immediately after taking out of the refrigerator) that the Rebif syringe or cartridge was not frozen in its pack or device. Only use a clear, particle-free solution with no visible signs of damage.
- Follow the instructions for use.

Where to inject Rebif

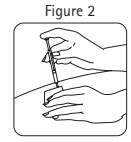


- Choose an injection site. Your doctor will suggest possible injection sites (recommended sites include the upper part of the thigh and the lower abdomen).
- Hold the syringe as you would hold a pencil. It is recommended that you keep track of and rotate your injection sites, so that you don't inject into one area too frequently, in order to minimize the risk of injection site necrosis.
  NOTE: Do not inject into areas in which you feel lumps, local swelling or pain. Talk to the doctor or nurse if you find areas like this.
- Before injecting, 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 feel a stinging sensation.

Instructions for use of the pre-filled syringe

Figure 1

Figure 2



- Gently pinch the skin around the site (to lift it up a bit); see Figure 1.
- Resting your wrist on the skin near the injection site, insert the needle at a right angle into the skin with a quick and firm motion; see Figure 2.
- Inject the medicine with a slow and steady push (push the plunger inward until the syringe is emptied); see Figure 2.
- Press with the wipe on the injection site. Remove the needle from the skin.
- Gently massage the injection site with a dry cotton swab or gauze.
- Dispose of all items: after you have completed the injection, immediately discard the syringe in the appropriate place; discard the needle in a collection bin.

If you have been prescribed a cartridge, insert it into the electronic injector device, RebiSmart, according to the instructions provided with the injector device.
Tests and follow-up
During the course of treatment, blood, liver function, kidney function and thyroid function tests may need to be performed (see also section 2).
If you took an overdose or if a child accidentally swallowed the medicine, immediately refer to a doctor or proceed to a hospital emergency room and bring the package of the medicine with you.
If you forget to take the medicine
In such a case, continue to inject from the day of the next scheduled dose, as per the treatment regimen. Do not inject a double dose to make up for a forgotten dose.
Adhere to the treatment regimen as recommended by the doctor.
Even if there is an improvement in your health, do not stop treatment with the medicine without consulting the doctor.
If you stop taking the medicine
You may not experience the effect of Rebif immediately. Therefore, do not stop using Rebif; rather, continue using the preparation to obtain the desired result. If this matter concerns you, refer to the doctor. Do not stop treatment without consulting the doctor.
Do not take medicines in the dark! Check the label and the dose each time you take a medicine. Wear glasses if you need them.
If you have further questions regarding use of the medicine, consult a doctor or pharmacist.

4. SIDE EFFECTS

As with any medicine, use of Rebif may cause side effects in some users. Do not be alarmed when reading the list of side effects, you may not suffer from any of them.
Refer to your doctor immediately and stop using Rebif if you notice the following serious side effects:

- **Serious allergic (hypersensitivity) reactions.** If, immediately following administration of a Rebif dose, you experience sudden breathing difficulties, which may appear in association with swelling of face, lips, tongue or throat, skin rash (urticaria), itching all over the body, weakness or fainting, refer immediately to a doctor or to any emergency medical center. These effects are rare (may occur in up to 1 in 1,000 users).
- Inform the doctor immediately if you experience symptoms of **liver problems**: jaundice (yellowing of the skin or of the whites of the eyes), widespread itching, loss of appetite accompanied by nausea and vomiting and bruising of the skin. Severe liver problems can be associated with additional signs, e.g., difficulty concentrating, sleepiness and confusion.
- **Depression** is common (may occur in up to 1 in 10 users) in patients with multiple sclerosis. **If you are depressed or develop suicidal thoughts**, refer to a doctor immediately!

Refer to the doctor if you experience any of the following side effects:

- **Flu-like symptoms**, such as: headache, fever, chills, muscle and joint pain, fatigue and nausea are very common (can occur in more than 1 in 10 users).
  These effects are usually mild, are more common at the start of the treatment and decrease with continued use. In order to reduce these symptoms, the doctor may advise you to take an antipyretic and analgesic medicine before starting the injection of Rebif and during the 24 hours after each injection.
- **Injection site reactions** including: redness, swelling, discoloration, inflammation, pain and cracks in the skin are very common. The occurrence of injection site reactions generally decreases over time. Tissue damage (necrosis), ulcers and lumps at the injection site are uncommon (can occur in up to 1 in 100 users).
  See recommendations in "Warnings and precautionary measures regarding use of the medicine" section to minimize the risk of injection site reactions.
  In certain cases, the injection site becomes infected (uncommon), the skin at the site becomes swollen, tender, hard and very painful. In such cases, refer to a doctor.
- There may be changes in a number of **laboratory test** results; these changes are generally not noticed by the patient, as they are not accompanied by symptoms and are usually mild and reversible, and do not require special treatment, e.g., decrease in the number of red blood cells, white blood cells or platelets, each individually (very common) or all at one time (rare). Possible symptoms resulting from these changes can include tiredness, reduced ability to fight infection, bruising or unexplained bleeding, disturbed liver function test results (very common). Inflammation of the liver has also been reported (uncommon). If you experience symptoms suggesting a liver function disorder, such as: loss of appetite accompanied by nausea, vomiting, jaundice, refer to the doctor immediately. See the "Refer to your doctor immediately..." section above.
- **Thyroid gland dysfunction** (uncommon). The thyroid gland can be hyperactive or underactive. These changes and their symptoms are usually not felt by the patient; your doctor will recommend the appropriate tests.
- **Multiple sclerosis pseudo-attack** (frequency unknown). There is a possibility that at the beginning of treatment with Rebif you will experience symptoms that resemble those of a multiple sclerosis attack. For example, your muscles will feel very tense or very weak, preventing you from moving as desired. In some cases, such symptoms are associated with fever and flu-like symptoms, as described above. If you notice these effects, inform the doctor.

Other possible side effects:
Very common (can occur in more than 1 in 10 users):
Headache.
Common (can occur in up to 1 in 10 users):
Insomnia, diarrhea, nausea, vomiting, itching, skin rash (skin reactions), muscle and joint pain, fatigue, fever and chills, hair loss.
Uncommon (can affect up to 1 in 100 users):
Hives, epileptic seizures, liver inflammation (jaundice), breathing difficulties, blood clots such as deep venous thrombosis, disorders of the retina (behind the eye) such as: inflammation or blood clots causing vision disorders (vision difficulties or loss of vision), increased sweating.
Rare (can occur in up to 1 in 1,000 users):
Suicide attempt, serious skin reactions - some with mucosal lesions, formation of blood clots in small blood vessels that may affect your kidneys (thrombotic thrombocytopenic purpura or hemolytic uremic syndrome – a disorder that may be manifested by small blood clots). The symptoms can include increased bruising, bleeding, decreased platelets, anemia, fever, extreme weakness, headache, dizziness and faint feeling. Your doctor may notice changes in your blood and kidney functions.
Rare side effects include nephrotic syndrome and glomerulosclerosis.
Drug-induced lupus erythematosus: a side effect that occurs upon long-term use of Rebif. Symptoms can include muscle pain, joint pain and swelling, and rash. You may experience other symptoms, such as fever, weight loss, and fatigue. Usually, the symptoms disappear during the first week or two after stopping treatment.
Kidney problems include scars that may reduce kidney functions. If you experience any or all of these symptoms: foamy urine, fatigue, swelling – especially in the ankles and eyelids and weight gain, inform your doctor as these may be signs of kidney problems.
The following side effects have been reported for interferon beta at an unknown frequency: Dizziness, nervousness, loss of appetite, dilatation of the blood vessels and palpitations, changes in the menstrual cycle, pulmonary arterial hypertension - a disease of severe narrowing of the blood vessels in the lungs resulting in high blood pressure in blood vessels that carry blood from the heart to the lungs. Pulmonary arterial hypertension has been seen at various time points during the course of treatment, including several years after starting Rebif treatment, inflammation of the fatty tissue under the skin (panniculitis), which can make the skin feel hard and possibly develop painful red lumps or patches.
Do not stop or change the medicine without the doctor's recommendation.
If a side effect occurs, if one of the side effects worsens or if you suffer from a side effect not mentioned in the leaflet, consult with the doctor.
Children and adolescents
Side effects in children and adolescents are similar to those observed in adults.
Reporting side effects
Side effects can be reported to the Ministry of Health by clicking on the "Report Side Effects of Drug Treatment" found on the Ministry of Health homepage (www.health.gov.il) that directs you to the online form for reporting side effects, or by entering the link: https://sideeffects.health.gov.il/

5. HOW TO STORE THE MEDICINE

Avoid poisoning! This medicine and any other medicine must be kept in a safe place out of the reach and sight of children and/or infants to avoid poisoning.
Do not induce vomiting unless explicitly instructed to do so by the doctor.
Do not use the medicine after the expiry date (exp. date) that appears on the package. The expiry date refers to the last day of that month.
Pre-filled syringe
Store the medicine in a refrigerator, at a temperature between 2°C–8°C; this is the cooling range of a household refrigerator. Do not freeze! (To prevent freezing, avoid storing close to the freezer compartment).
Cartridge to be inserted into the electronic syringe
An injection device that contains a Rebif cartridge (RebiSmart) must be stored in the device box, in the refrigerator, at a temperature of 2°C–8°C. Do not freeze! To prevent possibility of freezing, do not store in the refrigerator close to the freezer compartment. After the first injection from a Rebif cartridge, use within 28 days.
For the patient's convenience, Rebif can be taken out of the refrigerator and stored below 25°C for one single period of up to 14 days. After that, it must be returned to the refrigerator and used before the expiry date.
Store the medicine in its original package in order to protect from light.
Do not use Rebif if you notice signs of deterioration such as: if the solution contains particles or is not clear.
Do not dispose of medicines in the wastewater or household waste; it is recommended to bring medicines to a clinic, where there is a container to collect medicines for destruction. This is to protect the environment.

6. FURTHER INFORMATION

In addition to the active ingredient, the medicine also contains:
D-mannitol, benzyl alcohol, poloxamer 188, L-methionine, sodium acetate.
What the medicine looks like and the contents of the package:
Rebif 22 mcg and Rebif 44 mcg are available in two forms:

1. - A syringe filled with a solution ready for self-injection, at a volume of 0.5 mL of solution for injection, with an attached needle. The solution is transparent and clear.
   - Packs of 1, 3 or 12 pre-filled syringes.
     Not all package sizes may be marketed.
2. - Cartridge (Type 1 glass) with a rubber cap, with an aluminum ring, filled with a volume of 1.5 mL solution for injection, for use with an appropriate injector device, provided separately.
   - Each pack contains 4 cartridges.

License holder and address: Merck Serono Ltd., 18 Hakishon St., Yavne 81220

Manufacturer and address: Merck Europe B.V., Amsterdam, The Netherlands

Registration number of the medicine in the National Drug Registry of the Ministry of Health:
Rebif 22 micrograms: 110 94 29437 06
Rebif 44 micrograms: 116 35 29814 06
Revised in May 2021 according to MOH guidelines.