Package leaflet: Information for the user

Rebif 8.8 micrograms solution for injection in pre-filled pen
Rebif 22 micrograms solution for injection in pre-filled pen
interferon beta-1a
Initiation pack

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Rebif is and what it is used for

Rebif belongs to a class of medicines known as interferons. These are natural substances that transmit messages between cells. Interferons are produced by the body and play an essential role in the immune system. Through mechanisms that are not totally understood, interferons help to limit the damage of the central nervous system associated with multiple sclerosis.

Rebif is a highly purified soluble protein that is similar to the natural interferon beta that is produced in the human body.

Rebif is used for the treatment of multiple sclerosis. It has been shown to reduce the number and the severity of relapses and to slow the progression of disability. It is also approved for use in patients who have experienced a single clinical event likely to be a first sign of multiple sclerosis.

2. What you need to know before you use Rebif

Do not use Rebif
- if you are allergic to natural or recombinant interferon beta or any of the other ingredients of this medicine (listed in section 6).
- if you are severely depressed at present or are developing thoughts of suicide.

Warnings and precautions
Talk to your doctor, pharmacist or nurse before using Rebif.

- Rebif should only be used under the supervision of your doctor.
- Before treatment with Rebif, read carefully and follow the “RebiDose Instructions for Use” provided in a separate booklet, in order to minimise the risk of injection site necrosis (skin breakdown and tissue destruction) that has been reported in patients treated with Rebif. If you experience troubling local reactions, contact your doctor.

- Talk to your doctor or pharmacist before taking Rebif if you have an allergy (hypersensitivity) to any other medicines.
- Blood clots in the small blood vessels may occur during your treatment. These blood clots could affect your kidneys. This might happen several weeks to several years after starting Rebif. Your doctor may want to check your blood pressure, blood (platelet count) and the function of your kidney.

Inform your doctor if you have a disease of
- the bone marrow,
- kidney,
- liver,
- heart (which can cause symptoms such as chest pain (angina), particularly after any activity; swollen ankles, shortness of breath (congestive heart failure); or an irregular heartbeat (arrhythmias)),
- thyroid,
- or if you have experienced depression or thoughts about committing suicide,
- or if you have any history of epileptic seizures or other seizure disorders not controlled by medication,

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

Other medicines and Rebif
Tell your doctor or pharmacist if you are using, have recently used or might use any other medicines. In particular you should tell your doctor if you are using antiepileptics or antidepressants.

Pregnancy and breast-feeding
If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.
No harmful effects on the breastfed newborn/infant are anticipated. Rebif can be used during breast-feeding.

Driving and using machines
Effects of the disease itself or of its treatment might influence your ability to drive or to use machines. You should discuss this with your doctor if you are concerned.

Rebif contains sodium and benzyl alcohol
This medicine contains less than 1 mmol sodium (23 mg) per dose, that is to say it is essentially 'sodium-free'.

This medicine contains 1.0 mg benzyl alcohol per dose of 0.2 mL and 2.5 mg benzyl alcohol per dose of 0.5 mL. 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 a week in young children (less than 3 years old), unless advised by your doctor or pharmacist.

Ask your doctor or pharmacist for advice if you are pregnant or breast-feeding, or if you have a liver or kidney disease. 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 Rebif

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

Initiating treatment
Treatment is initiated by a gradual increase of the dose (a so-called "dose titration) over a period of 4 weeks, in order to reduce some of the side effects, it is recommended that:

- During weeks one and two, Rebif 8.8 micrograms should be injected three times per week.
- During weeks three and four, Rebif 22 micrograms should be injected three times per week.

From the fifth week onwards, after you have completed your initiation period, you will follow the usual dose regimen.

Dose
The usual dose is 44 micrograms (12 million IU) given three times per week.

A lower dose of 22 micrograms (6 million IU) given three times per week is recommended for patients with multiple sclerosis who cannot tolerate the higher dose.

Rebif should be administered three times per week, and if possible:

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

Use in children and teenagers (2 to 17 years old)
No formal clinical studies have been conducted in children or teenagers. However there is some clinical data available suggesting that the safety profile in children and teenagers receiving Rebif 22 micrograms or Rebif 44 micrograms three times per week is similar to that seen in adults.

Use in children (below 2 years of age)
Rebif is not recommended for use in children below 2 years of age.

Method of administration

- Rebif is given by injection under the skin (subcutaneously) using a pre-filled pen called "RebiDose".
- Use each RebiDose only once.
- The first injection(s) must be performed under the supervision of an appropriately qualified healthcare professional. After receiving adequate training, you, a family member, friend or carer can use Rebif pre-filled pen to administer the medicine at home.
- When you do this please read carefully and follow the *"RebiDose Instructions for Use"* provided separately in the booklet.

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

If you use more Rebif than you should
In case of overdose, contact your doctor immediately.

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

If you stop using Rebif
The effects of Rebif may not be noticed immediately. Therefore, you should not stop using Rebif but continue to use it regularly to achieve the desired result. If you are uncertain about the benefits, please consult your doctor.

You should not discontinue the treatment without first contacting your doctor.

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

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Tell your doctor immediately and stop using Rebif if you experience any of the following serious side effects:

- **Serious allergic (hypersensitivity) 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, nettle rash, itching all over the body, and a feeling of weakness or faintness, contact your doctor immediately or seek urgent medical attention. These reactions are *rare* (may affect up to 1 in 1,000 people).

- 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.

- **Depression** is *common* (may affect up to 1 in 10 people) in treated patients with multiple sclerosis. If you feel **depressed or develop thoughts of suicide**, report it immediately to your doctor.

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

- **Flu-like symptoms**, such as headache, fever, chills, muscle and joint pains, fatigue and nausea are very common (may affect more than 1 in 10 people).
  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** including redness, swelling, discoloration, inflammation, pain and skin breakdown are *very common*.
  The occurrence of injection site reactions usually decreases over time.
  Tissue destruction (necrosis), abscess and mass at injection site are *uncommon* (may affect up to 1 in 100 people).
  See recommendations in section "Warnings and precautions" to minimise the risk of injection site reactions.
  The injection site can become infected *(uncommon)*; 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.

- Certain **laboratory tests** may change. These changes are generally not noticed by the patient (no symptoms), are usually reversible and mild, and most often do not require particular treatment.
  The number of red blood cells, white blood cells or platelets may decrease either individually *(very common)* or all at one time *(rare)*. Possible symptoms resulting from these changes could include tiredness, reduced ability to fight infection, bruising or unexplained bleeding.
  Liver function tests may be disturbed *(very common)*. Inflammation of the liver has also been reported *(uncommon)*. If you experience symptoms suggesting a liver disorder, such as loss of appetite accompanied by other symptoms such as nausea, vomiting, jaundice, please contact your doctor immediately (see above "Tell your doctor immediately...").

- **Thyroid dysfunction** is *uncommon*. The thyroid gland may function either excessively, or insufficiently. These changes in the thyroid activity are almost always not felt by the patient as symptoms; however your doctor may recommend testing as appropriate.

- **MS pseudo-relapse** (*frequency not known*): There is a possibility that at the beginning of your treatment with Rebif you may experience 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. In some cases such symptoms are associated with fever or flu-like symptoms described above. If you notice any of these side effects talk to your doctor.

Other possible side effects include:

Very common (may affect more than 1 in 10 people):
- Headache

Common (may affect up to 1 in 10 people):
- Insomnia (sleeping difficulty)
- Diarrhoea, nausea, vomiting
- Itching, rash (skin eruptions)
- Muscle and joints pain
- Fatigue, fever, chills
- Hair loss

Uncommon (may affect up to 1 in 100 people):
- Hives
- Epileptic seizures
- Liver inflammation (hepatitis)
- Breathing difficulties
- Blood clots such as deep venous thrombosis
- Disorders of the retina (back of the eye) such as inflammation or blood clots with consequent vision disorders (vision disturbances, loss of vision)
- Increased sweating

Rare (may affect up to 1 in 1,000 people):
- Suicide attempt
- Serious skin reactions - some with mucosal lesions
- Blood clots in the small blood vessels that can affect your kidneys (thrombotic thrombocytopenic purpura or haemolytic uremic syndrome). Symptoms may include increased bruising, bleeding, fever, extreme weakness, headache, dizziness or light-headedness. Your doctor may find changes in your blood and the function of your kidneys.
- Drug-induced lupus erythematosus: a side-effect 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 within one or two weeks after treatment is stopped.
- Kidney problems including scarring that may reduce your kidney function.
  If you get some or all of these symptoms:
  - foamy urine
  - fatigue
  - swelling, particularly in the ankles and eyelids, and weight gain.

  Tell your doctor as they may be signs of a possible kidney problem.

The following side effects were reported for interferon beta (frequency not known)
- Dizziness
- Nervousness
- Loss of appetite
- Dilatation of the blood vessels and palpitation
- Irregularities and/or changes in menstrual flow.

- Pulmonary arterial hypertension - a disease of severe narrowing of the blood vessels in the lungs resulting in high blood pressure in the blood vessels that carry blood from the heart to the lungs. Pulmonary arterial hypertension has been seen at various time points during treatment, including several years after starting treatment with Rebif.
- Inflammation of the fatty tissue under the skin (panniculitis), which can make the skin feel hard and possibly develop painful red lumps or patches.

You should not stop or alter the medication without your doctor's advice.

Children and teenagers
Side effects in children and teenagers are similar to those observed in adults.

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via
Yellow Card Scheme
Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Rebif

Keep this medicine out of the sight and reach of children.

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

Store in a refrigerator (2°C – 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.

Do not use this medicine if you notice any visible signs of deterioration such as if the solution is no longer clear or if it contains particles.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away of medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Rebif contains
- The active substance is interferon beta-1a.
  - Each 8.8 micrograms pre-filled pen contains 8.8 micrograms of interferon beta-1a (2.4 million IU).
  - Each 22 micrograms pre-filled pen contains 22 micrograms of interferon beta-1a (6 million IU).
- The other ingredients are mannitol, poloxamer 188, L-methionine, benzyl alcohol, sodium acetate, acetic acid, sodium hydroxide and water for injections.

What Rebif looks like and contents of the pack
Rebif 8.8 micrograms is a solution for injection in a pre-filled pen for self-administration. The pre-filled pen is ready for use and contains 0.2 mL of solution.

Rebif 22 micrograms is a solution for injection in a pre-filled pen for self-administration. The pre-filled pen is ready for use and contains 0.5 mL of solution.

Rebif solution is clear to opalescent.

Rebif 8.8 micrograms and Rebif 22 micrograms are supplied in an initiation pack that is intended for use during the initial 4 weeks of treatment, during which a gradual increase in Rebif dose is recommended.

One-month initiation pack contains six Rebif 8.8 micrograms pre-filled pens and six Rebif 22 micrograms pre-filled pens.

Marketing Authorisation Holder
Merck Serono Limited
5 New Square
Bedfont Lakes Business Park
Feltham
Middlesex
TW14 8HA
UK

Manufacturer
Merck Serono S.p.A.
Via delle Magnolie 15
I-70026 Modugno (Bari)
Italy

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RebiDose Instructions for use

HOW TO USE REBIF PRE-FILLED PEN (RebiDose)

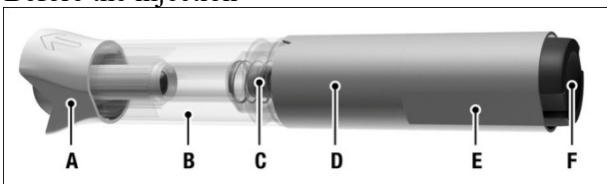
- This section tells you how to use RebiDose.
- Rebif is given by injection under the skin (subcutaneously).
- Use each RebiDose only once.
- The first injection(s) must be performed under the supervision of an appropriately qualified healthcare professional. After receiving adequate training, you, a family member, friend or carer can use RebiDose to administer the medicine at home. If you have questions about how to inject, please ask your doctor, nurse or pharmacist for assistance.
- **Read all the following instructions carefully before using RebiDose.**

Equipment

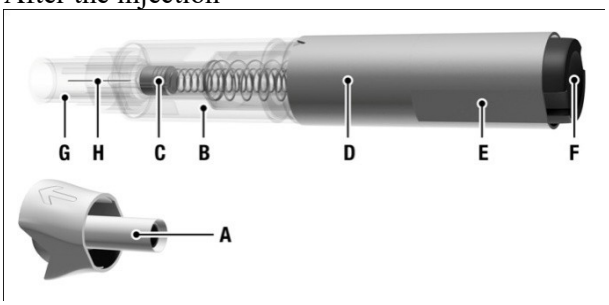
To give yourself an injection you will need:
- A new RebiDose and
- Alcohol wipes or similar.
- a dry cotton ball or gauze

Below is a picture showing what RebiDose looks like.

Before the injection



After the injection



A. Cap
B. Transparent window
C. Plunger
D. Label
E. Main body
F. Button
G. Safety guard
H. Needle

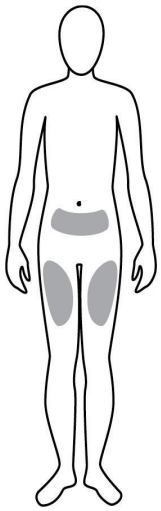
Before you start

- Wash your hands thoroughly with soap and water.
- Remove RebiDose from the blister pack by peeling back the plastic covering.
- Check the appearance of Rebif through the transparent window. It must be clear to opalescent, without particles and without any visible signs of deterioration. If there are particles or other

visible signs of deteriorations, do not use it and contact your doctor, nurse or pharmacist for assistance.

- Check the expiry date on the RebiDose label or on the outer box (as indicated as “EXP”). Do not use RebiDose if the expiry date has passed.

Where to inject with RebiDose

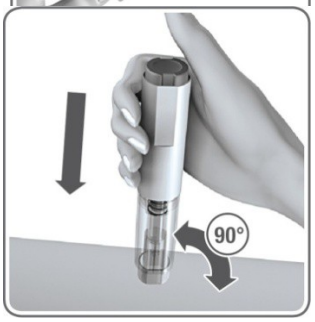


- Choose an injection site. Your doctor will advise you on the possible injection sites (good sites include the upper thighs and the lower abdomen.)
- Keep track of and rotate your injection sites, so that one area is not injected too often. This is to minimise the risk of skin damage (necrosis).
- NOTE: do not use any areas in which you feel lumps, firm knots, or pain; talk to your doctor or healthcare professional about anything you find.

How to inject with RebiDose

- **Do not** remove the cap until you are ready to administer the injection.
- 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.

- Hold RebiDose by the main body and use your other hand to remove the cap.



- Hold RebiDose at a right angle (90 degrees) to the injection site. Push the pen against your skin until you feel resistance. This action unlocks the button.

- Keep enough pressure on the skin and press the button with your thumb. You will hear a click which indicates the start of the injection and the plunger will start moving. Keep RebiDose pressed against the skin for at least 10 seconds in order to inject all of the medicine.
  It is not necessary to keep the button pressed down with your thumb after the injection has begun.

- Remove RebiDose from the injection site.
  The safety guard automatically surrounds the needle and locks into place to protect you from the needle.

After the injection

- Look through the transparent window to make sure that the plunger has moved to the bottom as indicated in the figure.
- Visually check that there is no liquid left. If there is liquid left, not all of the medicine has been injected and you should consult your doctor or nurse for assistance.
- Gently massage the injection site with a dry cotton ball or gauze.
- **Do not** put the needle cap back on the used RebiDose. This is because the needle is now covered by the safety guard. **Do not put your fingers in the safety guard**.
- RebiDose is for single use only and should **never** be reused.
- Once you have finished your injection, immediately discard RebiDose. Ask your pharmacist how to safely dispose of RebiDose.

If you have any further questions, please ask your doctor, nurse or pharmacist.

This "Instructions for use" was last revised in 01/2021