

PACKAGE LEAFLET

Read all of this leaflet carefully before you start using this medicine.

- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or your pharmacist.
- This medicine has been prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours

In this leaflet:

1. What Betaferon is and what it is used for
2. Before you use Betaferon
3. How to use Betaferon
4. Possible side effects
5. Storing Betaferon
6. Further information

THE NAME OF YOUR MEDICINE IS

Betaferon 250 microgram/ml, powder and solvent for solution for injection

The active substance is:

Interferon beta-1b, 250 microgram per 1 ml of reconstituted solution

The other ingredients are

in the powder: mannitol and human albumin

in the solvent: sodium chloride solution

THE MANUFACTURER OF BETAFERON IS

Schering AG

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Germany

1. WHAT BETAFERON IS AND WHAT IT IS USED FOR

Betaferon is a white to off-white powder and contains 250 microgram (8 million IU) of interferon beta-1b per millilitre of reconstituted solution. Each pack of Betaferon contains either 5 or 15 vials of Interferon beta-1b and either 5 or 15 pre-filled syringes containing sodium chloride solution (0.54% w/v). Betaferon belongs to the pharmacotherapeutic group of interferons, which are naturally occurring proteins.

Betaferon is indicated for use in ambulatory patients (patients who can walk) with relapsing-remitting multiple sclerosis characterised by at least two attacks of neurologic dysfunction over a two year period followed by complete or incomplete recovery. In this patient population Betaferon was shown to reduce the frequency and severity of clinical relapses, to reduce the number of multiple sclerosis related hospitalisations and to prolong the relapse-free time.

Betaferon is also indicated for patients suffering from secondary progressive multiple sclerosis with active disease evidenced by relapses. In this patient population Betaferon is used to slow the progression of disability and to reduce the frequency of relapses.

2. BEFORE YOU USE BETAFERON

The treatment with Betaferon should be initiated under the supervision of a physician experienced in the treatment of the disease.

You are not recommended to use Betaferon if you suffer from the so-called “relapsing-remitting” multiple sclerosis and have had fewer than two multiple sclerosis attacks in the previous two years. If you suffer from the so called ‘secondary-progressive multiple sclerosis’ you are not recommended to use Betaferon if you have had no active disease in the previous two years (in case of doubt ask your doctor).

Do not use Betaferon:

- if you are allergic (hypersensitive) to Interferon beta-1b or any of the other ingredients of Betaferon.
- if you are under 18 years of age, because Betaferon has not been investigated in this age group
- if you have a history of severe depressive illness and/or suicidal thoughts, liver failure or inadequately treated epilepsy

Take special care with Betaferon:

- If a serious hypersensitivity reaction (possible symptoms of which are for example: itching all over your body, swelling of your face, your tongue or a strong shortness of breath) occurs, contact a doctor immediately because such a reaction may become life threatening. Treatment with Betaferon must be discontinued.
- If you experience depression and suicidal thoughts, contact your doctor promptly. Such symptoms have been reported by patients. In rare cases this may lead to suicidal attempts.
- If you have a history of seizures or of depression or if you already suffer from a heart disorder, Betaferon must be administered with caution. Caution must also be exercised if you are taking anti-epileptic medicines.
- If you have a bone marrow disorder, anaemia or a low platelet level Betaferon must also be administered with caution.
- If your white blood cell count decreases, your doctor should monitor you closely for the development of fever or infection. The number of platelets (which help the blood to clot) may also fall and the number of platelets in the blood has been found to be extremely small.
- Your doctor will usually order blood tests (a complete blood count, differential white cell count and measurement of liver enzymes known as AST, ALT and γ -GT in the blood) before you start Betaferon and regularly whilst you are on it.
- If you know that you have suffered from an increase of certain blood fats (triglycerides) or if you have suffered from pancreatitis, please inform your doctor. In rare cases, pancreatitis was observed with Betaferon use, often associated with an increase of triglycerides.
- If you have kidney problems, your kidney function should be monitored during treatment. There is no information on the use of Betaferon in patients with such problems.
- It is not known if Betaferon has a negative effect on human fertility but based on the experience with other interferons, a decrease in male or female fertility cannot be ruled out.
- During the treatment with Betaferon your body may produce substances which may reduce the effectiveness of the treatment. This is called neutralising activity and only occurs in some patients. However, it is not possible to foresee whether or not you belong to this group of patients with reduced efficacy.
- Injection site reactions including redness, swelling, discoloration, inflammation, pain, hypersensitivity, and non-specific reactions occur frequently. Skin breakdown and tissue destruction (necrosis) are reported less frequently. The occurrence of injection site reactions usually decreases over time.
- Injection site skin breakdown and tissue destruction (necrosis, see section “Are there any side effects during the use of Betaferon?”) can be extensive and may involve muscle fascia as well as fat and can therefore result in scar formation. Occasionally debridement (the removal of foreign matter and dead tissue) and, less often, skin grafting are required and healing may take up to 6 months.
- If you have multiple lesions Betaferon must be discontinued until healing has taken place. Patients with single lesions may continue on Betaferon provided the necrosis is not too

extensive, as some patients have experienced healing of injection site necrosis whilst on Betaferon.

- To minimise the risk of injection site necrosis you must:
 - use an aseptic injection technique
 - rotate the injection sites with each dose
- The procedure for self-administration must be reviewed periodically by your doctor, especially if injection site reactions have occurred.
- If you experience symptoms like irregularity of your heart beat or fluid retention (swelling) in the lower part of your body (e.g. ankles, legs) or shortness of breath, contact your doctor immediately. During treatment with Betaferon a disease of the heart muscle (cardiomyopathy) has been reported in rare cases.
- If you think that you might have a disorder of the immune system in which abnormal proteins are found in the blood (monoclonal gammopathy), you must check this with your doctor before you use Betaferon. Patients who have the rare condition known as monoclonal gammopathy may develop problems with their small blood vessels (capillaries) leading to shock (collapse) which can be fatal, when they use medicines like Betaferon. See also “Possible side effects”.

Using Betaferon with food and drink:

Betaferon is injected under the skin. An influence by food or drinks is thus not to be expected.

Pregnancy

Betaferon should not be used during pregnancy or if you are trying to become pregnant. If you wish to become pregnant, discuss the matter with your doctor first. While using Betaferon women of childbearing age should take appropriate contraceptive measures. If you do become pregnant you should stop your treatment and contact your doctor immediately.

Breast-feeding

It is not known whether Interferon beta-1b is excreted in human milk. However, since serious adverse reactions to Interferon beta-1b in breast-fed infants are theoretically possible, you must discuss the matter with your doctor and make a decision whether to stop breast-feeding or using Betaferon.

Driving and using machines:

No studies on the effects of Betaferon on the ability to drive and use machines have been performed. However, central nervous system-related adverse events associated with the use of Betaferon might influence the ability to drive and use machines in susceptible patients.

Important information about some of the ingredients of Betaferon:

The inactive ingredients of Betaferon include small amounts of mannitol (a naturally occurring sugar) and human albumin (a protein). If you know that you are hypersensitive to human albumin or if you become so, you must not use Betaferon.

Using other medicines:

Please inform your doctor or pharmacist if you are taking or have recently taken any other medicines, even those not prescribed.

With the exception of corticoids or ACTH, Betaferon must not be used with substances that modify the immune system response.

Caution must be exercised when Interferon beta-1b is administered in combination with other medicines which need a certain liver enzyme system (known as cytochrome P450 system) for their

metabolism. These medicines include some widely used antipyretics (medicines against fever and pain) and anti-epileptics.

3. HOW TO USE BETAFERON

Before administration, the Betaferon solution for injection has to be prepared from a vial of Betaferon and 1.2 ml of liquid from the pre-filled solvent syringe. This will either be done by your doctor or his/her assistant or by yourself after you have been carefully and sufficiently instructed and trained. To assist you in subcutaneous self-administration of Betaferon (injection under the skin), detailed instructions for self-injection are provided with this leaflet (see “Annex: Self-injection”). These instructions also tell you how the Betaferon solution for injection is prepared.

Always use Betaferon exactly as your doctor has instructed you. You should check with your doctor or pharmacist if you are unsure.

Betaferon must be dosed as follows:

Every other day, 1.0 ml of the prepared Betaferon solution (see above) must be injected under the skin (subcutaneously). This equals 250 microgram (8 million IU)

If you have the impression that the effect of Betaferon is too strong or too weak, talk to your doctor or pharmacist.

The injection site must be changed regularly. See also “Take special care with Betaferon” and follow the instructions under “Rotating injection sites” under “Self-injection procedure”.

At present it is not known how long treatment with Betaferon should last. The efficacy of treatment for longer than two years has not been sufficiently demonstrated for relapsing-remitting multiple sclerosis. For secondary progressive multiple sclerosis, efficacy for a period of two years has been demonstrated under controlled clinical trial conditions, and there is limited data on what happens for a period of up to three years of treatment. The duration of treatment will be decided by your doctor.

If you use more Betaferon than you should:

Administration of many times the dose of Betaferon recommended for the treatment of multiple sclerosis has not led to life-threatening situations.

Please consult the doctor who prescribed Betaferon for you in the case of accidental overdose. In addition, should you administer your injection too frequently by mistake (e.g. one injection every 24 h instead of one injection every 48 h) you should consult your doctor.

If you forget to take Betaferon:

If you forget to administer your injection at the correct time you must take it as soon as you remember. Your next injection should be given 48 hours later.

Do not take a double dose to make up for forgotten individual doses.

Effects when treatment with Betaferon is stopped:

Acute withdrawal symptoms are not to be expected if you have forgotten to inject Betaferon or if you have stopped using it.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Betaferon can have side effects.

- a) At the beginning of treatment adverse reactions are common but in general they subside with further treatment. The most frequently observed adverse reactions are flu-like symptoms (fever, chills, headache, muscular pain, painful joints, malaise, or sweating) and injection site reactions.
- b) The following side effects listing is based on reports from clinical trials with Betaferon (*table 1*) and from side effects reports on the marketed product (*table 2; reporting rates classified as very common ($\geq 10\%$), common ($< 10\% - \geq 1\%$), uncommon ($< 1\% - \geq 1\%$), rare ($< 1\% - \geq 1/10.000$) and very rare ($< 1/10.000$)). In general, frequencies of side effects obtained from clinical trials are higher than those from the marketed product. This can be explained by the fact that patients included into clinical trials are directly asked for such side effects, whereas the data of the marketed product mostly consist of spontaneous reports.*

Experience with Betaferon in patients with multiple sclerosis is limited, consequently those adverse events of which occur very rarely may not yet have been observed:

Table 1 (side effects which have occurred in clinical trials with Betaferon very commonly (at a percentage of $\geq 10\%$) and at a higher percentage than those observed with placebo. The table also includes side effects which occur in less than 10% of the cases but which are of statistical importance)

Blood and the lymphatic system disorders

decrease of white cells in the blood, swollen lymph glands

Metabolism and nutrition disorders

the activity of the liver may be affected shown by rises in the blood levels of enzymes it produces, increase of sugar in the blood, occurrence of protein in the urine, accumulation of fluid in arm, leg or face

Nervous system disorders

dizziness, sleeplessness, depression, muscle stiffness, anxiety

Eye disorders

conjunctivitis

Ear disorders

ear pain

Heart disorders

palpitation

Blood vessel disorders

migraine, dilatation of blood vessels, increased blood pressure

Respiratory disorders

sinusitis, shortness of breath, cough (increased)

Digestion disorders

diarrhea, constipation, nausea, vomiting

Skin and subcutaneous tissue disorders

skin disorder, rash, sweating

Musculoskeletal disorders

painful muscles, muscular debility

Kidney and urinary disorders

urinary retention, urinary frequency, urinary incontinence, urinary urgency

Reproductive system disorders

painful monthly bleeding, menstrual disorder, profuse uterine bleeding especially between menstrual periods, impotence

General disorders and administration site conditions

injection site reaction (including redness, swelling, discoloration, inflammation, pain, hypersensitivity, see "Take special care with Betaferon"), skin breakdown and tissue destruction (necrosis) at injection site (see "Take special care with Betaferon"), headache, fever, flu-like symptoms, pain, chest pain, back pain, lack/loss of strength, infection, chills, abdominal pain, malaise, abscess, pain in extremity

Table 2; side effects reports on the marketed product classified as very common ($\geq 10\%$), common ($< 10\% - \geq 1\%$), uncommon ($< 1\% - \geq 1\%$), rare ($< 1\% - \geq 1/10.000$) and very rare ($< 1/10.000$)

Blood and the lymphatic system disorders

Uncommon the number of white cells and red cells in the blood may fall, the number of platelets (which help the blood to clot) may fall
rare swollen lymph glands

Hormonal disorders

Rare the thyroid gland does not work properly (too much or too little hormone is produced)

Metabolism and nutrition disorders

uncommon the activity of the liver may be affected shown by rises in the blood levels of enzymes it produces
rare a specific liver enzyme (gamma GT) may rise
 a fraction of blood fats (triglycerides) may increase (see "Take special care with Betaferon")
very rare low calcium in the blood, high uric acid in the blood

Nervous system disorders

uncommon muscle stiffness, depression (see "Take special care with Betaferon")
rare convulsion, confusion, anxiety, emotional lability
very rare depersonalisation (loss of identity or reality)

Heart disorders

rare disease of the heart muscle (cardiomyopathy, see "Take special care with Betaferon"), faster heart beat, palpitation

Blood vessel disorders

uncommon hypertension

Respiratory disorders

rare bronchospasm, shortness of breath

Digestion disorders

uncommon nausea, vomiting
rare pancreatitis (see "Take special care with Betaferon")

Liver disorders

rare hepatitis

Skin and subcutaneous tissue disorders

uncommon	loss of scalp hair, raised edematous and usually itching patches of skin or mucous membranes (urticaria), pruritus, rash
rare	skin discoloration, sweating

Musculoskeletal disorders

uncommon	painful muscles
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Reproductive system disorders

rare	menstrual disorders
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General disorders and administration site conditions

very common*	flu-like symptoms, chills, fever, injection site reaction (see “Take special care with Betaferon”), inflammation, pain at injection site
common*	skin breakdown and tissue destruction (necrosis) at injection site (see “Take special care with Betaferon”)
rare	suicide attempt (see “Take special care with Betaferon”), serious hypersensitivity reactions (contact a doctor immediately, for symptoms and necessary action see “Take special care with Betaferon”), malaise, chest pain

**frequencies based on clinical trials*

- c) Flu-like symptoms (fever, chills, headache, muscular pain, painful joints, a general feeling of being unwell or sweating) have been seen frequently. The occurrence of the symptoms decreased over time.

Injection site reactions including redness, swelling, discoloration, inflammation, pain, hypersensitivity, and non-specific reactions occur frequently (see “Take special care with Betaferon”). Skin breakdown and tissue destruction (necrosis) are reported less frequently. Swollen lymph glands have also been reported. The occurrence of injection site reactions usually decreases over time.

If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

5. STORING BETAFERON

Do not store above 25°C. Do not freeze.

Do not use after the expiry date stated on the pack.

After reconstitution an immediate use is recommended. However, the in-use stability has been demonstrated for 3 hours at 2-8 °C.

Keep out of the reach and sight of children.

Do not use Betaferon if you notice it contains particulate matter or is discoloured.

6. FURTHER INFORMATION

For any information about this medicinal product, please contact the local representative of the Marketing Authorisation Holder.

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