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

(interferon beta-1b)

UK5151059P94-1.0

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.

This product is called Betaferon 250 microgram/ml, powder and solvent for solution for injection but will be referred to as Betaferon throughout the leaflet.

What is in this leaflet

1. What Betaferon is and what it is used for

What Betaferon is

Betaferon is a type of medicine known as interferon used to treat multiple sclerosis. Interferons are proteins produced by the body that help fight against attacks on the immune system such as viral infections.

How Betaferon works

Multiple sclerosis (MS) is a long-term condition that affects the central nervous system (CNS), particularly the functioning of the brain and spinal cord. In MS, inflammation destroys the protective sheath (called *myelin*) around the nerves of the CNS and stops the nerves from working properly. This is called demyelination.
The exact cause of MS is unknown. An abnormal response by the body's immune system is thought to play an important part in the process which damages the CNS.

The damage to the CNS can occur within an MS attack *(relapse)*. It can cause disability temporarily, such as difficulty walking. Symptoms may disappear completely or partly.
Interferon beta-1b has been shown to change the response of the immune system and to help to reduce disease activity.

How Betaferon helps fight your disease

Single clinical event indicating a high risk of developing multiple sclerosis: Betaferon has been shown to delay progression to definite multiple sclerosis.

Relapsing-remitting multiple sclerosis: People with relapsing-remitting MS have occasional attacks or relapses during which symptoms become noticeably worse. Betaferon has been shown to cut down the number of attacks and make them less severe. It reduces the number of hospital stays due to the disease and prolongs the time without relapses.

Secondary progressive multiple sclerosis: In some cases people with relapsing-remitting MS find that their symptoms increase and they progress to another form of MS called secondary progressive MS. With this, people find themselves becoming increasingly impaired, whether or not they have relapses. Betaferon can reduce the number and severity of the attacks, and slow the progression of disability.

What Betaferon is used for Betaferon is for use in patients

- ► **who have experienced symptoms for the first time which indicate a high risk of developing multiple sclerosis.** Your doctor will rule out any other reasons which could explain these symptoms before you are treated.
- ► **who suffer from relapsing-remitting multiple sclerosis, with at least two relapses within the last two years**.
- ► **who suffer from secondary progressive multiple sclerosis with active disease shown by relapses.**

2. What you need to know before you use Betaferon

Do not use Betaferon

- **if you are allergic** *(hypersensitive)* to natural or recombinant interferon beta, human albumin or any of the other ingredients of this medicine (listed in section 6).
- **if you currently suffer from severe depression and/or suicidal thoughts** (see 'Warnings and precautions' and section 4 'Possible side effects').
- **if you have severe liver disease** (see 'Warnings and precautions', 'Other medicines and Betaferon' and section 4 'Possible side effects').

► **Tell your doctor** if any of the above applies to you.

Warnings and precautions

Talk to your doctor before you start using Betaferon:

- **If you have *monoclonal gammopathy*.** This is **a disorder of the immune system where an abnormal protein is found in the blood.** Problems with your small blood vessels *(capillaries)* may develop when using medicines like Betaferon *(systemic capillary leak syndrome)*. This can lead to shock *(collapse)* and even be fatal.
- **If you have had depression or are depressed or previously had thoughts of suicide.** Your doctor will closely monitor you during treatment. If your depression and/or suicidal thoughts are severe, you will not be prescribed Betaferon (see also 'Do not use Betaferon').
- **If you have ever had seizures or if you are taking medicines to treat epilepsy** *(anti-epileptics)*, your doctor will monitor your treatment carefully (see also 'Other medicines and Betaferon' and section 4. 'Possible side effects').
- **If you have severe kidney problems** your doctor may monitor your kidney function during treatment.

Your doctor also needs to know the following **whilst you are using Betaferon**:

- **If you experience symptoms such as itching all over your body, swelling of your face and/or your tongue or sudden shortness of breath.** These may be symptoms of a serious allergic reaction *(hypersensitivity)*, which may become life threatening.
- **If you feel noticeably more sad or hopeless than before the treatment with Betaferon, or if you develop thoughts of suicide.** If you become depressed while you are on Betaferon, you may need special treatment and your doctor will closely monitor you and may also consider stopping your treatment. If you suffer from severe depression and/or suicidal thoughts, you will not be treated with Betaferon (see also 'Do not use Betaferon').
- **If you notice any unusual bruising, excessive bleeding after injury or if you seem to be catching a lot of infections.** These may be symptoms of a fall in your blood cell count or in the number of platelets in your blood (cells, which help the blood to clot). You may need extra monitoring by your doctor.
- **If you have loss of appetite, fatigue, feeling sick *(nausea)*, repeated vomiting, especially if you notice widespread itching, yellowing of the skin or of the whites of the eyes, or easy bruising.** These symptoms may suggest problems with your liver. Changes to the liver function values occurred in patients treated with Betaferon during clinical studies. As for other beta interferons, severe liver damage, including cases of liver failure, have been reported rarely in patients taking Betaferon. The most serious were reported in patients taking other medicines or who were suffering from diseases that can affect the liver (e.g. alcohol abuse, severe infection).
- **If you experience symptoms like irregular heartbeat, swelling such as of the ankles or legs, or shortness of breath.** This may suggest a disease of the heart muscle *(cardiomyopathy)* which has been reported rarely in patients using Betaferon.
- **If you notice pain in your belly which is radiating to your back, and/or you feel sick or have a fever.** This may suggest an inflammation of the pancreas *(pancreatitis)*, which has been reported with Betaferon use. This is often associated with an increase of certain blood fats *(triglycerides)*.

► **Stop using Betaferon and tell your doctor immediately** if any of these happens to you.

Other things to consider when using Betaferon

- **You will need blood tests** to measure the number of your blood cells, blood chemistry and your liver enzymes. This will be done **before you start using Betaferon, regularly after treatment with Betaferon has been initiated and periodically whilst you are on it,** even if you have no particular symptoms. These blood tests will be in addition to the tests, which are normally done to monitor your MS.
- **If you have a heart disease, the flu-like symptoms, which often occur at the start of treatment, may prove stressful to you.** Betaferon must be used with caution, and your doctor will monitor you for worsening of your heart condition, particularly during the start of treatment. Betaferon itself does not affect the heart directly.
- **You will have a check of the function of your thyroid gland,** regularly or whenever thought necessary by your doctor for other reasons.
- **Betaferon contains human albumin and therefore carries a potential risk for transmission of viral diseases.** A risk of transmission of Creutzfeld-Jacob disease (CJD) cannot be ruled out.
- **During treatment with Betaferon your body may produce substances called *neutralising antibodies*,** which may react with Betaferon *(neutralising activity)*. It is not yet clear whether these neutralising antibodies reduce the effectiveness of the treatment. Neutralising antibodies are not produced in all patients. Currently it is not possible to predict which patients belong to this group.
- **During treatment with Betaferon, kidney problems that may reduce your kidney function, including scarring *(glomerulosclerosis)*, may occur.** Your doctor may perform tests to check your kidney function.
- **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 Betaferon. Your doctor may want to check your blood pressure, blood (platelet count) and the function of your kidney.
- **Paleness, yellow skin or dark-colored urine, possibly accompanied by unusual dizziness, tiredness or shortness of breath may occur during your treatment.** These may be symptoms of a breakdown of red blood cells. This might happen several weeks to several years after starting Betaferon. Your doctor may perform blood tests. Inform your doctor about other medicines that you are taking at the same time as Betaferon.

Injection site reactions

During Betaferon treatment you are likely to experience injection site reactions. Symptoms include redness, swelling, change in the skin colour, inflammation, pain and hypersensitivity. Infection around the injection site and skin breakdown and tissue damage *(necrosis)* are reported less frequently. Injection site reactions usually become less frequent over time.

Injection site skin and tissue breakdown can result in scars forming. If this is severe a doctor may have to remove foreign matter and dead tissue *(debridement)* and, less often, skin grafting is required and healing may take up to 6 months.

To reduce the risk of getting injection site reactions, such as infection or necrosis, you must:
- use a sterile *(aseptic)* injection technique,
- rotate the injection sites with each injection (see Annex 'Self-injection procedure', Part II, in the second part of this leaflet).

Injection site reactions may occur less frequently, if you use an auto-injector device and by rotating injection sites. Your doctor or nurse can tell you more about this.

If you experience any break in the skin, which may be associated with swelling or fluid leaking out from the injection site:

► **Stop injections with Betaferon** and talk to your doctor
► **If you have only one sore injection site** (*lesion*) **and the tissue damage** *(necrosis)* **is not too extensive you may continue using Betaferon.**
► **If you have more than one sore injection site** *(multiple lesions)* you must stop using Betaferon until your skin has healed.

Your doctor will regularly check the way you inject yourself, particularly if you have experienced injection site reactions.

Children and adolescents

There have been no formal clinical trials undertaken in children or adolescents.
However, there is some data available in children and adolescents from 12 to 16 years. This data suggests that the safety profile from this age is the same as in adults for use of Betaferon 8.0 million IU under the skin every other day. There is no information on the use of Betaferon in children under 12 years of age. Therefore, Betaferon should not be used in this population.

Other medicines and Betaferon

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

No formal interaction studies have been carried out to find out whether Betaferon affects other medicines or is affected by them.

Using Betaferon with other medicines that modify the immune system response is not recommended, except anti-inflammatory medicines called *corticosteroid*s or the *adrenocorticotropic hormone (ACTH)*.

Betaferon should be used with caution with:
- **medicines which need a certain liver enzyme system** (known as *cytochrome P450 system*) for their removal from the body, for example medicines used to treat epilepsy (like phenytoin).
- **medicines which affect the production of blood cells.**

Betaferon with food and drink

Betaferon is injected under the skin so any food or drink you consume is not thought to have any effect on Betaferon.

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. Betaferon can be used during breast-feeding.

Driving and using machines

Betaferon may cause side effects in the central nervous system (see section 4. 'Possible side effects'). If you are especially sensitive, this might affect your ability to drive or use machines.

Betaferon contains mannitol, human albumin and sodium

The inactive ingredients of Betaferon include
- small amounts of mannitol, a naturally occurring sugar and human albumin, a protein.
- sodium - this medicine contains less than 1 mmol sodium (23 mg) per ml, that is to say essentially 'sodium-free'.

If you know that you are allergic *(hypersensitive)* to any of the ingredients or if you become so, you must not use Betaferon.

3. How to use Betaferon

Treatment with Betaferon should be started under the supervision of a doctor who is experienced in the treatment of multiple sclerosis.

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

The recommended dose is:

Every other day (once every two days)**,** 1.0 ml of the prepared Betaferon solution (see Annex 'Self-injection procedure' in the second part of this leaflet) injected under the skin *(subcutaneously)*. This equals 250 microgram (8.0 million IU) interferon beta-1b.

When starting treatment with Betaferon, it is tolerated best by gradually increasing the dose, i.e. starting with just 0.25 ml of the medication and then increasing, after every 3rd injection, first to 0.5 ml, then to 0.75 ml and then finally to the full dose (1 ml) of Betaferon.
Your doctor may decide, together with you, to change the time interval between increases in the dose depending on side effects you may experience at the start of treatment. To easily increase the dosage during the first 12 injections, you may be given a special **titration pack**, containing four differently coloured packs with specially marked syringes and with detailed instructions on the separate introductory leaflet for titration pack.

Preparing the injection

Before injection, the Betaferon solution has to be prepared from a vial of Betaferon powder and 1.2 ml of liquid from the pre-filled solvent syringe. This will either be done by your doctor or nurse or by yourself after you have been carefully trained. For details how the Betaferon solution for injection is prepared see Annex 'Self-injection procedure', Part I.

Detailed instructions for self-injection of Betaferon under the skin are provided in Part IE of the Annex 'Self-injection procedure'.
The injection site must be changed regularly. See section 2. 'Warnings and precautions' and follow the instructions in Part II 'Rotating injection sites' and Part III (Betaferon Medication Record) of the Annex 'Self-injection procedure'.

Duration of treatment

At present it is not known how long treatment with Betaferon should last. **The length of treatment will be decided by your doctor together with you.**

If you use more Betaferon than you should

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

► **Talk to your doctor** if you injected too much Betaferon or injected it too often.

If you forget to use Betaferon

If you have forgotten to give yourself an injection at the right time do it as soon as you remember and then follow on with the next one 48 hours later.

Do not inject a double dose to make up for a forgotten single dose.

If you stop using Betaferon

Talk to your doctor if you stop or wish to stop treatment. Stopping Betaferon is not known to lead to acute withdrawal symptoms.

► 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.

Betaferon may cause serious side effects. If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor, pharmacist or nurse.

► **Tell your doctor immediately and stop using Betaferon:**

- if you experience symptoms such as **itching all over your body, swelling of your face and/or your tongue or sudden shortness of breath.**
- if you feel **noticeably more sad or hopeless than before the treatment with Betaferon, or if you develop thoughts of suicide.**
- if you notice **any unusual bruising, excessive bleeding after injury or if you seem to be catching a lot of infections.**
- if you have **loss of appetite, fatigue, feeling sick, repeated vomiting, especially if you notice widespread itching, yellowing of the skin or of the whites of the eyes, or easy bruising.**
- if you experience symptoms like **irregular heartbeat, swelling such as of the ankles or legs, or shortness of breath.**
- if you notice **pain in your belly which is radiating to your back, and/or you feel sick or have a fever.**

► **Tell your doctor immediately:**

- if you get some or all of these symptoms: **foamy urine, fatigue, swelling, particularly in the ankles and eyelids, and weight gain,** as they may be signs of a possible kidney problem.

At the beginning of treatment side effects are common but in general they become less with further treatment.

The most frequently observed side effects are:

► **Flu-like symptoms** such as fever, chills, painful joints, malaise, sweating, headache, or muscular pain. These symptoms may be reduced by taking paracetamol or non-steroidal anti-inflammatory medicines such as ibuprofen.

► **Injection site reactions**. Symptoms can be redness, swelling, discolouration, inflammation, infection, pain, hypersensitivity, tissue damage *(necrosis)*. See 'Warnings and precautions' in section 2 for more information and what to do, if you experience an injection site reaction. These may be reduced by the use of an auto-injector device and by rotating injection sites. Talk to your doctor, pharmacist or nurse for further information.

To reduce side effects at the start of treatment, your doctor should start you on a low dose of Betaferon and increase it gradually (see section 3. 'How to use Betaferon').

The following side effects listing is based on reports from clinical trials with Betaferon and from side effects reported on the marketed product.

► **Very common (may affect more than 1 in 10 users):**

- reduced number of white **blood cells**
- **headache**
- sleep disorder (insomnia)
- abdominal pain
- a specific liver enzyme (alanine aminotransferase or ALAT) may rise (this will show up in blood tests)
- rash
- **skin** disorder
- painful muscles (myalgia)
- **muscle** stiffness (hypertonia)
- painful joints (arthralgia)
- urinary urgency
- **injection site** reaction (including redness, swelling, discolouration, inflammation, pain, infection, allergic reactions (hypersensitivity)
- **flu-like** symptoms, pain, fever, chills, accumulation of fluid in arm or leg (peripheral oedema), lack/loss of strength (asthenia)

► **Common (may affect up to 1 in 10 users):**

- swollen **lymph glands** (lymphadenopathy)
- the number of red cells in the blood may fall *(anaemia)*
- the thyroid gland does not work properly (too little hormone is produced) *(hypothyroidism)*
- weight increase or decrease
- confusion
- abnormally rapid heartbeat *(tachycardia)*
- increased **blood pressure** (hypertension)
- a specific liver enzyme (aspartate aminotransferase or ASAT) may rise (this will show up in blood tests)
- **shortness of breath** (dyspnoea)
- a reddish yellow pigment *(bilirubin)*, which is produced by your liver, may rise (this will show up in blood tests)
- swollen and usually itchy patches of skin or mucous membranes *(urticaria)*
- itching *(pruritus)*
- loss of scalp hair *(alopecia)*
- menstrual disorders *(menorrhagia)*
- heavy uterine bleeding (metrorrhagia) especially between menstrual periods
- **impotence**
- skin breakdown and tissue damage (necrosis) at the injection site (see section 2'Warnings and precautions')
- chest pain
- malaise

► **Uncommon (may affect up to 1 in 100 users):**

- the number of platelets (which help the blood to clot) may fall *(thrombocytopenia)*
- a certain type of blood fats *(triglycerides)* may increase (will show up in blood tests), see section 2 'Warnings and precautions'
- suicide attempt
- mood swings
- convulsion
- a specific liver enzyme *(gamma GT)* which is produced by your liver, may rise (this will show up in blood tests)
- inflammation of the liver *(hepatitis)*
- skin discolouration
- kidney problems, including scarring (glomerulosclerosis) that may reduce your kidney function

► **Rare (may affect up to 1 in 1,000 users):**

- 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, dizziness or light-headedness. Your doctor may find changes in your blood and the function of your kidneys
- serious allergic *(anaphylactic*) reactions
- the thyroid gland does not work properly *(thyroid disorders),* too much hormone is produced *(hyperthyroidism)*
- severe loss of appetite leading to weight loss (anorexia)
- disease of the heart muscle (cardiomyopathy)
- sudden shortness of breath (bronchospasm)
- inflammation of the pancreas *(pancreatitis*), see section 2 'Warnings and precautions'
- the liver does not work properly (hepatic injury including hepatitis, hepatic failure)

► **Not known (frequency cannot be estimated from the available data)**

- breakdown of red blood cells (haemolytic anaemia)
- problems with your small blood vessels may develop when using medicines like Betaferon (systemic capillary leak syndrome)
- **depression, anxiety**
- dizziness
- irregular, rapid beating or pulsation of the heart (palpitation)
- redness and/or facial flushing due to widening of blood vessels (vasodilation)
- 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). Pulmonary arterial hypertension has been seen at various time points during treatment, including several years after starting treatment with Betaferon
- nausea
- vomiting
- diarrhoea
- rash, redness of the skin in the face, joint pain, fever, weakness and others caused by the medicine (drug-induced lupus erythematosus)
- **menstrual disorder**

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 the 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 Betaferon

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 pack. The expiry date refers to the last day of that month.

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

After preparing the solution you should use it immediately. However, if you are not able to do so, it will be suitable for use for 3 hours, if kept at 2-8 °C (in a refrigerator).

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

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

If the medicine becomes discolored or shows any other signs of deterioration, you should seek the advice of your pharmacist who will tell you what to do.

6. Contents of the pack and other information

What Betaferon contains

The active substance is interferon beta-1b, 250 microgram per millilitre when reconstituted.

The other ingredients are
- in the powder: mannitol and human albumin,
- in the solvent (sodium chloride solution 5.4 mg/ml (0.54% w/v)): sodium chloride, water for injection.

The Betaferon powder is provided in a 3-millilitre vial, containing 300 microgram (9.6 million IU) interferon beta-1b per vial. After reconstitution, each millilitre contains 250 microgram (8.0 million IU) interferon beta-1b.

The solvent for Betaferon is provided in a 2.25-millilitre pre-filled syringe and contains 1.2 ml sodium chloride solution 5.4 mg/ml (0.54% w/v).

What Betaferon looks like and contents of the pack

Betaferon is a sterile white to off-white powder for solution for injection. Betaferon is available in pack sizes of:

- multipacks comprising 15 single packs, each containing 1 vial with powder, 1 pre-filled syringe with solvent, 1 vial adapter with needle, 2 alcohol wipes.

Manufacturer:
Bayer AG
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13353 Berlin
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Procured from within the EU and repackaged for the PL Holder: Abacus Medicine Ltd., Abbey House, 282 Farnborough Road, Farnborough, GU14 7NA, United Kingdom

PL 45763/1064

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