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Patient leaflet in accordance with the Pharmacists' Regulations (Preparations) – 1986

This medicine is dispensed with a doctor's prescription only

Betaferon

Powder and solvent for solution for subcutaneous injection

Active ingredient and quantity:
interferon beta-1b 0.3 mg/vial
After reconstitution, 1 ml contains 250 micrograms (8.0 million international units) interferon beta-1b.

Inactive ingredients and allergens – see section 2 'Important information about some of this medicine's ingredients', and section 6 'Additional information'.

Read the entire leaflet carefully before you start using this medicine. This leaflet contains concise information about this medicine. If you have any further questions, consult your doctor or pharmacist.

This medicine has been prescribed to treat your illness. Do not pass it on to others. It may harm them, even if it seems to you that their medical condition is similar to yours.

Essential information about the medicine
This section presents a summary of the most essential information from the leaflet about treatment with Betaferon.

- Before injection, prepare the Betaferon solution by using the vial that contains Betaferon powder and the pre-filled syringe that contains a solvent. This will be prepared by your doctor or nurse, or by you after you have received appropriate training.
- Detailed instructions regarding preparation of the Betaferon solution and self-injection under the skin are provided in the Annex "Self-injection instructions."
- Routinely change the site of injection. See section 2 'Special warnings about using this medicine' and follow the instructions in the Annex, in part II 'Rotating injection sites'.

1) What is this medicine intended for?

- For treatment of ambulatory patients suffering from multiple sclerosis of the relapsing-remitting MS type and of the relapsing-progressive MS type, to reduce the frequency of clinical relapses.
- For treatment of multiple sclerosis of the secondary progressive MS type.
- For treatment of patients who experienced a single clinical event suggestive of multiple sclerosis, with an active inflammatory process, if it is severe enough to justify intravenous administration of corticosteroids, if other possible diagnoses have been ruled out, including the presence of MRI abnormalities characteristic of multiple sclerosis, and if the patients are determined to be at high risk of developing clinically significant multiple sclerosis.

Therapeutic group: This medicine belongs to a group called cytokines, interferons.

Betaferon is a type of medicine known as interferon, which is 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.

Damage to the CNS can occur within an MS attack (relapse). It can cause temporary disability, 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 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.

2) Before using this medicine

Do not use this medicine if:

- **You are sensitive (allergic)** to natural or recombinant interferon beta, human albumin or any of the other ingredients in this medicine (see section 6 'Additional information').
- **You currently suffer from severe depression and/or suicidal thoughts** (see 'Special warnings about using this medicine' in this section and section 4 'Side effects').
- **You have severe liver disease** (see 'Special warnings about using this medicine' and 'Drug interactions' in this section and section 4 'Side effects').

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

Special warnings about using this medicine

Before using Betaferon, tell your doctor 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) such as systemic capillary leak syndrome may develop when using Betaferon. This can lead to shock and even be fatal.
- **You are depressed, have had depression or previously had thoughts of suicide.** Your doctor will closely monitor you while you use the medicine. If your depression and/or suicidal thoughts are severe, you will not be prescribed Betaferon (see section 2 'Do not use this medicine if').
- **You have ever had epileptic seizures or if you are taking medicines to treat epilepsy**, your doctor will monitor your treatment carefully while you use the medicine (see 'Drug interactions' in section 2 and section 4 'Side effects').
- **You have severe kidney problems.** Your doctor may monitor your kidney function during treatment with the medicine.

Your doctor also needs to know if one of the following conditions affects you while you are being treated with the medicine:

- **You experience symptoms such as itching all over your body, swelling of your face and/or your tongue or sudden shortness of breath.** These symptoms may indicate a serious allergic reaction (hypersensitivity), which may become life threatening.
- **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 being treated with Betaferon, you may need special treatment, and your doctor will closely monitor you and may even consider stopping the treatment. If you suffer from severe depression and/or suicidal thoughts, you will not be treated with Betaferon (see section 2 'Do not use this medicine if').
- **You notice unusual bruising, excessive bleeding after injury or if you seem to be getting 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 closer monitoring by your doctor.
- **You have decreased 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.** These symptoms may suggest problems with your liver function. Changes to the liver function values were observed in patients who took with Betaferon during clinical trials of the medicine. As for other beta interferons, severe liver damage, including cases of liver failure, have been reported rarely in patients taking Betaferon. The most serious cases were reported in patients taking other medicines or who were suffering from diseases that can affect the liver (e.g. alcohol abuse, severe infection).
- **You experience symptoms like irregular heartbeat, swelling, such as of the ankles or legs, or shortness of breath.** These symptoms may suggest a disease of the heart muscle *(cardiomyopathy)* which has been reported rarely in patients who took Betaferon.
- **You notice pain in your belly which is radiating to your back, and/or you feel sick or have a fever.** These symptoms may suggest an inflammation of the pancreas (pancreatitis), which has been reported in patients who took Betaferon. This is often associated with an increase in certain blood fats (triglycerides).

Stop using Betaferon and tell your doctor immediately if you suffer from one or more of the conditions mentioned above.

Other things to consider when using Betaferon:

- **If you have a heart disease, the flu-like symptoms, which often occur at the start of treatment, may be difficult for you.** Betaferon must be used with caution, and your doctor will monitor you to prevent worsening of your heart condition, particularly during the start of treatment. The medicine Betaferon itself does not affect the heart directly.
- **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 neutralizing antibodies,** which may react with Betaferon (neutralizing activity). It is not yet clear whether the activity of these antibodies reduces the effectiveness of the treatment. Neutralizing antibodies are not produced in all patients who take Betaferon. Currently it is not possible to predict which patients will produce these anibodies and which patients won't.
- **During treatment with Betaferon, kidney problems that may reduce your kidney function, including scarring, may develop.** Your doctor may perform tests to check your kidney function.
- **Blood clots in the small blood vessels may occur during treatment with Betaferon.** These blood clots could affect your kidneys. This condition might develop several weeks to several years after starting treatment. Your doctor may check your blood pressure, ask you to take blood tests (including a platelet count) and monitor your kidney function.
- **Paleness, yellow skin or dark-colored urine, possibly accompanied by unusual dizziness, tiredness or shortness of breath may occur during treatment with Betaferon.** These symptoms may be due to breakdown of red blood cells. This might

happen several weeks to several years after starting treatment with Betaferon. Your doctor may ask you to have blood tests performed. Tell your doctor about other medicines that you are taking at the same time as your treatment with Betaferon.

Injection site reactions
During Betaferon treatment, you are likely to experience injection site reactions. Symptoms include redness, swelling, change in the skin color, inflammation, pain and hypersensitivity. Infection around the injection site, appearance of cracks in the skin and tissue damage (necrosis) have been reported less frequently. Injection site reactions usually become less frequent over time.
Injection site skin and tissue breakdown can result in scarring . If the scars are severe, a doctor may have to remove foreign matter and "dead" tissue (debridement) and, less often, skin grafting may be required and healing may take up to 6 months.

To reduce the risk of injection site reactions, such as infection or necrosis, you must:
- use a sterile injection technique when injecting the medicine.
- rotate the injection sites (see Annex 'Self-injection instructions').

Injection site reactions may occur less frequently if you use an auto-injector device and rotate injection sites. Your doctor 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 the injections with Betaferon** and contact your doctor.
- **If you have only one sore injection site** (lesion) **and the tissue damage** (necrosis) **is not very 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
No formal clinical trials have been performed regarding the use of Betaferon in adolescents and children. However, there is information regarding use of Betaferon in children and adolescents between the ages of 12-16 years. This data suggests that the safety of use in these ages is the same as in adults at a dose of 8.0 million IU injected under the skin once every two days (every other day). There is no data on the use of Betaferon in children under 12 years of age. Therefore, Betaferon should not be used in this population.

Tests and follow-up
When using the medicine, you must undergo the following medical tests:
- You will need to have blood tests performed to measure the number of blood cells, blood chemistry tests and liver enzyme level tests. These tests will be performed **before starting treatment with Betaferon, regularly after treatment has been initiated and periodically during the course of treatment**, even if you do not experience any symptoms. Have these tests performed in addition to the routine tests your doctor performs for multiple sclerosis.
- **You will have to perform thyroid function tests**, routinely or whenever the doctor decides that it is necessary.

Drug interactions
If you are taking or have recently taken other medicines, including nonprescription medications and dietary supplements, tell your doctor or pharmacist.
No formal interaction studies have been carried out to find out whether there are drug interactions between Betaferon and other medicines.

Using Betaferon concomitantly with other medicines that may affect the immune system response is not recommended, except for use of anti-inflammatory medicines called corticosteroids or the adrenocorticotropic hormone (ACTH).

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

Using Betaferon and food
Betaferon is injected under the skin; thus, consumption of any food or drink should not have any effect on the activity of Betaferon.

Pregnancy and breastfeeding

Pregnancy
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.
Breastfeeding
No harmful effects on the breastfed infant are anticipated. Betaferon can be used during breastfeeding.

Driving and using machines
Use of Betaferon may cause side effects in the central nervous system (see section 4 'Side effects'). If you are particularly sensitive, these effects may affect your ability to drive or operate machines.

Important information about some of this medicine's ingredients
The inactive ingredients of the medicine include:
- A small amount of mannitol, a naturally occurring sugar and human albumin, a type of protein, and sodium.
- Sodium: This medicine contains less than 1 mmol sodium (23 mg) per 1 ml, i.e. essentially 'sodium free'.

If you know that you are hypersensitive (allergic) to any of the ingredients in the medicine or if you develop such a sensitivity, stop using Betaferon.

3) How to use this medicine?
Treatment with Betaferon will be started under the supervision of a doctor who is experienced in the treatment of multiple sclerosis.
Always use this medicine according to your doctor's instructions. Check with your doctor or pharmacist if you are not sure about your dose or about how to take this medicine.

- Only your doctor will determine your dose and how you should take this medicine. The recommended dosage is usually 1.0 ml of the prepared Betaferon solution (see Annex 'Self-injection instructions') injected under the skin (subcutaneously) **once every two days**. This amount equals 250 micrograms (8.0 million IU) interferon beta-1b.

Generally, initial treatment will begin with administration of an initial low dosage of 0.25 ml (62.5 micrograms). The dosage will be gradually increased up to the full dosage of 1.0 ml (250 micrograms).
The dosage should be increased every fourth injection, in 4 stages (0.25 ml, 0.5 ml, 0.75 ml, 1.0 ml).

Your doctor may decide, together with you, to change the time interval between increases in the dose, depending on the side effects you may experience at the start of treatment.

Preparing the solution for injection:
- **Before injection, prepare the Betaferon solution for injection**, by using the vial that contains Betaferon powder and the pre-filled syringe that contains 1.2 ml solvent. This will be either be done by your doctor or nurse, or by yourself after you have received appropriate training. Instructions on how the solution for injection is prepared, see the Annex 'Self-injection instructions.'
- **Detailed instructions for self-injection of Betaferon under the skin** are provided in the Annex 'Self-injection instructions'.
- **Routinely change the site of injection**. See section 2 'Special warnings about using this medicine' and follow the instructions in the Annex, in Part II 'Rotating injection sites' and Part III 'Betaferon Injection Record'.

Do not exceed the recommended dose.

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

If you have accidentally taken a higher dose, namely, too much or too often, talk to your doctor.
Administration of Betaferon many times for the treatment of multiple sclerosis has not led to life-threatening situations.

If you forget to inject the medicine at the required time, inject as soon as you remember and inject the next dose 48 hours later.
Do not inject a double dose to make up for a forgotten single dose.

Adhere to the treatment as recommended by your doctor.

If you stop taking this medicine
Talk to your doctor if you want to stop or have stopped treatment with Betaferon.
Stopping treatment with Betaferon is not known to lead to acute withdrawal symptoms.

Do not take medicines in the dark! Check the label and dose <u>every time</u> you take a medicine. Wear glasses if you need them.

If you have any further questions about using this medicine, consult your doctor or pharmacist.

4) Side effects
Like with all medicines, using Betaferon may cause side effects in some users. Do not be alarmed by this list of side effects. You may not experience any of them.

Stop taking this medicine and consult your doctor immediately if:
- you experience symptoms such as **itching all over your body, swelling of your face and/or your tongue or sudden shortness of breath**.
- you feel **noticeably more sad or hopeless than before the treatment with Betaferon, or if you develop thoughts of suicide**.
- you notice **unusual bruising, excessive bleeding after injury or if you seem to be getting a lot of infections.**

- you have **decreased 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**.
- you experience symptoms like **irregular heartbeat, swelling of the ankles or legs, or shortness of breath.**
- 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 experience one or more of the following symptoms: **foamy urine, fatigue, swelling, particularly in the ankles and eyelids, and weight gain**, as they may be signs of a kidney function problem.

At the beginning of treatment, side effects are common, but in general they become less frequent with continued use of the medicine.

The most common side effects are:
- **Flu-like symptoms** such as fever, chills, painful joints, malaise, sweating, headaches, or muscular pain. These symptoms may be reduced by taking medicines containing paracetamol or non-steroidal anti-inflammatory medicines that contain ibuprofen.
- **Injection-related reactions.** Symptoms can be redness, swelling, change in skin color, inflammation, infection, pain, hypersensitivity, tissue damage (necrosis). For more information and what to do if you experience these reactions, see in section 2 'Special warnings about using this medicine'. These reactions 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 treatment with a low dose of Betaferon and increase the dose gradually (see section 3 'How to use this medicine?').

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

Very common side effects - may affect more than 1 in 10 users:
- reduced count of white **blood cells**
- **headache**
- sleep disorders (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
- **muscle** stiffness
- painful joints
- urinary urgency
- **injection site** reactions (including redness, swelling, discolouration, inflammation, pain, infection, allergic reactions (hypersensitivity))
- **flu-like** symptoms, pain, fever, chills, accumulation of fluid in arms or legs (peripheral oedema), lack/loss of strength

Common side effects - may affect up to 1 in 10 users:
- **swollen lymph glands**
- the count of red blood cells may decrease (anaemia)

- the thyroid gland does not work properly (too little hormone is produced in the gland)
- weight gain or loss
- confusion
- abnormally rapid heartbeat (tachycardia)
- increased **blood pressure**
- a specific liver enzyme (aspartate aminotransferase or ASAT) may rise (this will show up in blood tests)
- **shortness of breath**
- a reddish yellow pigment (bilirubin), which is produced by the liver, may rise (this will show up in blood tests)
- swollen and usually itchy patches of skin or mucous membranes (urticaria)
- itching
- loss of scalp hair *(*alopecia*)*
- menstrual disorders *(*menorrhagia*)*
- heavy uterine bleeding *(*metrorrhagia*)* especially between menstrual periods
- **impotence**
- formation of skin cracks and tissue damage *(*necrosis*)* at the injection site (see section 2 'Injection site reactions')
- chest pain
- malaise

Uncommon side effects - may affect up to 1 in 100 users:

- the blood platelet (cells that help the blood clotting process) count may fall (thrombocytopenia)
- a certain type of blood fats (triglycerides) may increase (will show up in blood tests), see section 2 'Special warnings about using this medicine'
- suicide attempts
- mood swings
- convulsions (epileptic fits)
- a specific liver enzyme (gamma GT) produced by the liver may rise in the blood (this will show up in blood tests)
- inflammation of the liver (hepatitis)
- changes in skin color
- kidney problems, including scarring (glomerulosclerosis) that may reduce your kidney function.

Rare side effects - may affect up to 1 in 1,000 users:

- blood clots in the small blood vessels that may affect your kidneys (thrombotic thrombocytopenic purpura [TTP] 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 test results and renal function.
- 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, see section 2 'Special warnings about using this medicine'
- the liver does not work properly *(*hepatic injury including hepatitis, hepatic failure*)*

Side effects of unknown frequency (frequency cannot be estimated from the available data)

- breakdown of red blood cells (haemolytic anaemia)

- problems with function of the small blood vessels may develop when using medicines like Betaferon *(*systemic capillary leak syndrome*)*
- **depression, anxiety**
- dizziness
- irregular, rapid heartbeat *(*palpitations*)*
- redness and/or facial flushing due to widening of blood vessels
- 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 additional reactions caused by the medicine (drug-induced lupus erythematosus)
- **menstrual disorders**
- sweating

If you experience any side effect, if any side effect gets worse, or if you experience a side effect not mentioned in this leaflet, consult your doctor.

Reporting side effects
You can report side effects to the Ministry of Health by following the link "Reporting Side Effects of Drug Treatment" on the Ministry of Health home page (www.health.gov.il) which links to an online form for reporting side effects. You can also use this link: https://sideeffects.health.gov.il/

5) How to store the medicine?

- Prevent poisoning! Keep this, and all other medicines, in a closed place, out of the reach and sight of children and/or infants and by doing so prevent poisoning. Do not induce vomiting unless explicitly instructed to do so by a doctor.

- Do not use the medicine after the expiry date (exp. date) which is stated on the package. The expiry date refers to the last day of that month.

- Store below 30˚C. Do not freeze.

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

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

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

6) Additional information

- In addition to the active ingredients, this medicine also contains:

in the powder: mannitol, human albumin
in the solvent: sodium chloride solution 0.54%, water for injection

- What the medicine looks like and contents of the pack
  - The Betaferon powder is provided in a 3-ml vial. The powder is sterile, white to off-white.
  - The solvent is provided in a 2.25-ml pre-filled syringe. The volume of the solvent is 1.2 ml.

- Betaferon comes in multipacks containing 12 or 15 single packs, each containing 1 vial with powder, 1 pre-filled syringe (volume of 2.25 ml) with solvent, 1 vial adapter with needle, 2 alcohol wipes.
- Not all pack sizes may be marketed.

- Registration holder's name and address: Bayer Israel Ltd., 36 Hacharash St., Hod Hasharon 45240.

- Manufacturer's name and address: Bayer AG, Berlin, Germany.

Revised in March 2023 according to MOH guidelines.

- Registration number of the medicine in the National Drug Registry of the Ministry of Health: 069 34 28359 00.