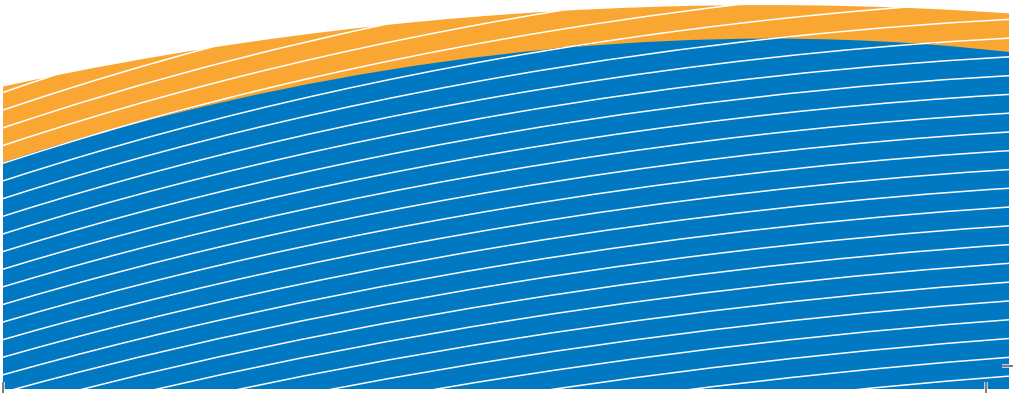
BETAFERON®

Interferon beta-1b 250 mcg/ml

Powder and solvent for preparing
a solution for subcutaneous injection

- Patient Leaflet
- Annex: Self-injection procedure



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 preparing a 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 procedure."
- Routinely change the site of injection. See section 2 'Special warnings regarding use of the 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 definite 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 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.

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 of this medicine (see section 6 'Additional information').
- **You are pregnant.** Do not commence treatment with the medicine during pregnancy (see 'Pregnancy and breastfeeding' in this section).
- **You currently suffer from severe depression and/or suicidal thoughts** (see 'Special warnings about using of this medicine' in this section and section 4 'Side effects').
- **You have severe liver disease** (see 'Special warnings about using this medicine' and 'Drug interaction' 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 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.** 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 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 of 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 patient 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 may occur during treatment with Betaferon.** These blood clots could affect your kidneys. This conduction 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 a 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. The appearance of cracks in the skin and tissue damage (necrosis) around the injection site have been reported less frequently. Injection site reactions usually become less frequent over time.

Injection site skin and tissue breakdown can result in scars forming. If the scars are 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 injection site reactions you must:

- use a sterile injection technique when injecting the medicine.
- rotate the injection sites (see Annex 'Self-injection procedure').

Injection site reactions may occur less frequently, if you use an auto-injector device. 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 commencing treatment with Betaferon, routinely upon commencement of treatment 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 so consumption of any food or drink should not have any effect on the activity of Betaferon.

Pregnancy and breastfeeding

Pregnancy
If you are of child-bearing age, use an appropriate method of contraception during the course of treatment with Betaferon.
- **If you are pregnant or there is a chance you are pregnant**, tell your doctor. Do not start treatment with Betaferon if you are pregnant (see 'Do not use this medicine if' in section 2). The existing data indicate that there may be an increased risk of spontaneous abortion.
- **If you want to become pregnant**, first consult your doctor about this.
- **If you become pregnant while being treated with Betaferon**, stop treatment with the medicine and contact your doctor immediately. You and your doctor will decide if your Betaferon treatment should be continued or not.

Consult your doctor before taking any medicine.

Breastfeeding
It is not known whether interferon beta-1b (the active ingredient in Betaferon) passes into breast milk. However, it is theoretically possible that a breastfed baby could experience serious side effects due to Betaferon.
- **Discuss this with your doctor first** in order to decide whether to stop breastfeeding or stop using Betaferon.

Consult your doctor before taking any medicine.

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 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 procedure') 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 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 procedure.'
- **Detailed instructions for self-injection of Betaferon under the skin** are provided in the Annex 'Self-injection procedure'.
- **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 length 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 severe withdrawal symptoms.

Do not take medicines in the dark! Check the label and dose <u>every time</u> you take 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 as soon as possible 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 **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**.
- 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 get 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 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, pain, hypersensitivity, tissue damage (necrosis). For more information and what to do if you experience these reactions, see 'Special warnings regarding use of this medicine.' These reactions may be reduced by the use of an auto-injector device. 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 (List 1) and from side effects reported on the marketed product (List 2).

List 1: Very common side effects which have been observed in clinical trials with Betaferon (at least 10% of the cases) and at a higher percentage than those observed when using placebo. The list also includes side effects that were observed in less than 10% but were significantly associated with the treatment with Betaferon.

– **infection**, abscess (pus-filled sore)
– lower **white blood cell** count, swollen **lymph glands**
– decrease in **blood sugar level**
– **depression, anxiety**
– **headaches, dizziness**, sleeplessness, migraine, **tingling feeling or numbness**
– **eye inflammation** (conjunctivitis), **abnormal vision**
– **ear** pain
– rapid and irregular beating or pulsation of the **heart**
– redness and/or facial flushing due to widening of **blood vessels**, increased **blood pressure**
– **runny nose**, cough, hoarseness due to infection of the upper **respiratory tract**, sinusitis, worsening cough, **shortness of breath**
– diarrhea, constipation, nausea, vomiting, abdominal pain
– rise in the blood levels of **liver** enzymes (will show up in blood tests)
– **skin** disorder, rash
– **muscle** stiffness, muscle pain, muscular weakness, **back** pain, pain in **extremities** such as fingers and toes
– difficulty urinating (urine retention), protein in the **urine** (will show up in urine tests), increased urinary frequency, urinary incontinence, urinary urgency
– painful periods, **menstrual** disorders, heavy uterine bleeding especially between menstrual periods, **impotence**
– **injection site** reaction (including redness, swelling, discoloration, inflammation, pain, allergic reaction), skin breakdown and tissue damage (necrosis) at injection site (see section 2 'Special warnings about using this medicine')
– **flu-like symptoms**, fever, pain, chest pain, **accumulation of fluid** in arm, leg or face (peripheral edema), **weakness**, chills, sweating, malaise

In addition, the following side effects have been identified during post-marketing information.

List 2: Side effects reported on the marketed medicnal product (frequency, where known, is based on clinical studies).

Very common side effects: may appear in more than 1 in 10 users:
– Painful joints

Common side effects: may appear in up to 1 in 10 users:
– the number of red cells in the blood may fall (anemia)
– the thyroid gland does not work properly (too little hormone is produced in the gland)
– weight gain or loss
– confusion
– abnormally rapid heartbeat (tachycardia)
– 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
– loss of scalp hair (alopecia)
– menstrual disorders (menorrhagia)

Uncommon side effects: may appear in 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 regarding using this medicine'
– suicide attempts
– mood swings
– convulsions (epileptic fits)
– a specific liver enzyme (gamma GT) which is produced by your liver, may rise in the blood (this will show up in blood tests)
– inflammation of the liver (hepatitis)
– change in skin color

Rare side effects: may appear in up to 1 in 1,000 users:
– serious allergic (anaphylactic) reactions
– the thyroid gland does not work properly (too much hormone is produced, hyperthyroidism)
– inflammation of the pancreas, see section 2 'Special warnings about using this medicine.'
– blood clots in the small blood vessels that can affect your kidney function (thrombotic thrombocytopenic purpura [TTP] or hemolytic uremic syndrome). Symptoms such as increased bruising, bleeding, fever, extreme weakness, headache, dizziness or light-headedness may appear. Your doctor may find changes in the results of the blood tests and the function of your kidneys.

Additional side effects reported only during post-marketing:
– breakdown of red blood cells (hemolytic anaemia), frequency unknown
– kidney problems including scarring that may reduce your kidney function, uncommon
– severe loss of appetite leading to weight loss (anorexia), rare
– disease of the heart muscle, rare
– sudden shortness of breath, rare
– Abnormal liver function (hepatic injury, hepatic failure, including hepatitis), rare
– problems with your small blood vessels may develop when using medicines like Betaferon (systemic capillary leak syndrome), frequency unknown
– rash, redness of the skin in the face, joint pain, fever, weakness and others caused by the medicine (drug-induced lupus erythematosus), frequency unknown
– 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), frequency unknown. Pulmonary arterial hypertension has been seen at various time points during treatment, including several years after starting treatment with Betaferon.

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 25°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-milliliter 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 pack sizes of:
  multipacks containing 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.
– Titration pack for the first 12 injections, containing 4 triple packs, each containing 3 vials with powder, 3 pre-filled syringes (with a volume of 2.25 ml each) with solvent, 3 vial adapters with needle, 6 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 February 2021 according to MOH guidelines.

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

Annex: Self-injection Instructions

Your doctor has prescribed Betaferon to treat your disease - multiple sclerosis.
To best adapt to the medicine, it is usually recommended to start with a low dose of Betaferon and gradually increase it to the full dose (see section 3 'How to use this medicine?' in the patient leaflet).

The following instructions and pictures explain how to prepare Betaferon for injection and how to administer the injection yourself. Please read the instructions carefully and follow them step by step. Your doctor will refer you to a Betaferon guiding nurse who will guide you and help you learn the process and technique of self-injection. Do not attempt to self-inject until you are sure that you understand how to prepare the solution for injection and give the injection to yourself.

Part I: Step-by-step instructions

The instructions include the following main steps:

A. General information
B. Getting ready to inject
C. Process of preparing the solution for injection, step by step
D. Preparing the syringe
E. Making the injection
F. Quick review of the entire process

A. General information

- **Get a good start!**

You will find that within a few weeks your treatment will become a natural part of your routine. As you get started, you may find the following suggestions helpful:

– Set up a permanent storage area in a convenient location out of the sight and reach of children so your Betaferon package and other supplies are always easy to find.
  For details on storage conditions, see section 5 'How to store the medicine?' in the patient leaflet.
– Try to inject at the same time of day on each day on which you have to take Betaferon. This makes it easier to remember and easier to plan a block of time when you will not be interrupted.
– Prepare each dose only when you are ready for an injection. After the mixing process, you should give the injection immediately (if Betaferon is not used immediately, see section 5 'How to store the medicine?' in the patient leaflet).

- **Important tips to keep in mind**
  – Be consistent - use Betaferon as described in section 3. 'How to use this medicine'? in the patient leaflet. Always double-check your dosage.
  – Keep your syringes and containers intended for disposal of syringes and needles out of the sight and reach of children; lock the supplies away if possible.
  – Never re-use syringes or needles.
  – Always use a sterile technique as described below.
  – Always place the used syringes in the proper disposal container.

B. Getting ready to inject

- **Choosing an injection site**

Before preparing your injection, decide where you are going to inject. You should inject Betaferon into the fatty layer between the skin and muscle (that is, subcutaneously, about 8 to 12 mm under the skin). The best places for injections are where the skin is loose and soft, and away from joints, nerves, or bones, for example the abdomen, arm, thigh or buttocks.

Very important: Do not inject to any areas where you can feel lumps, firm knots, bumps, pain or an area that is discolored, indented, scabbed, or where there is an open sore. Inform your doctor or Betaferon guiding nurse about these or any other unusual conditions, if any.

You should rotate and change the injection site at every injection. If some areas are too difficult for you to reach, you can have a family member or friend help you inject in these areas. Follow the injection rotation schedule described in the last part of these instructions (see Part II, 'Rotating injection sites'); this way, you will come back to your

first injection site area after 8 injections (16 days). This will give each injection site a chance to fully recover before receiving another injection.

Please refer to the injection rotation schedule in Part II of this Annex for an explanation about how to choose the injection site. In addition, for an explanation of how to keep track of your injection sites and dates, see “Example of a medication record”, in Part III of this Annex.

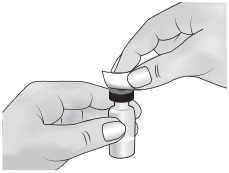
- **Checking the content of the pack**

Each single package of Betaferon contains:
– 1 Betaferon vial (with powder for solution for injection).
– 1 pre-filled syringe containing a solvent for the dilution of Betaferon (sodium chloride solution 5.4 mg/ml [0.54% w/v]).
– 1 vial adapter with a needle.
– 2 alcohol wipes to clean the skin and vial.
In addition, you will need a disposal container for used syringes and needles (may be obtained from the guiding nurse).
Use an appropriate disinfectant to disinfect the skin.

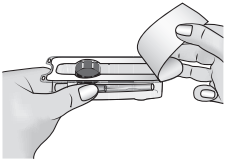
C. Process of preparing the solution for injection, step by step

1 - Wash your hands thoroughly with soap and water before beginning this process,

2 - Open the Betaferon vial and put it on the table. It is best to use your thumb rather than your nail as it could break.



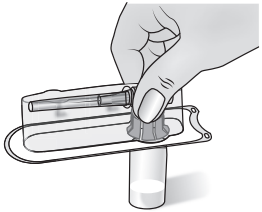
3 - Clean the top of the vial with an alcohol wipe, moving the wipe in one direction only and leave it on top of the vial.



4 – Open the pack containing the vial adapter, but leave it inside the pack.

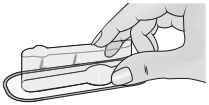
Do not remove the vial adapter from the pack at this stage.

Make sure not to touch the vial adapter in order to keep it sterile.

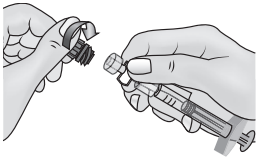


5 - Before attaching the adapter, remove the alcohol wipe from the top of the vial, and place the vial on a flat surface.

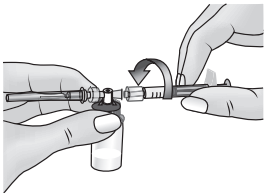
6 - Hold the vial adapter pack on the outside and place it on top of the vial. Push it down firmly until you feel the adapter snap into place.



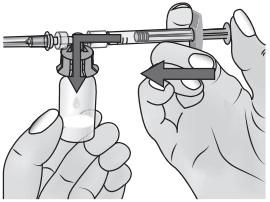
7 - Remove the adapter pack, while holding the edges of the pack. Now you are ready to attach the syringe containing the solvent to the vial adapter.



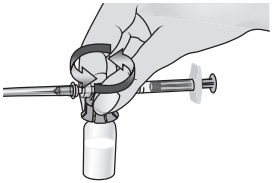
8 – Pick up the syringe. Be sure that the orange tip cap is firmly attached to the syringe. Remove the orange tip cap by twisting it off. Throw away the tip cap.



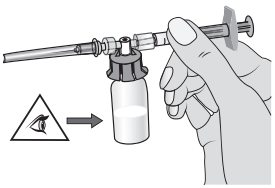
9 - Connect the syringe to the opening on the side of the vial adapter by inserting the end of the syringe and tightening carefully with a clockwise “push and twist” motion (see arrow).
You have now completed the syringe assembly.



10 - Hold the syringe assembly at the bottom of the vial. Slowly push the plunger of the syringe in all the way to transfer all of the solvent into the vial. Once you release the plunger, it may go back to its original position.

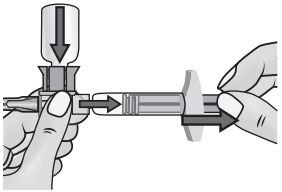


11 - With the syringe assembly still attached, swirl the vial around gently to completely dissolve the Betaferon powder. **Do not shake the vial.**

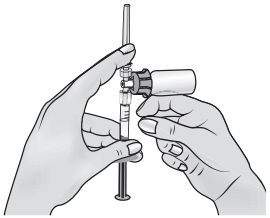


12 - Examine the solution carefully. It should be clear without any particles. If the solution is cloudy or contains particles, discard it and start again with a new single package. If foam is present, which can happen when the vial is shaken or swirled too much, let the vial sit undisturbed until the foam settles.

D. Preparing the syringe



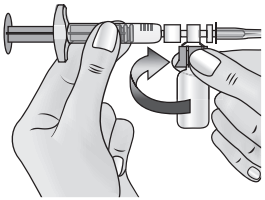
13 - If the plunger has moved back to its original position, push it in again and hold it in place. To prepare the syringe, turn the assembly over so that the vial is on top, cap side pointing down. This will allow the solution to flow down into the syringe.
Keep the syringe horizontal.
Slowly pull the plunger back to withdraw all the solution out of the vial and into the syringe.



14 - Turn the syringe assembly so that the needle is pointing up. This makes all air bubbles rise to the top of the solution.

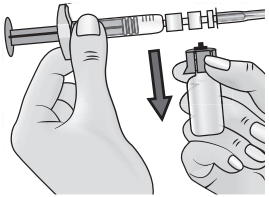
15 - Remove any air bubbles by gently tapping your finger on the syringe and pushing the plunger to the 1 ml mark, or to the volume prescribed for you by the doctor.

If too much solution enters the vial along with the air bubbles, get back into the horizontal position (see picture 13) and pull the plunger back a little to withdraw the solution back into the syringe.



16 - Next, hold the blue part of the vial adapter which is attached to the vial and remove it from the syringe by twisting it and then pulling it down, away from the syringe.

Only hold the blue part of the plastic adapter when removing. Keep the syringe in a horizontal position and the vial below the syringe.



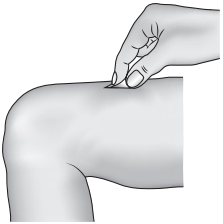
Removing the vial and adapter from the syringe ensures that the solution will flow out from the needle when injected.

17 - Dispose of the vial and any unused portion of the solution in the designated disposal container.

18 - You are now ready to inject.

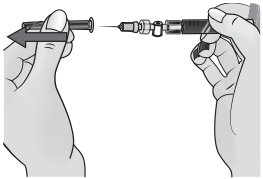
If, for some reason, you are not able to inject Betaferon immediately, you can keep the prepared solution in the syringe in a refrigerator for up to 3 hours before using. Do not freeze the solution, and do not wait longer than 3 hours to inject it. If more than 3 hours have passed, discard it and prepare a new injection. When you use the solution, you should warm it up a little with your hands before injecting to avoid pain.

E. Making the injection

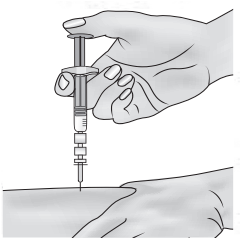


1 - Choose an area for the injection (see at the beginning of this Annex and in the diagrams at the end of this Annex) and make a note of it in your records.

2 - Use an alcohol wipe to clean the skin at the injection site. Let the skin air-dry.
Throw the wipe away. Use an appropriate disinfectant to disinfect the skin.



3 - Remove the cap from the needle by pulling it. Do not twist it.



4 - Gently pinch the skin upwards around the disinfected area (to raise it a bit).

5 - Hold the syringe like a pencil and insert the needle straight into the skin at a 90-degree angle with a quick, steady motion. Note: Betaferon can also be injected with an auto-injector device.

6 - Inject the medicine by pressing steadily and slowly (push the plunger all the way in until the syringe is empty).

7 - Discard the syringe in the designated disposal container.

F. Quick review of the entire process

– Take out the contents of one single package
– Attach vial adapter to the vial
– Connect the syringe to the vial adapter
– Push syringe plunger to transfer all the solvent into the vial
– Turn the syringe assembly over and withdraw the prescribed amount of the solution
– Remove vial from syringe - you are now ready to inject.

Note: The injection should be administered immediately after preparing the solution for injection (if the injection is delayed, refrigerate the solution and inject it within 3 hours). Do not freeze.

Part II: Rotating injection sites

It is essential to choose a new site for each injection to allow the area time to recover and help prevent infections. Advice on which areas to choose appears in the first part of this Annex. It is a good idea to know where you plan to inject before you prepare the syringe. The schedule shown in the diagram below will help you vary the sites appropriately. For example, if you give the first injection into the right side of the abdomen, choose the left side for the second injection. Then move to the right thigh for the third injection, and so on according to the diagram, until most suitable areas of the body have been used. Keep a record of where and when you last gave yourself an injection. One way to do that is to note the injection site on the enclosed injection record diagram.

By following this schedule, you will come back to your first area (i.e., the right side of the abdomen) after 8 injections (16 days). This process is called a rotation cycle. On the sample schedule, each area is split again into 6 injection sites (which adds up to 48 injection sites all together), right and left parts: Upper, middle and lower part of each area. If you come back to an area after one rotation cycle, choose the most distant injection site within this area. If an area becomes sore, contact your doctor or guiding nurse about choosing another injection site.

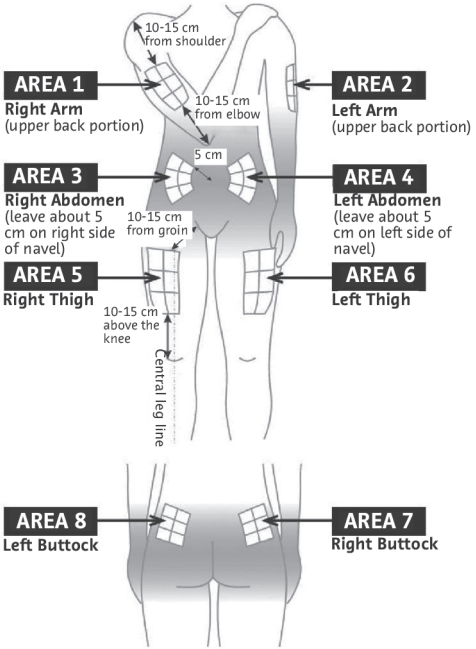
Injection rotation schedule

To help you rotate the injection sites appropriately, we recommend that you keep a record of the date and location of the injections. You can use the following rotation schedule:

Be sure to complete the full rotation cycle of 8 injection areas before going on to the next rotation cycle.
There will be 8 injections in each cycle (16 days), starting from area 1 through to area 8 in turn. By following this sequence, you will give each area a chance to recover before receiving another injection.

Injection rotation 1: Upper left section of each of the areas.
Injection rotation 2: Lower right section of each of the areas.
Injection rotation 3: Middle left section of each of the areas.
Injection rotation 4: Upper right section of each of the areas.
Injection rotation 5: Lower left section of each of the areas.
Injection rotation 6: Middle right section of each of the areas.

Injection rotation schedule



Part III: Betaferon medication record

Instructions for keeping track of your injection sites and dates

– Select an injection site for your first injection.
– Clean the injection site with an alcohol wipe and let it air-dry.
– After your injection, fill in the injection site and date in the appropriate place in your injection record diagram (see the example: “Recording and monitoring your injection sites and dates”).

Example of a medication record:
Keeping track of your injection sites and dates