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PROFESSIONAL INFORMATION

PATIENT INFORMATION LEAFLET

PATIENT INFORMATION LEAFLET

SCHEDULING STATUS: S4

PROPRIETARY NAME, STRENGTH AND PHARMACEUTICAL FORM:

BETAFERON
Recombinant interferon beta-1b 0,25 mg (8,0 million IU) lyophilised cake for solution

DILUENT FOR BETAFERON
Solution for injection

Please read all of this leaflet carefully before you start using BETAFERON.
- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or your pharmacist.
- BETAFERON has been prescribed for you personally and you should not share your medicine with other people. It may harm them, even if their symptoms are the same as yours.

What is in this leaflet
1. What BETAFERON is and what it is used for
2. What you need to know before you take BETAFERON
3. How to take BETAFERON
4. Possible side effects
5. How to store BETAFERON
6. Contents of the pack and other information

1. WHAT BETAFERON IS AND WHAT THEY ARE USED FOR:

BETAFERON belongs to the pharmacotherapeutic group of interferons, which are also naturally occurring proteins.

BETAFERON is indicated for use in:

- Patients with a single clinical event suggestive of multiple sclerosis ("Clinically Isolated Syndrome") to delay progression to definite multiple sclerosis.
- Ambulatory patients (patients who can walk) with relapsing-remitting multiple sclerosis characterised by at least two attacks of neurologic dysfunction over a 2 year period followed by a complete or incomplete recovery.
- Patients suffering from secondary progressive multiple sclerosis.

2. WHAT YOU NEED TO KNOW BEFORE YOU USE BETAFERON:

Treatment with BETAFERON should be initiated under the supervision of a medical doctor experienced in the treatment of the disease.

Do not use BETAFERON:

If you are hypersensitive (allergic) to interferon beta-1b, human albumin or any of the other ingredients of BETAFERON and DILUENT FOR BETAFERON.

Warnings and precautions:

Nervous system disorders:
Depression and suicidal thoughts have been reported by patients using BETAFERON.

If you feel noticeably more sad or hopeless than before the therapy with BETAFERON, or if you develop thoughts of suicide, you may need special treatment and your doctor will closely monitor you and may also consider stopping your treatment with BETAFERON (see "Possible side effects"). Please also tell your doctor if you ever had depression or thoughts of suicide before using BETAFERON.
Inform your doctor, if you ever had seizures. He/she will monitor your treatment carefully.

Blood changes:
In addition to those laboratory tests normally required for monitoring patients with multiple sclerosis, your doctor will usually order blood tests, e.g.

- a complete blood count,
- differential white blood cell counts,
- counts of platelets (a blood constituent which helps the blood to clot),
- blood chemistries, including liver function tests

This will be 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.
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.

Thrombotic microangiopathy (TMA)
There may be a formation of blood clots in the small blood vessels during your treatment, even up to several years after starting BETAFERON. Your doctor may want to monitor your blood pressure, blood (platelet count) and the function of your kidneys.

Pulmonary Arterial Hypertension (PAH):
Cases of pulmonary arterial hypertension - a lung disorder characterised by increased blood pressure in the pulmonary artery; have been reported with BETAFERON. If you develop suspicious symptoms (e.g. dyspnoea - sudden and severe shortness of breath or tiredness accompanied by shortness of breath) you should be assessed for PAH.

Inform your doctor if you notice paleness, yellow skin or dark-colored urine that may be accompanied by unusual dizziness, tiredness and shortness of breath. These may be symptoms of a breakdown of red blood cells. This might happen several weeks to several years after starting BETAFERON. Inform your doctor as well about other drugs that you are taking.

Thyroid disorders:
If you have ever suffered from problems with your thyroid, your doctor will regularly monitor the function of your thyroid gland.

Liver/biliary disorders:
Elevations of liver function values, in most cases mild and transient, occurred very commonly in patients treated with BETAFERON during clinical studies. Cases of severe liver damage, including liver failure, have been reported in patients using BETAFERON.

The most serious were reported in patients taking other medicines known to have a destructive effect on the liver or who were suffering from diseases that can affect the liver (e.g. metastasising malignant disease, alcohol abuse, severe infection, sepsis).
If you have loss of appetite, nausea, repeated vomiting, if you notice widespread itching, yellowing of the skin (jaundice), or of the whites of the eyes, or easy bruising, inform your doctor.
These symptoms may suggest problems with your liver. Inform your doctor as well about any other medicines or substances you are taking.
If the levels of some of your liver enzymes, which are measured in your blood, the so-called *transaminases* increase, your doctor will monitor and investigate you closely for signs of injuries to your liver during your treatment. If the levels of *transaminases* in your blood increase significantly, or if you

experience symptoms such as jaundice, your doctor will consider stopping your BETAFERON treatment.
If you have no signs of liver damage and your levels of liver enzymes have normalised again, restarting treatment with BETAFERON may be considered. In this case your liver function will be monitored.

Heart disorders:
While BETAFERON does not affect the heart directly, the flu-like symptoms [such as fever, chills and increased heart rate (tachycardia)], which often occur at the start of treatment, may exert cardiac stress and worsen your cardiac symptoms.
If you have a heart disorder, in particular significant heart disease, such as congestive heart failure, coronary artery disease or an irregular heartbeat (arrhythmia), BETAFERON must be used with caution. Inform your doctor who will monitor you for worsening of your heart conditions, particularly at the start of treatment.
During the treatment with BETAFERON cases of cardiomyopathy (disease of the heart muscle) have been reported. If you experience symptoms such as irregular heartbeat, swelling e.g. of the ankles or legs, or shortness of breath, contact your doctor immediately, who will consider to discontinue your BETAFERON treatment.

Gastrointestinal disorders:
An inflammation of the pancreas (pancreatitis) has been observed with BETAFERON use, often associated with an increase of certain blood fats (triglycerides). If you know that you have suffered from an increase of triglycerides or if you have suffered from pancreatitis, please inform your doctor.

Immune system disorders:
During treatment with BETAFERON your body may produce substances called neutralising antibodies, which may react with BETAFERON. It is not yet clear whether these neutralising antibodies reduce the effectiveness of the treatment. It is suggested that the decision to continue treatment with BETAFERON in patients who develop antibodies should be based on all aspects of the patient's disease status and not on the antibody status alone (see "Possible side effects").
If you have monoclonal gammopathy (a disorder of the immune system where an abnormal protein is found in the blood), tell your doctor. 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.

Allergic reactions (hypersensitivity):
If you experience symptoms such as itching all over your body, swelling of your face and/or your tongue or sudden shortness of breath, stop treatment with BETAFERON and contact your doctor immediately. These may be symptoms of a serious allergic reaction (hypersensitivity), which may become life-threatening.

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. Dead skin and tissue around the injection site (necrosis) have been reported. It can be extensive and may result in scar formation.

Occasionally, surgical cleaning of wound and, less often, skin grafting are required, and healing may take up to 6 months.
Injection site reactions usually become less frequent over time.
If you experience any break in the skin, which may be associated with swelling or fluid leaking out from the injection site:

- Talk to your doctor before continuing injections with BETAFERON.
- If you have only one sore injection site (lesion) and the tissue damage (necrosis) is not too extensive, you may continue using BETAFERON as some patients have experienced healing of injection site necrosis whilst on BETAFERON.
- If you have more than one sore injection sites (multiple skin lesions) BETAFERON should be discontinued until your skin has healed.

To reduce the risk of getting injection site reactions, such as infection, you should:
- Use an aseptic injection technique.
- Rotate the injection sites with each injection.
- Injection site reactions may occur less frequently when using an autoinjector.

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

Pregnancy and breastfeeding:

Pregnancy:
If you are pregnant or breastfeeding your baby you should not use BETAFERON.
BETAFERON should not be used during pregnancy or if you are trying to become pregnant. If you wish to become pregnant, you must discuss this with your doctor first. While using BETAFERON women of childbearing age should take appropriate contraceptive measures. If you do become pregnant while using BETAFERON, you should stop your treatment and contact your doctor immediately.

Breastfeeding:
It is not known whether interferon beta-1b in BETAFERON gets into the human breast milk. However, since serious adverse reactions to interferon beta-1b in breastfed infants are possible, you should stop breastfeeding.

BETAFERON contains human albumin and mannitol:

BETAFERON contains human albumin (a derivative of human blood) and is subject to effective donor screening and product manufacturing process. It carries a remote risk of viral diseases.
A risk of transmission of Creutzfeld-Jacob disease (CJD) cannot be ruled out. However no cases of transmission of viral diseases or CJD have ever been reported for albumin.
BETAFERON contains mannitol and may have a laxative effect.

Taking other medicines with BETAFERON:

If you are taking other medicines on a regular basis, including complementary or traditional medicines, the use of BETAFERON with these medicines may cause undesirable interactions. Please consult your doctor, pharmacist or other healthcare professional, for advice.

No formal medicine interaction studies have been carried out with BETAFERON to find out whether BETAFERON affects other medicines or is affected by them.
The effect of BETAFERON on medicine metabolism in multiple sclerosis patients is unknown.
With the exception of corticoids or ACTH, BETAFERON must not be used with substances that modify the immune system response.
Corticosteroid or ACTH treatment of relapses for periods of up to 28 days has been well tolerated in patients receiving BETAFERON.
Caution must be exercised when BETAFERON is administered in combination with other medicines, which need a certain liver system (known as cytochrome P450 system) for their metabolism. These medicines include some widely used antipyretics (medicines against fever and pain) and anti-epileptics.
Caution should also be exercised with medicines which affect the production of blood cells.
Please tell your doctor if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

3. HOW TO USE BETAFERON:

Do not share medicines prescribed for you with others.
Always use BETAFERON exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.
BETAFERON is injected subcutaneously (under the skin).

The treatment with BETAFERON should be initiated under the supervision of a doctor who is experienced in the treatment of multiple sclerosis.
Before administration, the BETAFERON solution for injection has to be prepared from a vial of BETAFERON and the solvent from the pre-filled syringe. This will either be done by your doctor or his/her assistant or by you after you have been carefully and sufficiently instructed and trained.

Adults:

Every other day 1,0 ml of the prepared BETAFERON solution for injection is injected subcutaneously. This is equal to 250 microgram (8 million IU).
In general, treatment should be started at a low dose of 0,25 ml (62,5 micrograms). Your doses will then be increased slowly to a dose of 1,0 ml (250 micrograms). Your individual tolerability of BETAFERON will determine the rate of dose increase. Your doctor will decide this with you. For the step-by-step increase of the dose a special titration pack is available.
The injection site must be changed regularly.
In the study in patients with a single clinical event, dosage was increased as shown in Table A.

Table A: Schedule for dose titration*

Treatment day	Dose	Volume
1, 3, 5	0,0625 mg	0,25 ml
7, 9, 11	0,125 mg	0,5 ml
13, 15, 17	0,1875 mg	0,75 ml
≥ 19	0,25 mg	1,0 ml

* Titration scheme as used in the study in patients with a single clinical event suggestive of multiple sclerosis. The titration period may be modified according to your individual tolerability.

Duration of treatment:

It is not known how long treatment with BETAFERON should last.
Efficacy for a period of up to three years of treatment has been demonstrated in a controlled clinical trial.
There are follow-up data under controlled clinical trial conditions for patients with relapsing-remitting multiple sclerosis for up to 5 years and for patients with secondary progressive multiple sclerosis for up to 3 years.
The available data for up to 5 years suggest sustained treatment efficacy of BETAFERON **for relapsing remitting multiple sclerosis** over the whole time period.
Efficacy for a period of two years and with limited data for a period of up to three years of treatment has been demonstrated **for secondary progressive multiple sclerosis** under controlled clinical trial conditions.
Efficacy has been demonstrated over a period of 5 years **in patients with a single clinical event suggestive of multiple sclerosis.**
The duration of treatment will be decided by your doctor.

Children and adolescents:
BETAFERON has not been investigated systematically in children and adolescents of less than 18 years of age. BETAFERON should not be administered to this age group.

Instructions for use/handling:
Before administration, the BETAFERON solution for injection has to be prepared from a vial of BETAFERON and 1,2 ml of liquid from the pre-filled solvent syringe. This will either be done by your doctor or his/her assistant or by yourself after you have been carefully and sufficiently instructed and trained.

Reconstitution:

BETAFERON vials and solvent vials (containing 2 ml solvent):
To reconstitute use a sterile syringe and needle to inject 1,2 ml of the supplied DILUENT FOR BETAFERON (sodium chloride solution 5,4 mg/ml (0,54 % w/v)) into the BETAFERON vial. Dissolve the powder completely without shaking.

BETAFERON vials and prefilled solvent syringes (no vial adapter) (1,2 ml syringe containing 1,2 ml solvent):
To reconstitute use the provided prefilled syringe with solvent and a needle to inject the 1,2 ml DILUENT FOR BETAFERON into the BETAFERON vial. Dissolve the powder completely without shaking.

BETAFERON vials and prefilled solvent syringes with vial adapter with attached needle (2,25 ml syringe containing 1,2 ml solvent):
To reconstitute connect the vial adapter with attached needle on the vial. Connect the prefilled syringe with solvent to the vial adapter and inject the 1,2 ml DILUENT FOR BETAFERON into the BETAFERON vial. Dissolve the powder completely without shaking.

After reconstitution draw all the liquid (1,2 ml) back into the syringe. Adjust the volume to the desired dose, e.g. 1 ml by injecting the excess solution into the vial.
Inspect the reconstituted product visually before use. The reconstituted product is colourless to light yellow and slightly opalescent to opalescent. Discard the product before use if it contains particulate matter or if it is discoloured.
To minimise the risk of injection site necrosis you must:
- Use an aseptic injection technique.
- Rotate the injection sites with each dose.

BETAFERON should not be mixed with other medicinal products, as compatibility studies have not been done.

A) Self-injection procedure

The following instructions are intended to explain how to prepare BETAFERON for administration and how to proceed in injecting BETAFERON yourself. Please read the instructions carefully and follow them step by step. Your doctor or his/her assistant will instruct and assist you in learning the procedure and the technique of self-administration. Do not attempt self-administration until you are sure that you understand the requirements for preparing the injection solution and giving the injection to yourself.

The instructions include the following main steps:

A1. Learning to use BETAFERON (Interferon beta-1b)
A2. Preparing for your injection
A3. The reconstitution process, step by step
A4. Preparing the injection
A5. Quick review of the process
A6. Choosing and preparing the injection site and injecting the BETAFERON solution (1,0 ml) subcutaneously (under the skin)

A1. Learning to use BETAFERON (interferon beta-1b)

In this Annex you will find instructions on how to reconstitute, prepare, and inject BETAFERON. Drawings also show you the steps in the process, so you can follow along and be confident that you are not missing or forgetting anything.

You will learn each of these techniques:
- Reconstituting BETAFERON by mixing the powdered medication with the solvent

- Selecting an injection site
- Preparing the injection
- Injecting the BETAFERON solution.

A1.1 Get a good start!

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

- Set up a permanent storage area in a convenient location out of the reach of children so your BETAFERON and other supplies are always easy to find.

(For details on storing conditions see section 5 'How to store BETAFERON' in the leaflet.)

- Try to take your injection at the same time of day. This makes it easier to remember and easier to schedule a block of time when you will not be interrupted.

(Please refer to section 3. 'How to use BETAFERON' in the leaflet for further details on how to use BETAFERON.)

- Prepare each dose only when you are ready for an injection. After mixing BETAFERON, you should administer the injection immediately (if BETAFERON is not used immediately, see section 5 'How to store BETAFERON' in the leaflet for storing instructions').

A1.2 Important tips to keep in mind

- Be consistent - Use BETAFERON as described in section 3. 'How to use BETAFERON'. Always double-check your dosage.
- Keep your syringes and syringe disposal unit out of the reach of children; lock up these supplies if possible.
- Never re-use syringes or needles.
- Always use an aseptic technique as described in here.
- Throw away used syringes only in the proper disposal unit.

A2. Preparing for your injection

A2.1 Choosing an injection site

Before preparing your injection, decide which injection site you will use. BETAFERON should be injected 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, bones, and other important or sensitive structures.

The injection site should be rotated at every injection. If some areas seem to be too hard for you to reach, you may need a family member or a friend to help you with these injections. By following the sequence described in the schedule beneath, you will come back to your first injection site area after 8 injections (16 days). This will give each area a chance to recover fully before receiving another injection.

Please refer to the rotation schedule at the end of this Annex to learn how to choose an injection site. Also, an example of a medication record is included. This is meant to give you an idea how you can keep track of your injection sites and dates.

A2.2 Medication

You will find in the BETAFERON pack:

- 1 BETAFERON vial (with powder for solution for injection)
- 1 pre-filled syringe with solvent for BETAFERON (sodium chloride solution 5,4 mg/ml (0,54 %)).

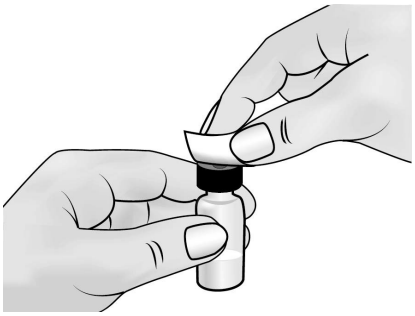
- (Be sure that the tip cap is firmly attached to the solvent syringe!)
- 1 vial adapter with a pre-attached needle
- 2 alcohol swabs for skin and vial cleaning

In addition you will need a disposal unit for used syringes and needles.
For skin disinfection use an appropriate disinfectant.

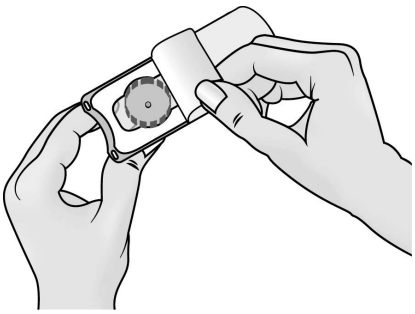
A3. The reconstitution process, step by step

1 - Wash your hands thoroughly with soap and water before beginning.

2 - Open the BETAFERON vial and put it on the table. It is better not to use your nail as it could break - use your thumb.



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

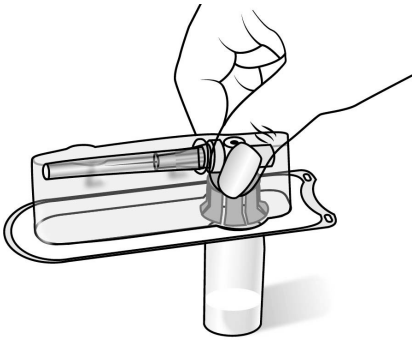


4 - Open the blister pack that holds the vial adapter, but leave the vial adapter still inside.

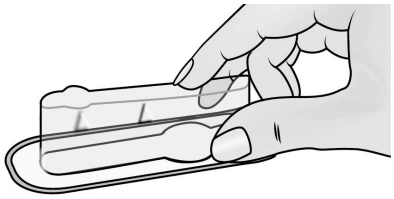
Do not remove the vial adapter from the blister pack.

Also, be sure you do not touch the vial adapter. It’s important to keep it sterile.

5 - Rest the vial on a flat surface while attaching the adapter.

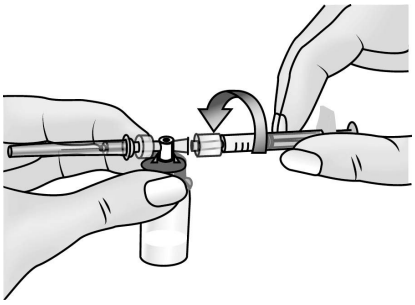


6 - Remove the alcohol wipe from the top of the BETAFERON vial. Place the blister pack containing the vial adapter transfer device on top of the vial. Push it down with your thumb and forefinger or the palm of your hand until you feel it snap into place.

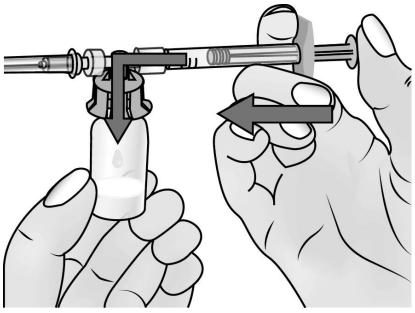


7 - Remove the blister pack from the vial adapter, holding the blister edges. Now you are ready to attach the pre-filled solvent syringe to the transfer device.

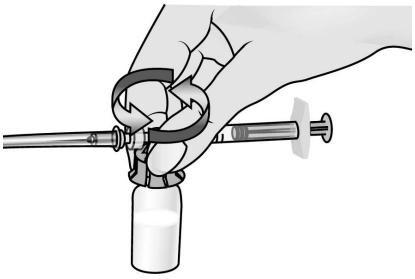
8 - Pick up the syringe. Remove the orange tip cap, using a ‘twist-and-pull’ motion. Discard the tip cap.



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

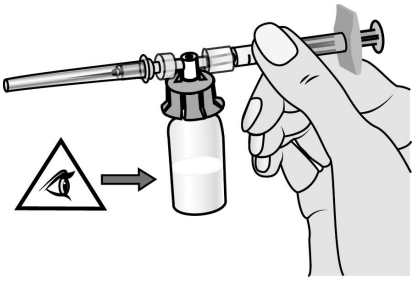


10 - Hold the syringe assembly on the bottom of the vial. Slowly push the plunger of the syringe in all the way to transfer all the solvent to the vial. Release the plunger. The plunger may return to its original position.



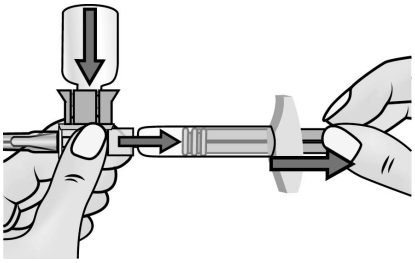
11 - With the syringe assembly still attached, swirl the vial gently to completely dissolve the dry BETAFERON powder.

Do not shake the vial.

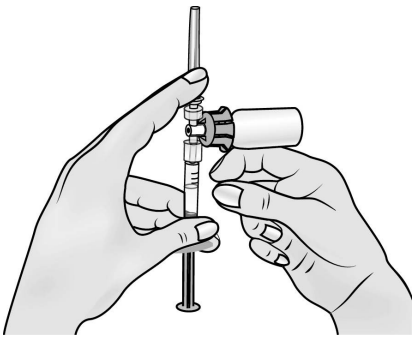


12 - Examine the solution carefully. It should be clear and contain no particles. If the solution is discoloured or contains particles, discard it and start again with a new single pack of supplies. If foam is present - which can happen if the vial is shaken or swirled too vigorously - let the vial sit undisturbed until the foam settles.

A4. PREPARING THE INJECTION



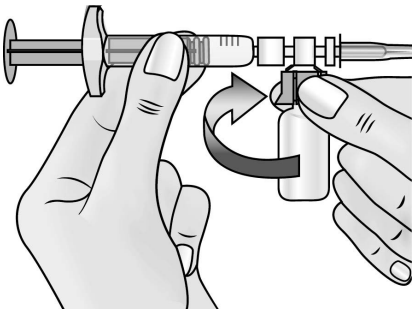
13 - In case the plunger moved back to the original position push it in again and hold it in place. To prepare your injection, turn the assembly over so that the vial is on top, cap side pointing down. Doing this allows the solution to flow down into the syringe.
Keep the syringe horizontal.
Slowly pull 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 causes any air bubbles to rise to the top of the solution.

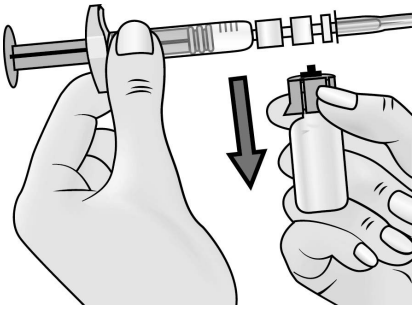
15 - Remove any air bubbles by gently tapping the syringe and pushing the plunger to the 1-ml mark, or to the volume prescribed by your doctor.
If too much of the solution is expelled into the vial along with the air bubbles, pull back the plunger a little to redraw the solution from the vial back into the syringe. Do this until all the air is gone and there is 1 ml of reconstituted solution in the syringe.

Important: Return the syringe assembly to a horizontal position with the vial on top when withdrawing solution again.



16 - Next, grasp the blue vial adapter with the attached vial and remove it from the syringe by **twisting** it toward you and then pulling it away from the syringe.

Grasp only the blue plastic adapter when removing. Hold the syringe in a horizontal position and the vial below the syringe.



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

18 - You are now ready to inject.
If, for some reason, you are not able to inject BETAFERON immediately, you may refrigerate the reconstituted solution in the syringe 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 pass, discard the medication and prepare a new injection. It is better to warm it up in your hands before injecting to avoid pain.

19 - Dispose of the vial and the remaining unused portion of the solution into the disposal unit.

A5. Quick review of the process

1. Take out the contents of the unit package
2. Attach vial adapter to the vial
3. Connect the syringe to the vial adapter
4. Push syringe plunger to transfer solvent

5. Turn the syringe assembly over, then withdraw plunger
6. Remove vial from syringe - you are now ready to inject

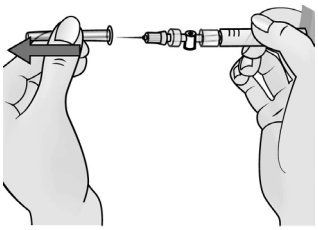
NOTE: The injection should be administered immediately after mixing (if the injection is delayed, refrigerate the solution and inject it within 3 hours). Do not freeze.

A6. Choosing and preparing the injection site and injecting the BETAFERON solution (1,0 ml) subcutaneously (under the skin)

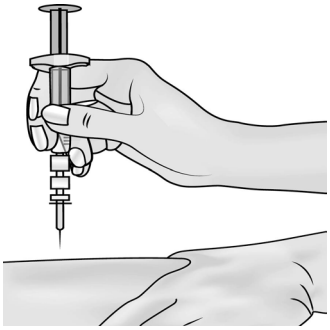
1 - Choose an area for the injection (see diagrams at the end of this Annex), and make a note of it in your medication record.

IMPORTANT: Do not use any area in which you feel lumps, bumps, firm knots, pain or that is discoloured, depressed, scabbed, or broken open. Talk to your physician or healthcare professional about these or any other unusual conditions you may find.

2 - Use an alcohol swab to clean the skin at the injection site. Let the skin air-dry. Discard the swab.
For skin disinfection use an appropriate disinfectant.



3 - Uncap the needle. Pull the cap, do not twist it.



4 - Gently pinch the skin together around the disinfected site (to lift it up a little).

5 - Stick the needle straight into the skin at a 90˚ angle with a quick, firm motion. Hold the syringe like a pencil or a dart.

6 - Inject the drug by using a slow, steady push. (Push the plunger all the way in until the syringe is empty.)

7- Discard the syringe in the disposal unit.

B) Rotating injection sites

It is necessary to choose a new site for each injection as changing sites each time gives the area time to recover and helps prevent infection. It is a good idea to know where the injection is to go before you prepare your syringe. The schedule shown in the diagram will help you to vary the sites adequately. For example, if you administer 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, and so on through the diagram until as many suitable areas of the body as possible 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 medication record card.

By following this schedule, you will come back to your first area (e.g. the right side of the abdomen) after 8 injections (16 days). This is called a Rotation Cycle. On our example schedule each area is split again into 6 injection sites (which counts up to 48 injection sites all together), left and right, upper, middle and lower part of the respective area. If you come back to one area after one Rotation Cycle choose the most distant injection site within this area. If an area becomes sore, talk to your doctor or nurse about choosing other injection sites.

Rotation Schedule:

To help you rotate the injection sites properly we recommend you to keep a record of the date and location of your injection. You can use the following rotation schedule.

Rotation Cycle 1:	Your first 8 injections should be given in sequence from area 1 through area 8, using only the upper left section of each area
Rotation Cycle 2:	Your next 8 injections should start again in area 1, but be given in the lower right section of each area
Rotation Cycle 3:	Your following 8 injections in the series should start in area 1 and rotate through the middle left section of each area

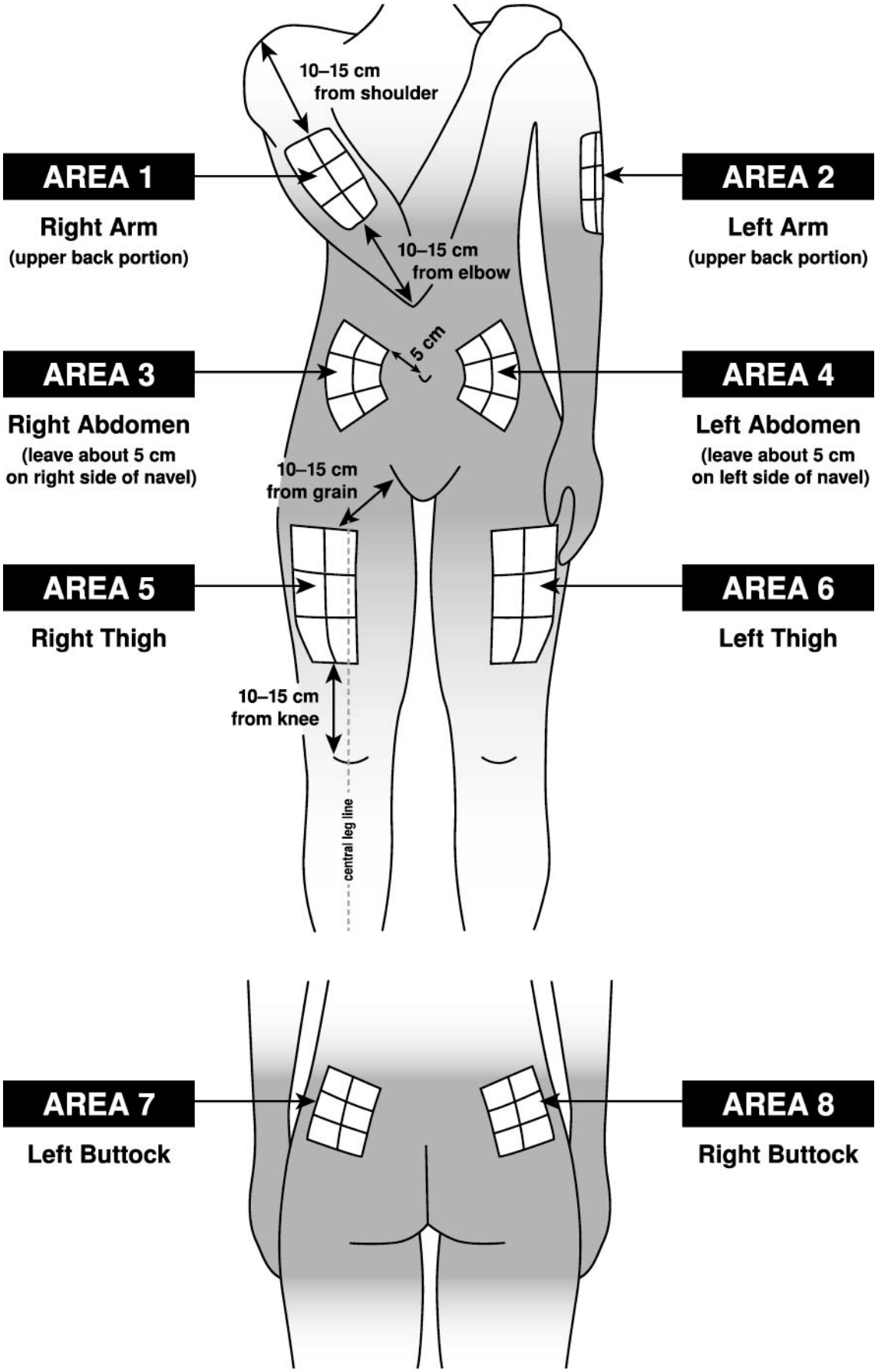
By following this sequence, you will give each area a chance to recover fully before receiving another injection.

C) BETAFERON Medication record

Instructions for keeping track of your injection sites and dates
Start with your first injection (or your last injection if you are not a new BETAFERON user).

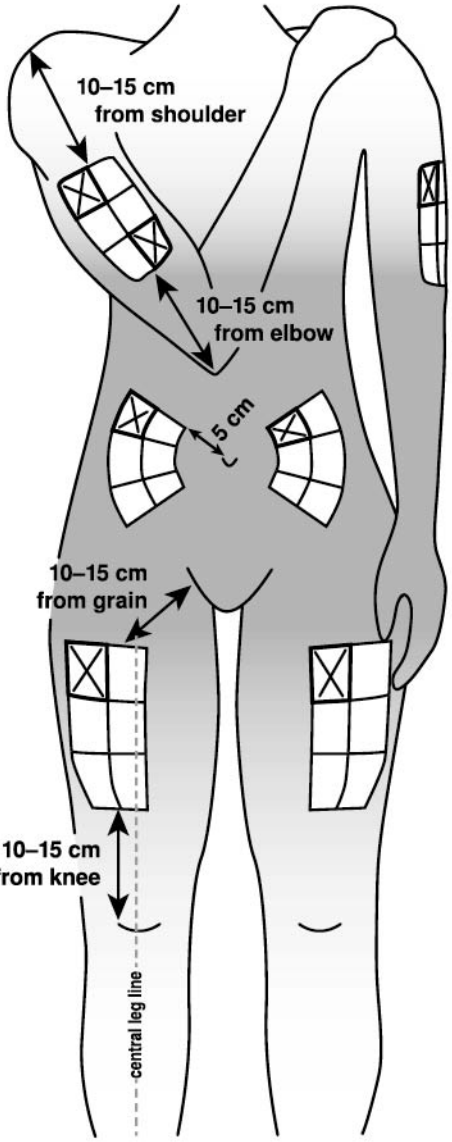
Select an injection site. If you have already been using BETAFERON start with the area that has not been used during the last rotation cycle, i.e. the past 16 days).
After your injection, fill in the used injection site and date in the table in your injection record (See the example: Keeping track of your injection sites and dates).

ROTATION SCHEDULE:



EXAMPLE OF A MEDICATION RECORD:

Keeping track of your injection sites and dates



Right Arm	
04/12	
	20/12

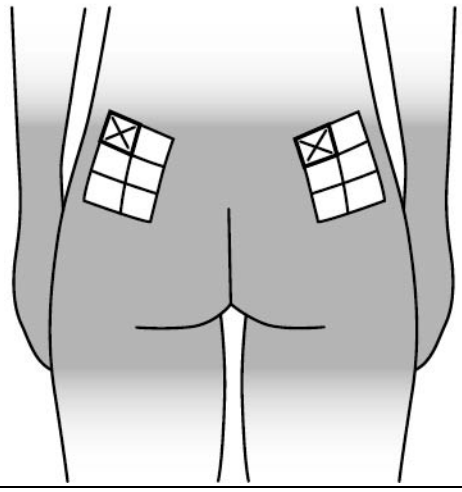
Left Arm	
06/12	

Right Abdomen	
08/12	

Left Abdomen	
10/12	

Right Thigh	
12/12	

Left Thigh	
14/12	



Left Thigh	
18/12	

Right Thigh	
16/12	

If you use more BETAFERON than you should:

Administration of many times the dose (5,5 mg (176 million IU) into a vein three times a week) of BETAFERON recommended for the treatment of multiple sclerosis did not lead to life-threatening situations.
However, in the case of accidental overdosage, please consult the doctor who has prescribed BETAFERON for you. Also, if by mistake you administer your injection too frequently (e.g. one injection every day instead of one injection every other day) you should consult your doctor or pharmacist. **If neither is available, seek help at the nearest hospital or poison control centre.**

If you forget to use BETAFERON:

If you forget to administer your injection at the correct time you must administer it as soon as you remember. Your next injection should be given 48 hours later.
Do not inject a double dose to make up for forgotten individual doses.

If you stop using BETAFERON:

Acute withdrawal symptoms are not expected if you have forgotten to inject BETAFERON or if you have stopped using it. If you stop or wish to stop treatment, you should discuss this with your doctor first.

4. POSSIBLE SIDE EFFECTS:

BETAFERON can cause side effects.
Not all side effects reported for BETAFERON are included in this leaflet. Should your general health worsen or if you experience any untoward effects while taking this medicine, please consult your doctor, pharmacist or other healthcare professional for advice.
If you are not sure what the side effects below are, ask your doctor to explain them to you.

Allergic reactions (hypersensitivity):

- If you experience symptoms such as itching all over your body, swelling of your face and/or your tongue or sudden shortness of breath, stop treatment with BETAFERON and contact your doctor immediately. These may be symptoms of a serious allergic reaction (hypersensitivity), which may become life-threatening.

Flu-like symptoms (fever, chills, painful joints, a general feeling of being unwell, sweating, headache, or muscular pain) have been seen frequently. The occurrence of the symptoms decreased over time. Generally, a step-by-step increase of the dose is recommended at the start of treatment in order to increase tolerability of BETAFERON. Flu-like symptoms may also be reduced by the administration of anti-inflammatory medicines. Please consult your doctor for further information.
Injection site reactions including redness, swelling, discolouration, inflammation, infection, pain, hypersensitivity, skin breakdown and tissue destruction (necrosis), and non-specific reactions occurred frequently. (see section 2 “What you need to know before you use BETAFERON” / “Take special care with BETAFERON”). The occurrence of injection site reactions decreases over time and may be reduced by the use of an autoinjector and by rotating injection sites.
The following adverse events listing is based on reports from clinical trials with BETAFERON and from side effects reports on the marketed product.
In general, frequencies of side effects obtained from clinical trials are higher than those from the marketed product. This can be explained by the fact that patients included into clinical trials are directly asked for such side effects, whereas the data of the marketed product mostly consist of spontaneous reports.

Frequency is not known means that the frequency cannot be estimated from the available data.

Frequent side effects:

- decrease of white cells in the blood:
  white blood cell count decreased (< 3000/mm^3)
  lymphocytes count decreased (< 1500/mm^3)
  absolute neutrophil count decreased (< 1500/mm^3)
- headache
- sleeplessness
- lack of coordination of muscular movements (incoordination)
- abdominal pain
- disturbance of the activity of the liver shown by increases in the blood levels of enzymes produced: alanine aminotransferase increased (ALT > 5 times baseline)
- rash
- skin disorders
- painful muscles (myalgia)
- muscle stiffness (hypertonia)
- urinary urgency
- injection site reactions
  (comprises all adverse events occurring at the injection site (except skin breakdown/tissue destruction [injection site necrosis]), e.g ~~i.e.~~ injection site <u>infection</u> ~~reaction~~, bleeding at injection site [injection site haemorrhage], injection site hypersensitivity, injection site inflammation, injection site mass, injection site pain, fluid build-up at the injection site (injection site oedema) and injection site atrophy)
- flu-like symptoms - (flu syndromes and/or a combination of at least two of the following side effects: fever, chills, painful muscles [myalgia], malaise, sweating)
- pain
- fever
- chills
- accumulation of fluid in arm, leg or face (peripheral oedema)
- lack/loss of strength (asthenia)
- swollen lymph glands (lymphadenopathy)
- hypertension
- shortness of breath (dyspnoea)
- disturbance of the activity of the liver shown by increases in the blood levels of enzymes produced: aspartate aminotransferase increased (AST > 5 times baseline)
- impotence
- irregular uterine bleeding (metrorrhagia)(in pre-menopausal women)
- skin breakdown/tissue destruction (injection site necrosis)
- chest pain
- malaise

Side effects for which frequency is not known:

- serious hypersensitivity (anaphylactic) reactions (contact a doctor immediately, for symptoms and necessary action see “Take special care with BETAFERON”)
- reduced amount of oxygen-carrying pigment (haemoglobin) in the blood (anaemia)
- reduced number of platelets (which help the blood to clot) (thrombocytopenia)
- reduced number of white cells in the blood (leukopenia)
- capillary leak syndrome (leaking of plasma fluid and proteins into the space around vessels, resulting in sometimes fatal low blood pressure and reduced organ perfusion) in pre-existing monoclonal gammopathy (a disturbance of the immune system where abnormal proteins are found in the blood)
- disturbance of the activity of the thyroid gland (too much [hyperthyroidism] or too little [hypothyroidism] hormone is produced)
- breakdown of red blood cells (hemolytic anaemia)
- increase of certain blood fats (triglycerides)
- severe loss of appetite leading to weight loss (anorexia)
- weight gain or loss
- depression (see “Take special care with BETAFERON”)

- suicide attempts (see "Take special care with BETAFERON")
- confusion
- anxiety
- emotional lability
- convulsion
- dizziness
- disease of the heart muscle (cardiomyopathy, see "Take special care with BETAFERON")
- increased heart rate (tachycardia)
- palpitations
- widening of blood vessels (vasodilation)
- bronchospasm
- nausea
- vomiting
- inflammation of the pancreas (pancreatitis)
- diarrhoea
- increase of a specific liver enzyme (gamma GT) and a reddish yellow pigment (bilirubin), which is produced by your liver, in the blood
- hepatic injury (including hepatitis)
- hepatic failure
- raised oedematous and usually itching patches of skin or mucous membranes (urticaria)
- hair loss (alopecia)
- generalised itching (pruritus)
- skin discolouration
- joint pain (arthralgia)
- menstrual disorder
- abnormal heavy uterine bleeding (menorrhagia)
- sweating

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

Disorders of the immune system/immunogenicity:

During the treatment with BETAFERON your body may produce so-called neutralising antibodies against the active ingredient of BETAFERON (see "Before you use BETAFERON"/"Take special care with BETAFERON"/"Immune system disorders").
At present, no consistent effects of such antibodies on treatment efficacy have been noted. Adverse events have not been associated with the development of neutralising activity.
It is suggested that the decision to continue treatment with BETAFERON in patients who develop antibodies should be based on all aspects of the patient's disease status and not on the antibody status alone.

5. HOW TO STORE BETAFERON:

Store at or below 30 °C.
Do not use after the expiry date stated on the pack.
After reconstitution immediate use is recommended. However, the in-use stability has been demonstrated for 3 hours at 2 to 8 °C.
Do not use BETAFERON if you notice it contains particulate matter or is discoloured after reconstitution.
Return all unused medicine to your pharmacist.
Do not dispose of unused medicine in drains or sewerage systems (e.g. toilets).
KEEP OUT OF THE REACH AND SIGHT OF CHILDREN.

6. Contents of the pack and other information

What BETAFERON contains:

The active substance is a synthetic interferon beta-1b produced by recombinant techniques. Each 1 ml of reconstituted solution contains 8 million IU (250 micrograms) of interferon beta-1b.
The other ingredients are human albumin and mannitol.
Contains sugar: mannitol

DILUENT FOR BETAFERON vials or pre-filled syringes:

The vials and pre-filled syringes contain sterile sodium chloride solution 5,4 mg/ml (0,54% w/v sodium chloride and water for injection).
Each pre-filled syringe contains 1,2 ml sterile sodium chloride solution (equivalent to 6,48 mg of sodium chloride per 1,2 ml).
Each vial contains 2,0 ml sterile sodium chloride solution (equivalent to 10,80 mg of sodium chloride per 2,0 ml).
DILUENT FOR BETAFERON is used to dissolve (reconstitute) the BETAFERON, to produce a solution for injection.

What BETAFERON looks like and contents of the pack

BETAFERON is available in the following pack sizes:

- Packs with 5 or 15 single packs. Each single pack contains 1 BETAFERON vial (containing interferon beta-1b), with rubber stopper and aluminium overseal. 1 pre-filled syringe with solvent (clear and colourless sodium chloride solution), 1 vial adapter with needle and 2 alcohol wipes.

Identification of BETAFERON:

BETAFERON:
3 ml clear glass vial containing a white lyophilised cake (powder).
DILUENT FOR BETAFERON:
Pre-filled syringes (1,2 ml or 2,25 ml syringe) containing 1,2 ml of a clear colourless solution.

Holder of Certificate of Registration:

Bayer (Pty) Ltd
Reg. No.: 1968/011192/07
27 Wrench Road
ISANDO,1609

This leaflet was last revised in:

19 December 2023

REGISTRATION NUMBERS:

BETAFERON: 30/34/0185
DILUENT FOR BETAFERON: 30/34/0186