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Due to regulatory changes, the content of the following Patient Information Leaflet may vary from the one found in your medicine pack. Please compare the 'Leaflet prepared/revised date' towards the end of the leaflet to establish if there have been any changes.

If you have any doubts or queries about your medication, please contact your doctor or pharmacist.

Package leaflet: Information for the user

Betaferon 250 microgram/ml, powder and solvent for solution for injection interferon beta-1b

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Betaferon is and what it is used for
2. What you need to know before you use Betaferon
3. How to use Betaferon
4. Possible side effects
5. How to store Betaferon
6. Contents of the pack and other information
Annex – self injection procedure

1. What Betaferon is and what it is used for

What Betaferon is

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

How Betaferon works

Multiple sclerosis (MS) is a long-term condition that affects the central nervous system (CNS), particularly the functioning of the brain and spinal cord. In MS, inflammation destroys the protective sheath (called *myelin*) around the nerves of the CNS and stops the nerves from working properly. This is called demyelination.

The exact cause of MS is unknown. An abnormal response by the body's immune system is thought to play an important part in the process which damages the CNS.

The damage to the CNS can occur within an MS attack (*relapse*). It can cause disability temporarily, such as difficulty walking. Symptoms may disappear completely or partly.

Interferon beta-1b has been shown to change the response of the immune system and to help to reduce disease activity.

How Betaferon helps fight your disease

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

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

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

What Betaferon is used for

Betaferon is for use in patients

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

2. What you need to know before you use Betaferon

Do not use Betaferon

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

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

Warnings and precautions

Talk to your doctor before you start using Betaferon:

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

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

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

Other things to consider when using Betaferon

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

Injection site reactions

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

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

To reduce the risk of getting injection site reactions you must:

- use a sterile (*aseptic*) injection technique,
- rotate the injection sites with each injection (see Annex ‘Self-injection procedure’, Part II, in the second part of this leaflet).

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

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

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

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

Children and adolescents

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

Other medicines and Betaferon

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

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

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

Betaferon should be used with caution with:

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

Betaferon with food and drink

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

Pregnancy and breast-feeding

If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

No harmful effects on the breastfed newborn/infant are anticipated. Betaferon can be used during breast-feeding.

Driving and using machines

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

Betaferon contains mannitol, human albumin and sodium

The inactive ingredients of Betaferon include:

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

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

3. How to use Betaferon

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

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

The recommended dose is:

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

When starting treatment with Betaferon, it is tolerated best by gradually increasing the dose, i.e. starting with just 0.25 ml of the medication and then increasing, after every 3rd injection, first to 0.5 ml, then to 0.75 ml and then finally to the full dose (1 ml) of Betaferon.

Your doctor may decide, together with you, to change the time interval between increases in the dose depending on side effects you may experience at the start of treatment. To easily increase the dosage during the first 12 injections, you may be given a special **titration pack**, containing four differently coloured packs with specially marked syringes and with detailed instructions on the separate introductory leaflet for titration pack.

Preparing the injection

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

Detailed instructions for self-injection of Betaferon under the skin are provided in Part IE of the Annex 'Self-injection procedure'.

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

Duration of treatment

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

If you use more Betaferon than you should

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

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

If you forget to use Betaferon

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

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

If you stop using Betaferon

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

- ▶ If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

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

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

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

▶ **Tell your doctor immediately:**

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

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

The most frequently observed side effects are:

- ▶ **Flu-like symptoms** such as fever, chills, painful joints, malaise, sweating, headache, or muscular pain. These symptoms may be reduced by taking paracetamol or non-steroidal anti-inflammatory medicines such as ibuprofen.
- ▶ **Injection site reactions.** Symptoms can be redness, swelling, discolouration, inflammation, pain, hypersensitivity, tissue damage (*necrosis*). See ‘Warnings and precautions’ in section 2 for more information and what to do, if you experience an injection site reaction. These may be reduced by the use of an auto-injector device. Talk to your doctor, pharmacist or nurse for further information.

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

The following side effects listing is based on reports from clinical trials with Betaferon (list 1) and from side effects reported on the marketed product (list 2).

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

- **infection**, abscess
- reduced number of white **blood cells**, swollen **lymph glands** (*lymphadenopathy*)
- decrease of **sugar in the blood** (*hypoglycaemia*)
- **depression, anxiety**
- **headache, dizziness**, sleeplessness, migraine, **numbness or tingling** feeling (*paraesthesia*)
- **eye inflammation** (*conjunctivitis*), **abnormal vision**
- **ear pain**
- irregular, rapid beating or pulsation of the **heart** (*palpitation*)
- redness and/or facial flushing due to widening of **blood vessels** (*vasodilation*), increased **blood pressure** (*hypertension*)
- **runny nose**, cough, hoarseness due to infection of the upper **respiratory tract**, sinusitis, cough increased, **shortness of breath** (*dyspnoea*)
- diarrhoea, constipation, nausea, vomiting, abdominal pain
- rises in the blood levels of **liver** enzymes (will show up in blood tests)
- **skin** disorder, rash
- **muscle** stiffness (*hypertonia*), painful muscles (*myalgia*), muscular weakness (*myasthenia*), **back** pain, pain in **extremities** such as fingers and toes
- difficulty urinating (*urine retention*), protein in the **urine** (will show up in urine tests), urinary frequency, inability to hold back urination (*urinary incontinence*), urinary urgency
- painful periods (*dysmenorrhoea*), **menstrual disorder**, heavy uterine bleeding (*metrorrhagia*) especially between menstrual periods, **impotence**
- **injection site** reaction (including redness, swelling, discolouration, inflammation, pain, allergic reactions (*hypersensitivity*), skin breakdown and tissue damage (*necrosis*) at injection site (see section 2 ‘Warnings and precautions’)
- **flu-like symptoms**, fever, pain, chest pain, **accumulation of fluid** in arm, leg or face (*peripheral oedema*), **lack/loss of strength** (*asthenia*), chills, sweating, malaise

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

List 2: Side effects reported on the marketed product (from spontaneous reporting, frequencies – where known - based on clinical trials)

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

- painful joints (*arthralgia*)

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

- the number of red cells in the blood may fall (*anaemia*)
- the thyroid gland does not work properly (too little hormone is produced) (*hypothyroidism*)
- weight increase or decrease
- confusion
- abnormally rapid heartbeat (*tachycardia*)
- a reddish yellow pigment (*bilirubin*), which is produced by your liver, may rise (this will show up in blood tests)
- swollen and usually itchy patches of skin or mucous membranes (*urticaria*)
- itching (*pruritus*)
- loss of scalp hair (*alopecia*)
- menstrual disorders (*menorrhagia*)

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

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

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

- serious allergic (*anaphylactic*) reactions
- the thyroid gland does not work properly (*thyroid disorders*), too much hormone is produced (*hyperthyroidism*)
- inflammation of the pancreas (*pancreatitis*), see section 2 'Warnings and precautions'
- blood clots in the small blood vessels that can affect your kidneys (thrombotic thrombocytopenic purpura or haemolytic uremic syndrome). Symptoms may include increased bruising, bleeding, fever, extreme weakness, headache, dizziness or light-headedness. Your doctor may find changes in your blood and the function of your kidneys.

Side effects derived only during post-marketing:

- breakdown of red blood cells (*haemolytic anaemia*), frequency unknown
- kidney problems including scarring (*glomerulosclerosis*) that may reduce your kidney function, uncommon
- severe loss of appetite leading to weight loss (*anorexia*), rare
- disease of the heart muscle (*cardiomyopathy*), rare
- sudden shortness of breath (*bronchospasm*), rare
- the liver does not work properly (*hepatic injury* (including *hepatitis*, *hepatic failure*), 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.

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly (see details below). By reporting side effects, you can help provide more information on the safety of this medicine.

United Kingdom

Yellow Card Scheme

Website: www.mhra.gov.uk/yellowcard

or search for MHRA Yellow Card in the Google Play or Apple App Store

Ireland

HPRA Pharmacovigilance

Earlsfort Terrace

IRL - Dublin 2

Tel: +353 1 6764971

Fax: +353 1 6762517

Website: www.hpra.ie

e-mail: medsafety@hpra.ie

Malta

ADR Reporting

Website: www.medicinesauthority.gov.mt/adrportal

5. How to store Betaferon

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the pack. The expiry date refers to the last day of that month.

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

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

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

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

6. Contents of the pack and other information

What Betaferon contains

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

The other ingredients are

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

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

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

What Betaferon looks like and contents of the pack

Betaferon is a sterile white to off-white powder for solution for injection.

Betaferon is available in pack sizes of:

- multipacks comprising 5 single packs, each containing 1 vial with powder, 1 pre-filled syringe with solvent, 1 vial adapter with needle, 2 alcohol wipes or
- multipacks comprising 12 single packs, each containing 1 vial with powder, 1 pre-filled syringe with solvent, 1 vial adapter with needle, 2 alcohol wipes or
- multipacks comprising 14 single packs, each containing 1 vial with powder, 1 pre-filled syringe with solvent, 1 vial adapter with needle, 2 alcohol wipes or
- multipacks comprising 15 single packs, each containing 1 vial with powder, 1 pre-filled syringe with solvent, 1 vial adapter with needle, 2 alcohol wipes or
- 2-month packs comprising 2x14 single packs, each containing 1 vial with powder, 1 pre-filled syringe with solvent, 1 vial adapter with needle, 2 alcohol wipes or
- 3-month packs comprising 3x15 single packs, each containing 1 vial with powder, 1 pre-filled syringe with solvent, 1 vial adapter with needle, 2 alcohol wipes or
- 3-month packs comprising 3x14 single packs, each containing 1 vial with powder, 1 pre-filled syringe with solvent, 1 vial adapter with needle, 2 alcohol wipes or
- titration pack for the first 12 injections comprising 4 triple packs, each containing 3 vials with powder, 3 pre-filled syringes with solvent, 3 vial adapters with needle, 6 alcohol wipes

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder

Bayer AG
51368 Leverkusen
Germany

Manufacturer

Bayer AG
Müllerstraße 178
13353 Berlin
Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

Ireland

Bayer Limited
Tel: +353 1 216 3300

Malta

Alfred Gera and Sons Ltd.
Tel: +356-21 44 62 05

United Kingdom

Bayer plc
Tel: +44 (0)118 206 3000

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Other sources of information

Detailed information on this medicine is available on the European Medicines Agency website:

<http://www.ema.europa.eu>.

Annex: SELF-INJECTION PROCEDURE

Your doctor has prescribed Betaferon to treat your MS. You will best tolerate Betaferon in the beginning if you start with a low dose and gradually increase to the full standard dose (see first part of this leaflet, section 3. 'How to use Betaferon'). To easily increase the dosage during the first 12 injections, you may be given a special titration pack, containing four differently coloured triple packs with special marked syringes and with detailed instructions on the separate introductory leaflet for titration pack. The syringes in this titration pack are marked accordingly with the appropriate doses (0.25; 0.5; 0.75 or 1.0 ml).

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

PART I: STEP BY STEP INSTRUCTIONS

The instructions include the following main steps:

- A) General advice**
- B) Getting ready to inject**
- C) Reconstituting the solution, step by step**
- D) Drawing up the injection**
- E) Making the injection**
- F) Quick review of the process**

A) General advice

► 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 helpful:

- Set up a permanent storage area in a convenient location out of the sight and reach of children so your Betaferon and other supplies are always easy to find.
For details on storage conditions, see section 5. 'How to store Betaferon' in the first part of this leaflet.
- Try to give your injection at the same time of day. 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 mixing Betaferon, you should give the injection immediately (if Betaferon is not used immediately, see section 5. 'How to store Betaferon' in the first part of this leaflet).

► Important tips to keep in mind

- Be consistent - use Betaferon as described in section 3. 'How to use Betaferon' in the first part of this leaflet. Always double-check your dosage.
- Keep your syringes and syringe disposal unit out of the sight and reach of children; lock the supplies away if possible.
- Never re-use syringes or needles.
- Always use a sterile (*aseptic*) technique as described in here.
- Always place the used syringes in the proper disposal unit.

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.

Important: Do not use any area where you can feel lumps, bumps, firm knots, pain or an area that is discoloured, indented, scabbed, or where the skin is broken. Talk to your doctor or nurse about these or any other unusual conditions you may find.

You should rotate the injection site at every injection. If some areas are too difficult for you to reach, you may need a family member or friend to help you with these injections. Follow the sequence described in the schedule at the end of the Annex (see Part II, 'Rotating injection sites') and 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 rotation schedule at the end of this Annex to learn how to choose an injection site. An example of a medication record is also included (see Annex Part III). This should give you an idea of how you can keep track of your injection sites and dates.

► Checking the content of the pack

In the Betaferon pack you will find:

- 1 Betaferon vial (with powder for solution for injection),
- 1 pre-filled syringe of solvent for Betaferon (sodium chloride solution 5.4 mg/ml (0.54% w/v)),
- 1 vial adapter with a pre-attached needle,
- 2 alcohol swabs to clean the skin and vial.

In addition you will need a disposal unit for used syringes and needles.

For skin disinfection use an appropriate disinfectant.

If you have a Betaferon titration pack you will find 4 differently coloured and numbered triple packs, each containing:

- 3 Betaferon vials (with powder for solution for injection)
- 3 pre-filled syringes with solvent for the Betaferon powder (sodium chloride solution 5.4 mg/ml (0.54% w/v))
- 3 vial adapters with a pre-attached needle
- 6 alcohol wipes 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.

Start with the **yellow triple pack 1** containing 3 syringes with a 0.25-ml marking, for treatment days 1, 3 and 5.

Use then the **red triple pack 2** containing 3 syringes with a 0.5-ml marking, for treatment days 7, 9 and 11.

Continue with the **green triple pack 3** containing 3 syringes with a 0.75-ml marking, for treatment days 13, 15 and 17.

Use the **blue triple pack 4** containing 3 syringes with a 0.25; 0.5; 0.75 and 1.0-ml marking, for treatment days 19, 21 and 23.

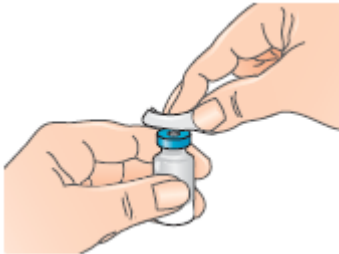
C) Reconstituting the solution, step by step



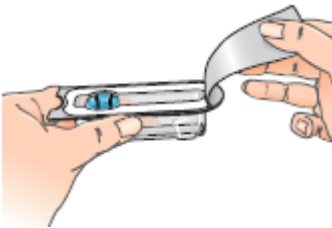
1 - Wash your hands thoroughly with soap and water before beginning this process.



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.



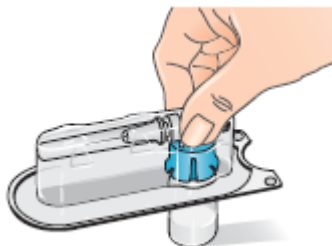
3 - Clean the top of the vial with an alcohol wipe, moving the wipe in one direction only. Leave the wipe on top of the vial.



4 - Open the blister pack containing the vial adapter, but leave the vial adapter inside.

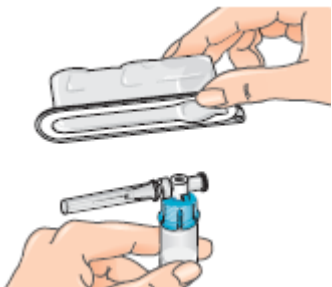
Do not remove the vial adapter from the blister pack at this stage.

Do not touch the vial adapter. This is to keep it sterile.

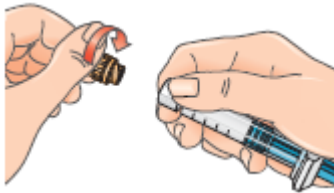


5 - Before attaching the adapter remove and discard the alcohol wipe and rest the vial on a flat surface.

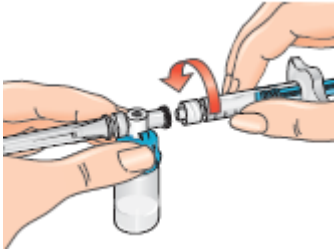
6 - Hold the blister pack on the outside and place it on top of the vial. Push it down firmly until you feel it snap into place on the vial.



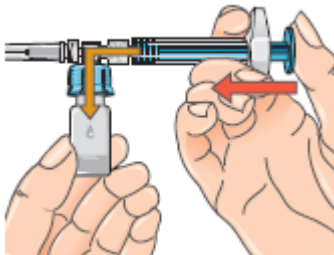
7 - Remove the blister pack from the vial adapter, holding the blister edges. Now you are ready to attach the pre-filled solvent syringe to the vial adapter.



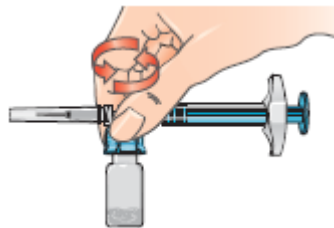
8 - Pick up the syringe. Be sure that the orange tip cap is firmly attached to the solvent syringe!
Remove the tip cap by twisting it off. Throw away the tip cap.



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). This will form the syringe assembly.

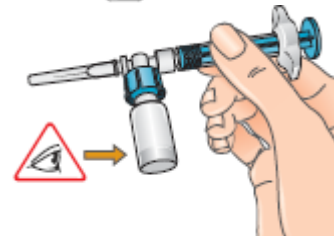


10 - Hold the syringe assembly at the bottom of the vial. Slowly push the plunger of the syringe in all the way to transfer all of the solvent into the vial. Release the plunger, which may go back to its original position.
This applies also to the titration pack.



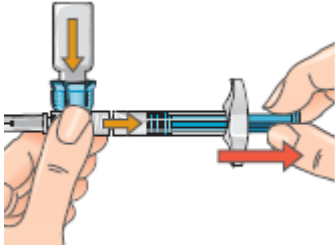
11 - With the syringe assembly still attached, swirl the vial around gently to completely dissolve the dry Betaferon powder.

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 much — let the vial sit undisturbed until the foam settles.

D) Drawing up the injection



13 - If the plunger has moved back to its 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.

With the titration pack, withdraw solution **only up to the mark on the syringe:**

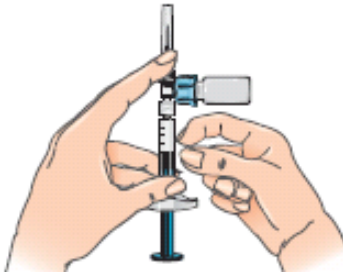
0.25 ml for first three injections (at day 1, 3, 5 of therapy), **or**

0.5 ml for the injections at day 7, 9, 11 of therapy, **or**

0.75 ml for the injections at day 13, 15, 17 of therapy.

Discard the vial with any remaining solution.

From day 19 you are injecting the **full dose 1.0 ml.**

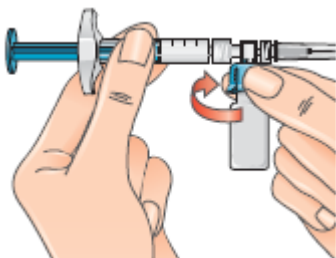


14 - After drawing up the solution turn the syringe assembly so that the needle is pointing up. This allows any air bubbles to rise to the top of the solution.

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.

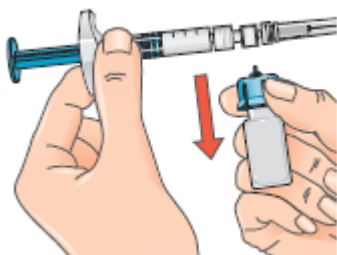
If you are injecting less than 1 ml with the titration pack there might not be any air bubbles, however for full dose injection some air bubbles might turn up. Remove them by gently tapping the syringe and pushing the plunger to the respective marking on the syringe.

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



16 - Next, hold the blue vial adapter with the attached vial and remove it from the syringe by twisting it and then pulling it down, away from the syringe.

Only hold the blue 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.

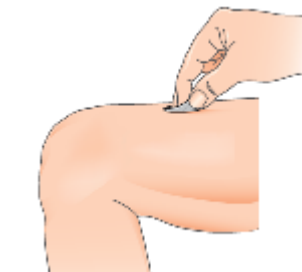
17 - Dispose of the vial and any unused portion of the solution in the disposal unit

18 - You are now ready to inject.

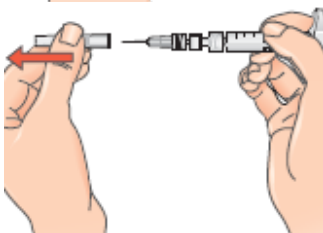
If, for some reason, you are not able to inject the Betaferon immediately, you can keep the reconstituted solution in the syringe in a refrigerator for up to 3 hours before using. Do not freeze the solution, and do not wait longer than 3 hours to inject it. If more than 3 hours pass, discard the reconstituted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

E) Making the injection

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



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



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



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

5 - Holding the syringe like a pencil or a dart, push the needle straight into the skin at a 90° angle with a quick, firm motion. Please note: Betaferon can also be administered with an auto-injector.

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

7 - Discard the syringe in the disposal unit.

F) Quick review of the process

- Take out the required content for one injection
- 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 draw up the prescribed amount of the solution
- 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.

PART II: ROTATING INJECTION SITES

You need to choose a new site for each injection to allow the area time to recover and help prevent infection. Advice on which areas to choose is given in the first part of this Annex. It is a good idea to know where you plan to inject before you prepare your syringe. The schedule shown in the diagram below will help you to vary the sites appropriately. For example, 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, and so on through the diagram until all 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 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 adds up to 48 injection sites all together), left and right: 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, talk to your doctor or nurse about choosing other injection sites.

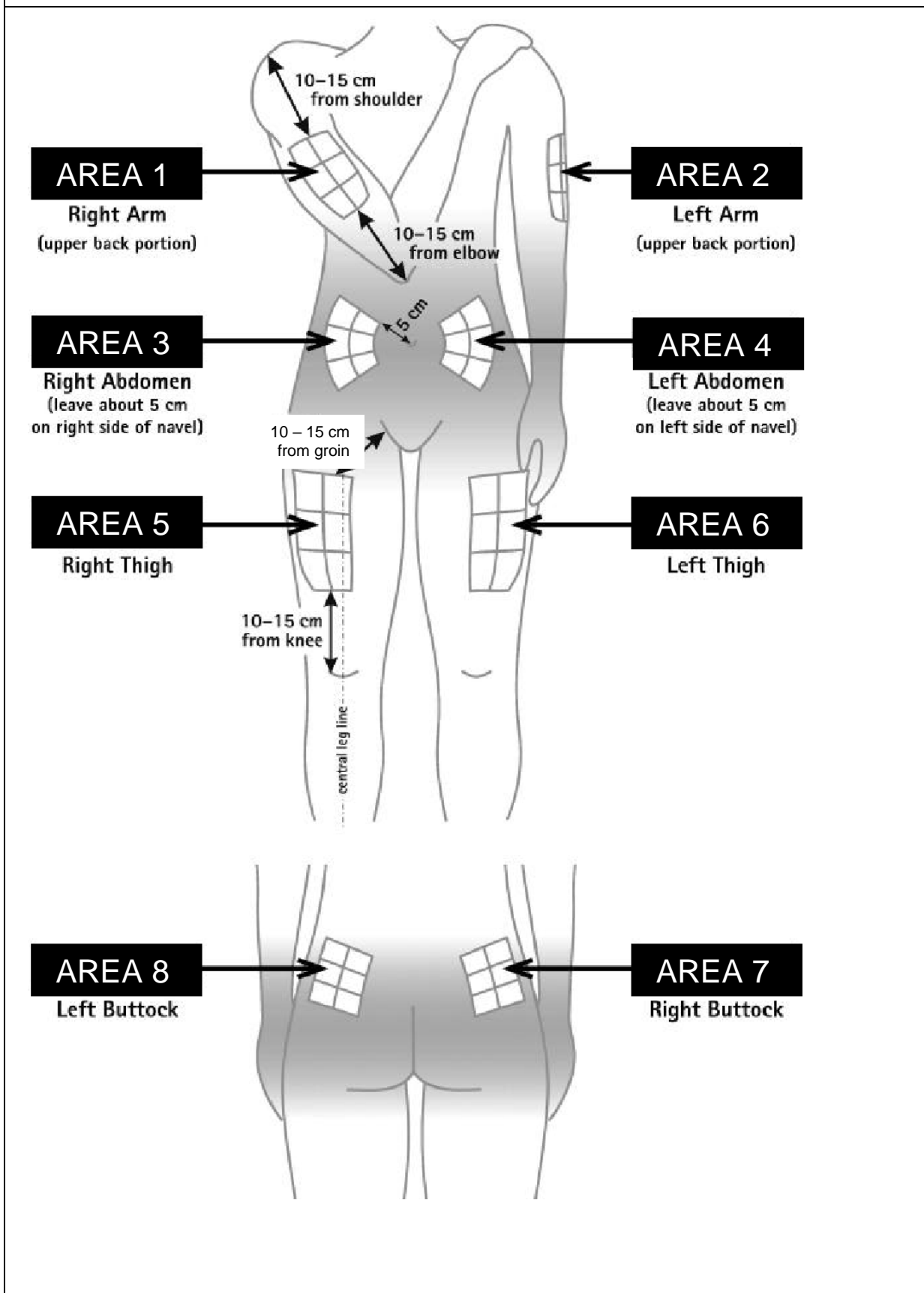
Rotation Schedule:

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

Work through each rotation cycle in turn. Each cycle will be 8 injections (16 days), given in 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.

- Rotation Cycle 1:** Upper left section of each area
- Rotation Cycle 2:** Lower right section of each area
- Rotation Cycle 3:** Middle left section of each area
- Rotation Cycle 4:** Upper right section of each area
- Rotation Cycle 5:** Lower left section of each area
- Rotation Cycle 6:** Middle right section of each area

ROTATION SCHEDULE:



PART III: BETA FERON 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 used injection site and date on the table in your injection record (see the example: 'Keeping track of your injection sites and dates').

EXAMPLE OF A MEDICATION RECORD:

Keeping track of your injection sites and dates

The diagram illustrates various injection sites on a human body with the following measurement guidelines:

- Right Arm:** 10–15 cm from shoulder
- Left Arm:** 10–15 cm from elbow
- Right Abdomen:** 5 cm from the midline
- Left Abdomen:** 5 cm from the midline
- Right Thigh:** 10–15 cm from groin
- Left Thigh:** 10–15 cm from groin
- Right Leg:** 10–15 cm from knee
- Left Leg:** 10–15 cm from knee
- Right Buttock:** 16/12
- Left Buttock:** 18/12

The central leg line is indicated by a dashed line. Each injection site is marked with a grid and an 'X' to denote the specific location and date of the injection.

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	

Right Buttock

16/12	

Left Buttock

18/12	

Separate Annex: INTRODUCTORY LEAFLET FOR TITRATION PACK

Your doctor has prescribed Betaferon to treat your MS. You will best tolerate Betaferon in the beginning if you start with a low dose and gradually increase to the full standard dose (see first part of the package leaflet, section 3. 'How to use Betaferon'). The syringes in this titration pack are marked accordingly with the appropriate doses (0.25; 0.5; 0.75 or 1.0 ml).

► Checking the content of the pack

You will find in the Betaferon titration pack 4 differently coloured and numbered triple packs, each containing:

- 3 Betaferon vials (with powder for solution for injection)
- 3 pre-filled syringes with solvent for the Betaferon powder (sodium chloride solution 5.4 mg/ml (0.54% w/v))
- 3 vial adapters with a pre-attached needle
- 6 alcohol wipes for skin and vial cleaning

Each triple pack contains the syringes you will require for preparing each dose. The syringes have special markings for this dose. Please follow in detail the instructions for use below. For each titration step use the complete amount of solvent for reconstitution of the Betaferon powder, then draw up the required dose into the syringe.

Start by using the **yellow triple pack** which is clearly marked with a "1" on the top right hand side of the box.

This first triple pack should be used for treatment days 1, 3 and 5.

It contains specially marked syringes with **0.25 ml** marking. This will help you to inject the required dose only.

After finishing with the yellow pack, start using the **red triple pack** which is clearly marked with a "2" on the top right hand side of the box.

This second triple pack should be used for treatment days 7, 9 and 11.

It contains specially marked syringes with **0.50 ml** marking. This will help you to inject the required dose only.

After finishing with the red pack, start using the **green triple pack** which is clearly marked with a "3" on the top right hand side of the box

This third triple pack should be used for treatment days 13, 15 and 17.

It contains specially marked syringes with **0.75 ml** marking. This will help you to inject the required dose only.

Finally, after finishing with the green pack, start using the **blue triple pack** which is clearly marked with a "4" on the top right hand side of the box. This last triple pack should be used for treatment days 19, 21 and 23.

It contains syringes with **0.25, 0.5, 0.75 and 1.0 ml** markings. With triple pack "4" you can inject the full dose 1.0 ml.

For a description of how to prepare and use the Betaferon powder, please refer to section 3. 'How to use Betaferon' in the first part of the package leaflet and to the Annex 'Self-injection procedure' in the second part of the package leaflet.

In addition you will need a disposal unit for used syringes and needles.