

ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

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

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Recombinant interferon beta-1b* 250 microgram (8.0 million IU) per ml when reconstituted.

Betaferon contains 300 microgram (9.6 million IU) of recombinant interferon beta-1b per vial.

For the full list of excipients, see section 6.1.

* produced by genetic engineering from a strain of *Escherichia coli*.

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection.

Sterile white to off-white powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Betaferon is indicated for the treatment of

- patients with a single demyelinating event with an active inflammatory process, if it is severe enough to warrant treatment with intravenous corticosteroids, if alternative diagnoses have been excluded, and if they are determined to be at high risk of developing clinically definite multiple sclerosis (see section 5.1).
- patients with relapsing-remitting multiple sclerosis and two or more relapses within the last two years.
- patients with secondary progressive multiple sclerosis with active disease, evidenced by relapses.

4.2 Posology and method of administration

The treatment with Betaferon should be initiated under the supervision of a physician experienced in the treatment of the disease.

Posology

Adults

The recommended dose of Betaferon is 250 microgram (8.0 million IU), contained in 1 ml of the reconstituted solution (see section 6.6), to be injected subcutaneously every other day.

Paediatric population

No formal clinical trials or pharmacokinetic studies have been conducted in children or adolescents. However, limited published data suggest that the safety profile in adolescents from 12 to 16 years of age receiving Betaferon 8.0 million IU subcutaneously every other day is similar to that seen in adults. 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.

Generally, dose titration is recommended at the start of treatment.

Patients should be started at 62.5 microgram (0.25 ml) subcutaneously every other day, and increased slowly to a dose of 250 microgram (1.0 ml) every other day (see Table A). The titration period may be adjusted, if any significant adverse reaction occurs. In order to obtain adequate efficacy, a dose of 250 microgram (1.0 ml) every other day should be reached.

A titration pack composed of four triple packs is available for the titration period and the patient's initial treatment with Betaferon. This package meets the patient's needs for the first 12 injections. The triple packs are highlighted in different colours (see section 6.5).

Table A: Schedule for dose titration*

treatment day	dose	volume
1, 3, 5	62.5 microgram	0.25 ml
7, 9, 11	125 microgram	0.5 ml
13, 15, 17	187.5 microgram	0.75 ml
19, 21, 23 et seq.	250 microgram	1.0 ml

* The titration period may be adjusted, if any significant adverse reaction occurs.

The optimal dose has not been fully clarified.

At the present time, it is not known how long the patient should be treated for. There are follow-up data under controlled clinical conditions for patients with relapsing-remitting MS for up to 5 years and for patients with secondary progressive MS for up to 3 years. For relapsing-remitting MS, efficacy has been demonstrated for therapy for the first two years. The available data for the additional three years are consistent with sustained treatment efficacy of Betaferon over the whole time period.

In patients with a single clinical event suggestive of multiple sclerosis, the progression to clinically definite multiple sclerosis was significantly delayed over a period of five years.

Treatment is not recommended in patients with relapsing-remitting multiple sclerosis who have experienced less than 2 relapses in the previous 2 years or in patients with secondary-progressive multiple sclerosis who have had no active disease in the previous 2 years.

If the patient fails to respond, for example a steady progression in EDSS for 6 months occurs or treatment with at least 3 courses of ACTH or corticosteroids during a one year period is required despite Betaferon therapy, treatment with Betaferon should be stopped.

Method of administration

For subcutaneous injection.

For instructions on reconstitution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

- Patients with a history of hypersensitivity to natural or recombinant interferon beta, human albumin or to any of the excipients listed in section 6.1.
- Patients with current severe depression and/or suicidal ideation (see sections 4.4 and 4.8).
- Patients with decompensated liver disease (see sections 4.4, 4.5 and 4.8).

4.4 Special warnings and precautions for use

Traceability

In order to improve traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Immune system disorders

The administration of cytokines to patients with a pre-existing monoclonal gammopathy has been associated with the development of systemic capillary leak syndrome with shock-like symptoms and fatal outcome.

Gastrointestinal disorders

In rare cases, pancreatitis was observed with Betaferon use, often associated with hypertriglyceridaemia.

Nervous system disorders

Betaferon should be administered with caution to patients with previous or current depressive disorders, in particular to those with antecedents of suicidal ideation (see section 4.3). Depression and suicidal ideation are known to occur with increased frequency in the multiple sclerosis population and in association with interferon use. Patients treated with Betaferon should be advised to report any symptoms of depression and/or suicidal ideation to their prescribing physician immediately. Patients exhibiting depression should be monitored closely during therapy with Betaferon and treated appropriately. Cessation of therapy with Betaferon should be considered (see also sections 4.3 and 4.8).

Betaferon should be administered with caution to patients with a history of seizures and to those receiving treatment with anti-epileptics, particularly if their epilepsy is not adequately controlled with anti-epileptics (see sections 4.5 and 4.8).

This product contains human albumin and hence carries a potential risk for transmission of viral diseases. A risk for transmission of Creutzfeld-Jacob disease (CJD) cannot be excluded.

Laboratory test

Thyroid function tests are recommended regularly in patients with a history of thyroid dysfunction or as clinically indicated.

In addition to those laboratory tests normally required for monitoring patients with multiple sclerosis, complete blood and differential white blood cell counts, platelet counts, and blood chemistries, including liver function tests (e.g. AST (SGOT), ALT (SGPT) and γ -GT), are recommended prior to initiation and at regular intervals following introduction of Betaferon therapy, and then periodically thereafter in the absence of clinical symptoms.

Patients with anaemia, thrombocytopenia, leukopenia (alone or in any combination) may require more intensive monitoring of complete blood cell counts, with differential and platelet counts. Patients who develop neutropenia should be monitored closely for the development of fever or infection. There have been reports of thrombocytopenia, with profound decreases in platelet count.

Hepatobiliary disorders

Asymptomatic elevations of serum transaminases, in most cases mild and transient, occurred very commonly in patients treated with Betaferon during clinical trials. As for other beta interferons, severe hepatic injury, including cases of hepatic failure, has been reported rarely in patients treated with Betaferon. The most serious events often occurred in patients exposed to other drugs or substances known to be associated with hepatotoxicity or in the presence of comorbid medical conditions (e.g. metastasising malignant disease, severe infection and sepsis, alcohol abuse).

Patients should be monitored for signs of hepatic injury. The occurrence of elevations in serum transaminases should lead to close monitoring and investigation. Withdrawal of Betaferon should be considered if the levels significantly increase or if they are associated with clinical symptoms such as jaundice. In the absence of clinical evidence for liver damage and after normalisation of liver enzymes a reintroduction of therapy could be considered with appropriate follow-up of hepatic functions.

Renal and urinary disorders

Caution should be used and close monitoring considered when administering interferon beta to patients with severe renal failure.

Nephrotic Syndrome

Cases of nephrotic syndrome with different underlying nephropathies including collapsing focal segmental glomerulosclerosis (FSGS), minimal change disease (MCD), membranoproliferative glomerulonephritis (MPGN) and membranous glomerulopathy (MGN) have been reported during treatment with interferon beta products. Events were reported at various time points during treatment and may occur after several years of treatment with interferon beta. Periodic monitoring of early signs or symptoms, e.g. oedema, proteinuria and impaired renal function is recommended, especially in patients at higher risk of renal disease. Prompt treatment of nephrotic syndrome is required and discontinuation of treatment with Betaferon should be considered.

Cardiac disorders

Betaferon should also be used with caution in patients who suffer from pre-existing cardiac disorders. Patients with pre-existing significant cardiac disease, such as congestive heart failure, coronary artery disease or arrhythmia, should be monitored for worsening of their cardiac condition, particularly during initiation of treatment with Betaferon.

While Betaferon does not have any known direct-acting cardiac toxicity, symptoms of the flu-like syndrome associated with beta interferons may prove stressful to patients with pre-existing significant cardiac disease. During the post-marketing period very rare reports have been received of worsening of cardiac status in patients with pre-existing significant cardiac disease temporarily associated with the initiation of Betaferon therapy.

Rare cases of cardiomyopathy have been reported. If this occurs and a relationship to Betaferon is suspected, treatment should be discontinued.

Thrombotic microangiopathy (TMA)

Cases of thrombotic microangiopathy, manifested as thrombotic thrombocytopenic purpura (TTP) or haemolytic uraemic syndrome (HUS), including fatal cases, have been reported with interferon beta products. Events were reported at various time points during treatment and may occur several weeks to several years after starting treatment with interferon beta. Early clinical features include thrombocytopenia, new onset hypertension, fever, central nervous system symptoms (e.g. confusion, paresis) and impaired renal function. Laboratory findings suggestive of TMA include decreased platelet counts, increased serum lactate dehydrogenase (LDH) due to haemolysis and schistocytes (erythrocyte fragmentation) on a blood film. Therefore if clinical features of TMA are observed, further testing of blood platelet levels, serum LDH, blood films and renal function is recommended. If TMA is diagnosed, prompt treatment is required (considering plasma exchange) and immediate discontinuation of Betaferon is recommended.

General disorders and administration site conditions

Serious hypersensitivity reactions (rare but severe acute reactions such as bronchospasm, anaphylaxis and urticaria) may occur. If reactions are severe, Betaferon should be discontinued and appropriate medical intervention instituted.

Injection site necrosis has been reported in patients using Betaferon (see section 4.8). It can be extensive and may involve muscle fascia as well as fat and therefore can result in scar formation. Occasionally debridement and, less often, skin grafting are required and healing may take up to 6 months.

If the patient experiences any break in the skin, which may be associated with swelling or drainage of fluid from the injection site, the patient should be advised to consult with his/her physician before continuing injections with Betaferon.

If the patient has multiple lesions Betaferon should be discontinued until healing has occurred. Patients with single lesions may continue on Betaferon provided the necrosis is not too extensive, as some patients have experienced healing of injection site necrosis whilst on Betaferon.

To minimise the risk of injection site necrosis patients should be advised to:

- use an aseptic injection technique
- rotate the injection sites with each dose.

The incidence of injection site reactions may be reduced by the use of an autoinjector. In the pivotal study of patients with a single clinical event suggestive of multiple sclerosis an autoinjector was used in the majority of patients. Injection site reactions as well as injection site necroses were observed less frequently in this study than in the other pivotal studies.

The procedure for the self-administration by the patient should be reviewed periodically especially if injection site reactions have occurred.

Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. Serum samples in controlled clinical trials were collected every 3 months for monitoring of development of antibodies to Betaferon.

In the different controlled clinical trials in relapsing-remitting multiple sclerosis and secondary progressive multiple sclerosis, between 23% and 41% of the patients developed serum interferon beta-1b neutralising activity confirmed by at least two consecutive positive titres; of these patients, between 43% and 55% converted to a stable antibody negative status (based on two consecutive negative titres) during the subsequent observational period of the respective study.

The development of neutralising activity in these studies is associated with a reduction in clinical efficacy only with regard to relapse activity. Some analyses suggest that this effect might be larger in patients with higher titre levels of neutralising activity.

In the study of patients with a single clinical event suggestive of multiple sclerosis, neutralising activity measured every 6 months was observed at least once in 32% (89) of the patients treated immediately with Betaferon; of these, 60% (53) returned to negative status based on the last available assessment within the 5 year period. Within this period, the development of neutralising activity was associated with a significant increase in newly active lesions and T2 lesion volume on magnetic resonance imaging. However, this did not seem to be associated with a reduction in clinical efficacy (with regard to time to clinically definite multiple sclerosis (CDMS), time to confirmed EDSS progression and relapse rate).

New adverse events have not been associated with the development of neutralising activity.

It has been demonstrated *in vitro* that Betaferon cross-reacts with natural interferon beta. However, this has not been investigated *in vivo* and its clinical significance is uncertain.

There are sparse and inconclusive data on patients who have developed neutralising activity and have completed Betaferon therapy.

The decision to continue or discontinue treatment should be based on all aspects of the patient's disease status rather than on neutralising activity status alone.

Excipients

This medicinal product contains less than 1 mmol sodium (23 mg) per ml, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

The effect of alternate-day administration of 250 microgram (8.0 million IU) of Betaferon on drug metabolism in multiple sclerosis patients is unknown. Corticosteroid or ACTH treatment of relapses for periods of up to 28 days has been well tolerated in patients receiving Betaferon.

Due to the lack of clinical experience in multiple sclerosis patients, the use of Betaferon together with immunomodulators other than corticosteroids or ACTH is not recommended.

Interferons have been reported to reduce the activity of hepatic cytochrome P450-dependent enzymes in humans and animals. Caution should be exercised when Betaferon is administered in combination with medicinal products that have a narrow therapeutic index and are largely dependent on the hepatic cytochrome P450 system for clearance, e.g. anti-epileptics. Additional caution should be exercised with any co-medication which has an effect on the haematopoietic system.

No interaction studies with anti-epileptics have been carried out.

4.6 Fertility, pregnancy and lactation

Pregnancy

A large amount of data (more than 1000 pregnancy outcomes) from interferon beta registries, national registries and post-marketing experience indicates no increased risk of major congenital anomalies after pre-conception exposure or exposure during the first trimester of pregnancy. However, the duration of exposure during the first trimester is uncertain, because data were collected when interferon beta use was contraindicated during pregnancy, and treatment likely interrupted when pregnancy was detected and/or confirmed. Experience with exposure during the second and third trimester is very limited.

Based on animal data (see section 5.3), there is a possibly increased risk for spontaneous abortion. The risk of spontaneous abortions in pregnant women exposed to interferon beta cannot adequately be evaluated based on the currently available data, but the data do not suggest an increased risk so far.

If clinically needed, the use of Betaferon may be considered during pregnancy.

Breast-feeding

Limited information available on the transfer of interferon beta-1b into breast milk, together with the chemical / physiological characteristics of interferon beta, suggests that levels of interferon beta-1b excreted in human milk are negligible. No harmful effects on the breastfed newborn/infant are anticipated.

Betaferon can be used during breast-feeding.

Fertility

No investigations on fertility have been conducted (see section 5.3).

4.7 Effects on ability to drive and use machines

No studies of the effects on the ability to drive and use machines have been performed.

Central nervous system-related adverse events associated with the use of Betaferon might influence the ability to drive and use machines in susceptible patients.

4.8 Undesirable effects

Summary of the safety profile

At the beginning of treatment adverse reactions are common but in general they subside with further treatment. The most frequently observed adverse reactions are a flu-like symptom complex (fever, chills, arthralgia, malaise, sweating, headache, or myalgia), which is mainly due to the

pharmacological effects of the medicinal product, and injection site reactions. Injection site reactions occurred frequently after administration of Betaferon. Redness, swelling, discolouration, inflammation, pain, hypersensitivity, necrosis and non-specific reactions were significantly associated with 250 microgram (8.0 million IU) Betaferon treatment.

Generally, dose titration is recommended at the start of treatment in order to increase tolerability to Betaferon (see section 4.2). Flu-like symptoms may also be reduced by administration of non-steroidal anti-inflammatory drugs. The incidence of injection site reactions may be reduced by the use of an autoinjector.

Tabulated list of adverse reactions

The following adverse event listing is based on reports from clinical trials (*Table 1, adverse events and laboratory abnormalities*) and from the post-marketing surveillance (*Table 2, frequencies – where known- based on pooled clinical trials (very common $\geq 1/10$, common $\geq 1/100$ to $< 1/10$, uncommon $\geq 1/1,000$ to $< 1/100$, rare $\geq 1/10,000$ to $< 1/1,000$, very rare $< 1/10,000$)*) of Betaferon use. Experience with Betaferon in patients with MS is limited, consequently those adverse events which occur very rarely may not yet have been observed.

Table 1: Adverse events and laboratory abnormalities with incidence rates $\geq 10\%$ and the respective percentages under placebo; significantly associated side effects $< 10\%$ based on reports from clinical trials

System Organ Class Adverse Event and Laboratory Abnormalities	Single Event suggestive of Multiple Sclerosis (BENEFIT) #	Secondary Progressive Multiple Sclerosis (European Study)	Secondary Progressive Multiple Sclerosis (North American Study)	Relapsing- Remitting Multiple Sclerosis
	Betaferon 250 microgram (Placebo) n=292 (n=176)	Betaferon 250 microgram (Placebo) n=360 (n=358)	Betaferon 250 microgram (Placebo) n=317 (n=308)	Betaferon 250 microgram (Placebo) n=124 (n=123)
Infections and infestations				
Infection	6% (3%)	13% (11%)	11% (10%)	14% (13%)
Abscess	0% (1%)	4% (2%)	4% (5%)	1% (6%)
Blood and lymphatic system disorders				
Lymphocyte count decreased ($< 1,500/\text{mm}^3$) [×] [△] °	79% (45%)	53% (28%)	88% (68%)	82% (67%)
Absolute neutrophil count decreased ($< 1,500/\text{mm}^3$) [×] [△] * °	11% (2%)	18% (5%)	4% (10%)	18% (5%)
White blood cell count decreased ($< 3,000/\text{mm}^3$) [×] [△] * °	11% (2%)	13% (4%)	13% (4%)	16% (4%)
Lymphadenopathy	1% (1%)	3% (1%)	11% (5%)	14% (11%)
Metabolism and nutrition disorders				
Blood glucose decreased ($< 55 \text{ mg/dl}$) [×]	3% (5%)	27% (27%)	5% (3%)	15% (13%)
Psychiatric disorders				
Depression	10% (11%)	24% (31%)	44% (41%)	25% (24%)
Anxiety	3% (5%)	6% (5%)	10% (11%)	15% (13%)
Nervous system disorders				
Headache [△]	27% (17%)	47% (41%)	55% (46%)	84% (77%)

System Organ Class Adverse Event and Laboratory Abnormalities	Single Event suggestive of Multiple Sclerosis (BENEFIT) #	Secondary Progressive Multiple Sclerosis (European Study)	Secondary Progressive Multiple Sclerosis (North American Study)	Relapsing- Remitting Multiple Sclerosis
	Betaferon 250 microgram (Placebo) n=292 (n=176)	Betaferon 250 microgram (Placebo) n=360 (n=358)	Betaferon 250 microgram (Placebo) n=317 (n=308)	Betaferon 250 microgram (Placebo) n=124 (n=123)
Dizziness	3% (4%)	14% (14%)	28% (26%)	35% (28%)
Insomnia	8% (4%)	12% (8%)	26% (25%)	31% (33%)
Migraine	2% (2%)	4% (3%)	5% (4%)	12% (7%)
Paraesthesia	16% (17%)	35% (39%)	40% (43%)	19% (21%)
Eye disorders				
Conjunctivitis	1% (1%)	2% (3%)	6% (6%)	12% (10%)
Abnormal vision [^]	3% (1%)	11% (15%)	11% (11%)	7% (4%)
Ear and labyrinth disorders				
Ear pain	0% (1%)	<1% (1%)	6% (8%)	16% (15%)
Cardiac disorders				
Palpitation *	1% (1%)	2% (3%)	5% (2%)	8% (2%)
Vascular disorders				
Vasodilatation	0% (0%)	6% (4%)	13% (8%)	18% (17%)
Hypertension ^o	2% (0%)	4% (2%)	9% (8%)	7% (2%)
Respiratory, thoracic and mediastinal disorders				
Upper respiratory infection	18% (19%)	3% (2%)		
Sinusitis	4% (6%)	6% (6%)	16% (18%)	36% (26%)
Cough increased	2% (2%)	5% (10%)	11% (15%)	31% (23%)
Dyspnoea *	0% (0%)	3% (2%)	8% (6%)	8% (2%)
Gastrointestinal disorders				
Diarrhoea	4% (2%)	7% (10%)	21% (19%)	35% (29%)
Constipation	1% (1%)	12% (12%)	22% (24%)	24% (18%)
Nausea	3% (4%)	13% (13%)	32% (30%)	48% (49%)
Vomiting [^]	5% (1%)	4% (6%)	10% (12%)	21% (19%)
Abdominal pain ^o	5% (3%)	11% (6%)	18% (16%)	32% (24%)
Hepatobiliary disorders				
Alanine aminotransferase increased (SGPT> 5 times baseline) ^{x ^ * o}	18% (5%)	14% (5%)	4% (2%)	19% (6%)
Aspartate aminotransferase increased (SGOT > 5 times baseline) ^{x ^ * o}	6% (1%)	4% (1%)	2% (1%)	4% (0%)
Skin and subcutaneous tissue disorders				
Skin disorder	1% (0%)	4% (4%)	19% (17%)	6% (8%)
Rash ^{^ o}	11% (3%)	20% (12%)	26% (20%)	27% (32%)
Musculoskeletal and connective tissue disorders				
Hypertonia ^o	2% (1%)	41% (31%)	57% (57%)	26% (24%)
Myalgia * ^o	8% (8%)	23% (9%)	19% (29%)	44% (28%)
Myasthenia	2% (2%)	39% (40%)	57% (60%)	13% (10%)
Back pain	10% (7%)	26% (24%)	31% (32%)	36% (37%)
Pain in extremity	6% (3%)	14% (12%)		0% (0%)

System Organ Class Adverse Event and Laboratory Abnormalities	Single Event suggestive of Multiple Sclerosis (BENEFIT) #	Secondary Progressive Multiple Sclerosis (European Study)	Secondary Progressive Multiple Sclerosis (North American Study)	Relapsing- Remitting Multiple Sclerosis
	Betaferon 250 microgram (Placebo) n=292 (n=176)	Betaferon 250 microgram (Placebo) n=360 (n=358)	Betaferon 250 microgram (Placebo) n=317 (n=308)	Betaferon 250 microgram (Placebo) n=124 (n=123)
Renal and urinary disorders				
Urinary retention	1% (1%)	4% (6%)	15% (13%)	
Urinary protein positive (> 1+) ^x	25% (26%)	14% (11%)	5% (5%)	5% (3%)
Urinary frequency	1% (1%)	6% (5%)	12% (11%)	3% (5%)
Urinary incontinence	1% (1%)	8% (15%)	20% (19%)	2% (1%)
Urinary urgency	1% (1%)	8% (7%)	21% (17%)	4% (2%)
Reproductive system and breast disorders				
Dysmenorrhoea	2% (0%)	<1% (<1%)	6% (5%)	18% (11%)
Menstrual disorder *	1% (2%)	9% (13%)	10% (8%)	17% (8%)
Metrorrhagia	2% (0%)	12% (6%)	10% (10%)	15% (8%)
Impotence	1% (0%)	7% (4%)	10% (11%)	2% (1%)
General disorders and administration site conditions				
Injection site reaction (various kinds) ^{^ * ° §}	52% (11%)	78% (20%)	89% (37%)	85% (37%)
Injection site necrosis ^{* °}	1% (0%)	5% (0%)	6% (0%)	5% (0%)
Flu-like symptoms ^{& ^ * °}	44% (18%)	61% (40%)	43% (33%)	52% (48%)
Fever ^{^ * °}	13% (5%)	40% (13%)	29% (24%)	59% (41%)
Pain	4% (4%)	31% (25%)	59% (59%)	52% (48%)
Chest pain [°]	1% (0%)	5% (4%)	15% (8%)	15% (15%)
Peripheral oedema	0% (0%)	7% (7%)	21% (18%)	7% (8%)
Asthenia *	22% (17%)	63% (58%)	64% (58%)	49% (35%)
Chills ^{^ * °}	5% (1%)	23% (7%)	22% (12%)	46% (19%)
Sweating *	2% (1%)	6% (6%)	10% (10%)	23% (11%)
Malaise *	0% (1%)	8% (5%)	6% (2%)	15% (3%)
<p>^x Laboratory abnormality</p> <p>[^] Significantly associated with Betaferon treatment for patients with first event suggestive of MS, p < 0.05</p> <p>[*] Significantly associated with Betaferon treatment for RRMS, p < 0.05</p> <p>[°] Significantly associated with Betaferon treatment for SPMS, p < 0.05</p> <p>[§] Injection site reaction (various kinds) comprises all adverse events occurring at the injection site, i.e. the following terms: injection site haemorrhage, injection site hypersensitivity, injection site inflammation, injection site mass, injection site necrosis, injection site pain, injection site reaction, injection site oedema, and injection site atrophy</p> <p>^{&} “Flu-like symptom complex” denotes flu syndrome and/or a combination of at least two AEs from fever, chills, myalgia, malaise, sweating.</p> <p>[#] During the BENEFIT follow-up study, no change in the known risk profile of Betaferon was observed.</p>				

The most appropriate MedDRA term is used to describe a certain reaction and its synonyms and related conditions.

Table 2: Adverse drug reactions (ADRs) identified during post-marketing surveillance (frequencies - where known - calculated based on pooled clinical trial data N= 1093)

System Organ Class	Very common ($\geq 1/10$)¹	Common ($\geq 1/100$ to < $1/10$)¹	Uncommon ($\geq 1/1,000$ to < $1/100$)¹	Rare ($\geq 1/10,000$ to < $1/1,000$)¹	Frequency not known
Blood and lymphatic system disorders		Anaemia	Thrombocytopenia	Thrombotic microangiopathy including thrombotic thrombocytopenic purpura/ haemolytic uraemic syndrome ³	
Immune system disorders				Anaphylactic reactions	Capillary leak syndrome in pre-existing monoclonal gammopathy ²
Endocrine disorders		Hypothyroidism		Hyperthyroidism, Thyroid disorders	
Metabolism and nutrition disorders		Weight increased, Weight decreased	Blood triglycerides increased	Anorexia ²	
Psychiatric disorders		Confusional state	Suicide attempt (see also section 4.4), Emotional lability		
Nervous system disorders			Convulsion		
Cardiac disorders		Tachycardia		Cardiomyopathy ²	
Respiratory, thoracic and mediastinal disorders				Bronchospasm ²	Pulmonary arterial hypertension ⁴
Gastrointestinal disorders				Pancreatitis	
Hepatobiliary disorders		Blood bilirubin increased	Gamma-glutamyl-transferase increased, Hepatitis	Hepatic injury (including hepatitis), Hepatic failure ²	
Skin and subcutaneous tissue disorders		Urticaria, Pruritus, Alopecia	Skin discolouration		
Musculoskeletal and connective tissue disorders	Arthralgia				Drug-induced lupus erythematosus
Renal and urinary disorders			Nephrotic syndrome, glomerulosclerosis (see section 4.4) ^{2,3}		
Reproductive system and breast disorders		Menorrhagia			

System Organ Class	Very common ($\geq 1/10$) ¹	Common ($\geq 1/100$ to $< 1/10$) ¹	Uncommon ($\geq 1/1,000$ to $< 1/100$) ¹	Rare ($\geq 1/10,000$ to $< 1/1,000$) ¹	Frequency not known
¹ frequencies based on pooled clinical trials (very common $\geq 1/10$, common $\geq 1/100$ to $< 1/10$, uncommon $\geq 1/1,000$ to $< 1/100$, rare $\geq 1/10,000$ to $< 1/1,000$, very rare $< 1/10,000$).					
² ADRs derived only during post-marketing					
³ Class label for interferon beta products (see section 4.4).					
⁴ Class label for interferon products, see below Pulmonary arterial hypertension.					

The most appropriate MedDRA term is used to describe a certain reaction and its synonyms and related conditions.

Pulmonary arterial hypertension

Cases of pulmonary arterial hypertension (PAH) have been reported with interferon beta products. Events were reported at various time points including up to several years after starting treatment with interferon beta.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in [Appendix V](#).

4.9 Overdose

Interferon beta-1b has been given without serious adverse events compromising vital functions to adult cancer patients at individual doses as high as 5,500 microgram (176 million IU) intravenously three times a week.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Cytokines, Interferons,
ATC Code: L03 AB 08

Mechanism of action

Interferons belong to the family of cytokines, which are naturally occurring proteins. Interferons have molecular weights ranging from 15,000 to 21,000 Daltons. Three major classes of interferons have been identified: alpha, beta, and gamma. Interferon alpha, interferon beta, and interferon gamma have overlapping yet distinct biologic activities. The activities of interferon beta-1b are species-restricted and therefore, the most pertinent pharmacological information on interferon beta-1b is derived from studies of human cells in culture or in human *in vivo* studies.

Interferon beta-1b has been shown to possess both antiviral and immunoregulatory activities. The mechanisms by which interferon beta-1b exerts its actions in multiple sclerosis are not clearly understood. However, it is known that the biologic response-modifying properties of interferon beta-1b are mediated through its interactions with specific cell receptors found on the surface of human cells. The binding of interferon beta-1b to these receptors induces the expression of a number of gene products that are believed to be the mediators of the biological actions of interferon beta-1b. A number of these products have been measured in the serum and cellular fractions of blood collected from patients treated with interferon beta-1b. Interferon beta-1b both decreases the binding affinity and enhances the internalisation and degradation of the interferon-gamma receptor. Interferon beta-1b also enhances the suppressor activity of peripheral blood mononuclear cells.

No separate investigations were performed regarding the influence of Betaferon on the cardiovascular system, respiratory system and the function of endocrine organs.

Clinical efficacy and safety

RR-MS

One controlled clinical trial with Betaferon in patients with relapsing-remitting multiple sclerosis and able to walk unaided (baseline EDSS 0 to 5.5) was performed. Patients receiving Betaferon showed a reduction in frequency (30%) and severity of clinical relapses, as well as the number of hospitalisations due to disease. Furthermore, there was a prolongation of the relapse-free interval. There is no evidence of an effect of Betaferon on the duration of relapses or on symptoms in between relapses, and no significant effect was seen on the progression of the disease in relapsing-remitting multiple sclerosis.

SP-MS

Two controlled clinical trials with Betaferon involving a total of 1,657 patients with secondary progressive multiple sclerosis (baseline EDSS 3 to 6.5, i.e. patients were able to walk) were performed. Patients with mild disease and those unable to walk were not studied. The two studies showed inconsistent results for the primary endpoint time to confirmed progression, representing delay of disability progression:

One of the two studies demonstrated a statistically significant delay in the time to disability progression (Hazard Ratio = 0.69, 95% confidence interval (0.55, 0.86), $p=0.0010$, corresponding to a 31% risk reduction due to Betaferon) and in the time to becoming wheelchair bound (Hazard Ratio = 0.61, 95% confidence interval (0.44, 0.85), $p=0.0036$, corresponding to a 39% risk reduction due to Betaferon) in patients who received Betaferon. This effect continued over the observation period of up to 33 months. The treatment effect occurred in patients at all levels of disability investigated and independent of relapse activity.

In the second trial of Betaferon in secondary progressive multiple sclerosis, no delay in the time to disability progression was observed. There is evidence that the patients included in this study had overall less active disease than in the other study in secondary progressive multiple sclerosis.

In retrospective meta-analyses including the data of both studies, an overall treatment effect was found which was statistically significant ($p=0.0076$; 8.0 million IU Betaferon versus all placebo patients).

Retrospective analyses in subgroups showed that a treatment effect on disability progression is most likely in patients with active disease before treatment commences (Hazard Ratio 0.72, 95% confidence interval (0.59, 0.88), $p=0.0011$, corresponding to a 28 % risk reduction due to Betaferon in patients with relapses or pronounced EDSS progression, 8.0 million IU Betaferon versus all placebo patients).

From these retrospective subgroup analyses there was evidence to suggest that relapses as well as pronounced EDSS progression (EDSS >1 point or >0.5 point for EDSS ≥ 6 in the previous two years) can help to identify patients with active disease.

In both trials secondary progressive multiple sclerosis patients receiving Betaferon showed a reduction in frequency (30%) of clinical relapses. There is no evidence of Betaferon having an effect on the duration of relapses.

Single clinical event suggestive of MS

One controlled clinical trial with Betaferon was performed in patients with a single clinical event and MRI features suggestive of multiple sclerosis (at least two clinically silent lesions on the T2-weighted MRI). Patients with monofocal or multifocal onset of the disease were included (i.e. patients with clinical evidence for a single or at least two lesions, respectively, of the central nervous system). Any disease other than multiple sclerosis that could better explain signs and symptoms of the patient had to be excluded. This study consisted of two phases, a placebo-controlled phase followed by a pre-planned follow-up phase. The placebo-controlled phase lasted for 2 years or until the patient developed clinically definite multiple sclerosis (CDMS), whichever came first. After the placebo-controlled phase, patients entered a pre-planned follow-up phase with Betaferon to evaluate the effects of immediate versus delayed start of Betaferon treatment, comparing patients initially randomized to Betaferon ("immediate treatment group") or to placebo ("delayed treatment group"). Patients and investigators remained blinded to the initial treatment allocation.

Table 3: Primary efficacy results of the BENEFIT and the BENEFIT Follow-up study

	Year 2 results Placebo-controlled phase		Year 3 results Open-label follow-up		Year 5 results Open-label follow-up	
	Betaferon 250 mcg n=292	Placebo n=176	Imme- diate Betaferon 250 mcg n=292	Delayed Betaferon 250 mcg n=176	Imme- diate Betaferon 250 mcg n=292	Delayed Betaferon 250 mcg n=176
Number of patients completed the trial phase	271 (93%)	166 (94%)	249 (85%)	143 (81%)	235 (80%)	123 (70%)
Primary efficacy variables						
Time to CDMS						
Kaplan-Meier estimates	28%	45%	37%	51%	46%	57%
Risk reduction	47% versus placebo		41% versus delayed Betaferon		37% versus delayed Betaferon	
Hazard ratio with 95% confidence interval	HR = 0.53 [0.39, 0.73]		HR = 0.59 [0.42, 0.83]		HR = 0.63 [0.48, 0.83]	
log-rank test	p < 0.0001		p = 0.0011		p = 0.0027	
Time to McDonald MS						
Kaplan-Meier	69%	85%	No primary endpoint		No primary endpoint	

estimates					
Risk reduction	43% versus placebo				
Hazard ratio with 95% confidence interval	HR = 0.57 [0.46, 0.71]				
log-rank test	p < 0.00001				
Time to confirmed EDSS progression					
Kaplan-Meier estimates	No primary endpoint	16%	24%	25%	29%
Risk reduction		40% versus delayed Betaferon		24% versus delayed Betaferon	
Hazard ratio with 95% confidence interval		HR = 0.60 [0.39, 0.92]		HR = 0.76 [0.52, 1.11]	
log-rank test		p = 0.022		p=0.177	

In the placebo-controlled phase, Betaferon delayed the progression from the first clinical event to CDMS in a statistically significant and clinically meaningful manner. The robustness of the treatment effect was also shown by the delay of progression to multiple sclerosis according to McDonald criteria (Table 3).

Subgroup analyses according to baseline factors demonstrated evidence of efficacy on progression to CDMS in all subgroups evaluated. The risk for progression to CDMS within 2 years was higher in monofocal patients with at least 9 T2-lesions or Gd-enhancement on brain MRI at baseline. In multifocal patients, the risk for CDMS was independent from MRI findings at baseline, indicating a high risk for CDMS because of the dissemination of the disease based on clinical findings. For the time being there is no well-established definition of a high risk patient, although a more conservative approach is to accept at least nine T2 hyperintense lesions on the initial scan and at least one new T2 or one new Gd-enhancing lesion on a follow-up scan taken at least 1 month after the initial scan. In any case, treatment should only be considered for patients classified as high risk.

Therapy with Betaferon was well accepted as indicated by a high rate of trial completion (93% in the Betaferon group). To increase tolerability of Betaferon, a dose titration was applied and non-steroidal anti-inflammatory drugs were administered at start of therapy. Moreover, an autoinjector was used by the majority of patients throughout the study.

In the open-label follow-up phase, the treatment effect on CDMS was still evident after 3 and 5 years (Table 3) even though the majority of patients from the placebo-group were treated with Betaferon at least from the second year onwards. EDSS progression (confirmed increase in EDSS of at least one point compared to baseline) was lower in the immediate treatment group (Table 3, significant effect after 3 years, no significant effect after 5 years). The majority of patients in both treatment groups had no disability progression over the 5-year period. Robust evidence for benefit on this outcome parameter could not be demonstrated for 'immediate' treatment. No benefit, attributable to immediate Betaferon treatment, in quality of life (as measured by FAMS - Functional Assessment of MS: Treatment Outcomes Index) was seen.

RR-MS, SP-MS and single clinical event suggestive of MS

Betaferon was effective in all multiple sclerosis studies to reduce disease activity (acute inflammation in the central nervous system and permanent tissue alterations) as measured by magnetic resonance imaging (MRI). The relation of multiple sclerosis disease activity as measured by MRI and clinical outcome is currently not fully understood.

5.2 Pharmacokinetic properties

Betaferon serum levels were followed in patients and volunteers by means of a not completely specific bioassay. Maximum serum levels of about 40 IU/ml were found 1-8 hours after subcutaneous injection of 500 microgram (16.0 million IU) interferon beta-1b. From various studies mean clearance rates and half-lives of disposition phases from serum were estimated to be at most $30 \text{ ml} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$ and 5 hours, respectively.

Betaferon injections given every other day do not lead to serum level increases, and the pharmacokinetics does not seem to change during therapy.

The absolute bioavailability of subcutaneously administered interferon beta-1b was approximately 50%.

5.3 Preclinical safety data

No acute toxicity studies have been carried out. As rodents do not react to human interferon beta, repeated dose studies were carried out with rhesus monkeys. Transitory hyperthermia was observed, as well as a significant rise in lymphocytes and a significant decrease in thrombocytes and segmented neutrophils.

No long-term studies have been conducted. Reproduction studies with rhesus monkeys revealed maternal toxicity and an increased rate of abortion, resulting in prenatal mortality. No malformations have been observed in the surviving animals.

No investigations on fertility have been conducted. No influence on the monkey oestrous cycle has been observed. Experience with other interferons suggests a potential for impairment of male and female fertility.

In one single genotoxicity study (Ames test), no mutagenic effect has been observed. Carcinogenicity studies have not been performed. An *in vitro* cell transformation test gave no indication of tumorigenic potential.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients:

Vial (with powder for solution for injection):

Human albumin
Mannitol

Solvent (sodium chloride solution 5.4 mg/ml (0.54% w/v)):

Sodium chloride
Water for injection

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except for the supplied solvent mentioned in section 6.6.

6.3 Shelf life

2 years.

After reconstitution, immediate use is recommended. However, the in-use stability has been demonstrated for 3 hours at 2-8 °C.

6.4 Special precautions for storage

Do not store above 25°C.

Do not freeze.

For storage conditions of the reconstituted medicinal product, see section 6.3.

6.5 Nature and contents of container

Vial (with powder for solution for injection):

3 ml clear vial (type I glass) with a butyl rubber stopper (type I) and aluminium overseal and

Solvent (with sodium chloride solution 5.4 mg/ml (0.54% w/v)):

2.25 ml pre-filled syringe (type I glass) with 1.2 ml solvent.

Pack sizes

- Pack with 5 single packs, each containing 1 vial with powder, 1 pre-filled syringe with solvent, 1 vial adapter with needle, 2 alcohol wipes or
- Pack with 15 single packs, each containing 1 vial with powder, 1 pre-filled syringe with solvent, 1 vial adapter with needle, 2 alcohol wipes or
- Pack with 14 single packs, each containing 1 vial with powder, 1 pre-filled syringe with solvent, 1 vial adapter with needle, 2 alcohol wipes or
- Pack with 12 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 pack with 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 pack with 3x14 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 pack with 3x15 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 dose titration with 4 differently coloured and numbered triple packs:
 - yellow, with number “1”(treatment days 1, 3 and 5; 0.25-ml syringe marking),
 - red, with number “2” (treatment days 7, 9 and 11; 0.5-ml syringe marking),
 - green, with number “3” (treatment days 13, 15 and 17; 0.75-ml syringe marking),
 - blue, with number “4” (treatment days 19, 21 and 23; 0.25, 0.5, 0.75 and 1-ml syringe marking)Each triple pack contains 3 vials with powder, 3 pre-filled syringes with solvent, 3 vial adapters with pre-attached needle and 6 alcohol wipes for skin and vial cleaning.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Reconstitution:

To reconstitute lyophilised interferon beta-1b for injection, connect the vial adapter with the attached needle on the vial. Connect the pre-filled syringe with solvent to the vial adapter and inject the 1.2 ml of the solvent (sodium chloride solution, 5.4 mg/ml (0.54% w/v)) into the Betaferon vial. Dissolve the powder completely without shaking.

After reconstitution, draw 1.0 ml from the vial into the syringe for the administration of 250 microgram Betaferon. For the dose titration at the start of treatment, draw the respective volume as given in section 4.2.

Remove the vial with the vial adapter from the pre-filled syringe before injection.
Betaferon may also be administered with a suitable autoinjector.

Inspection prior to use

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 is discoloured.

Disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Bayer AG
51368 Leverkusen
Germany

8. MARKETING AUTHORISATION NUMBERS

EU/1/95/003/005
EU/1/95/003/006
EU/1/95/003/007
EU/1/95/003/008
EU/1/95/003/009
EU/1/95/003/010
EU/1/95/003/011
EU/1/95/003/012

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 30 November 1995
Date of last renewal: 31 January 2006

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>.

ANNEX II

- A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE
AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE
MARKETING AUTHORISATION**
- D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE
AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers of the biological active substance

Boehringer Ingelheim RCV GmbH & Co KG
Dr.-Boehringer-Gasse 5-11
A-1121 Vienna
Austria

Name and address of the manufacturer responsible for batch release

Bayer AG
Müllerstraße 178
13353 Berlin
Germany

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports(PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON OF MULTIPACK (INCLUDING BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

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

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 ml contains 250 microgram (8.0 million IU) interferon beta-1b when reconstituted.

3. LIST OF EXCIPIENTS

Excipients: Human albumin, mannitol

4. PHARMACEUTICAL FORM AND CONTENTS

Multipack comprising 15 single packs, each containing:

Multipack comprising 5 single packs, each containing:

Multipack comprising 14 single packs, each containing:

Multipack comprising 12 single packs, each containing:

I. 1 vial with powder for solution for injection contains 300 microgram (9.6 million IU). After reconstitution, 1 ml contains 250 microgram (8.0 million IU) interferon beta-1b*.

II. 1 pre-filled syringe with 1.2 ml solvent for reconstitution contains sodium chloride solution 5.4 mg/ml.

III. 1 vial adapter with needle + 2 alcohol wipes

*Betaferon is formulated to contain a calculated overfill of 20 %.

5. METHOD AND ROUTE OF ADMINISTRATION

For subcutaneous injection after reconstitution with 1.2 ml of solvent.

Single use.

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

After reconstitution, immediate use is recommended. In-use stability demonstrated for 3 hours at 2-8°C.

9. SPECIAL STORAGE CONDITIONS

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

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Bayer AG
51368 Leverkusen
Germany

12. MARKETING AUTHORISATION NUMBER

EU/1/95/003/005
EU/1/95/003/006
EU/1/95/003/009
EU/1/95/003/011

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY**15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE**

Betaferon

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON OF MULTI-MONTH PACK (INCLUDING BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

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

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 ml contains 250 microgram (8.0 million IU) interferon beta-1b when reconstituted.

3. LIST OF EXCIPIENTS

Excipients: Human albumin, mannitol

4. PHARMACEUTICAL FORM AND CONTENTS

3-month pack comprising 45 (3x15) single packs, each containing:

3-month pack comprising 42 (3x14) single packs, each containing:

2-month pack comprising 28 (2x14) single packs, each containing:

- I. 1 vial with powder for solution for injection** contains 300 microgram (9.6 million IU). After reconstitution, 1 ml contains 250 microgram (8.0 million IU) interferon beta-1b*.
- II. 1 pre-filled syringe with 1.2 ml solvent for reconstitution** contains sodium chloride solution 5.4 mg/ml.
- III. 1 vial adapter with needle + 2 alcohol wipes**

*Betaferon is formulated to contain a calculated overfill of 20 %.

5. METHOD AND ROUTE OF ADMINISTRATION

For subcutaneous injection after reconstitution with 1.2 ml of solvent.
Single use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

After reconstitution, immediate use is recommended. In-use stability demonstrated for 3 hours at 2-8 °C.

9. SPECIAL STORAGE CONDITIONS

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

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Bayer AG
51368 Leverkusen
Germany

12. MARKETING AUTHORISATION NUMBER

EU/1/95/003/007
EU/1/95/003/010
EU/1/95/003/012

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY**15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE**

Betaferon

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

**CARTON OF MULTIPACK AS AN INTERMEDIATE PACK OF MULTI-MONTH PACK
(WITHOUT BLUE BOX)**

1. NAME OF THE MEDICINAL PRODUCT

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

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 ml contains 250 microgram (8.0 million IU) interferon beta-1b when reconstituted.

3. LIST OF EXCIPIENTS

Excipients: Human albumin, mannitol

4. PHARMACEUTICAL FORM AND CONTENTS

Pack comprising 15 single packs, part of a 3-month pack containing 45 (3 x 15) single packs. No individual sale of single packs.

Pack comprising 14 single packs, part of a 3-month pack containing 42 (3 x 14) single packs. No individual sale of single packs.

Pack comprising 14 single packs, part of a 2-month pack containing 28 (2 x 14) single packs. No individual sale of single packs.

Each single pack contains:

- I. 1 vial with powder for solution for injection** contains 300 microgram (9.6 million IU). After reconstitution, 1 ml contains 250 microgram (8.0 million IU) interferon beta-1b*.
- II. 1 pre-filled syringe with 1.2 ml solvent for reconstitution** contains sodium chloride solution 5.4 mg/ml.
- III. 1 vial adapter with needle + 2 alcohol wipes**

*Betaferon is formulated to contain a calculated overfill of 20 %.

5. METHOD AND ROUTE OF ADMINISTRATION

For subcutaneous injection after reconstitution with 1.2 ml of solvent.
Single use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

After reconstitution, immediate use is recommended. In-use stability demonstrated for 3 hours at 2-8 °C.

9. SPECIAL STORAGE CONDITIONS

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

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Bayer AG
51368 Leverkusen
Germany

12. MARKETING AUTHORISATION NUMBER

EU/1/95/003/007
EU/1/95/003/010
EU/1/95/003/012

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Betaferon

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON OF THE SINGLE PACK AS AN INTERMEDIATE PACK OF MULTIPACKS OR MULTI-MONTH PACKS (WITHOUT BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

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

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 ml contains 250 microgram (8.0 million IU) interferon beta-1b when reconstituted.

3. LIST OF EXCIPIENTS

Excipients: Human albumin, mannitol

4. PHARMACEUTICAL FORM AND CONTENTS

Part of a multipack containing 15 single packs. No individual sale of single packs.

Part of a multipack containing 5 single packs. No individual sale of single packs.

Part of a pack containing 15 single packs in a 3-month pack of 3x15 single packs. No individual sale of single packs.

Part of a multipack containing 14 single packs. No individual sale of single packs.

Part of a pack containing 14 single packs in a 3-month pack of 3x14 single packs. No individual sale of single packs.

Part of a multipack containing 12 single packs. No individual sale of single packs.

Part of a pack containing 14 single packs in a 2-month pack of 2x14 single packs. No individual sale of single packs.

1 vial with powder: 300 microgram (9.6 m IU) per vial. When reconstituted 250 microgram/ml (8.0 m IU/ml) interferon beta-1b.

1 pre-filled syringe with 1.2 ml solvent: sodium chloride solution 5.4 mg/ml,

1 vial adapter with needle + 2 alcohol wipes

5. METHOD AND ROUTE OF ADMINISTRATION

For subcutaneous injection after reconstitution with 1.2 ml of solvent.

Single use.

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

After reconstitution, immediate use is recommended. In-use stability demonstrated for 3 hours at 2-8 °C.

9. SPECIAL STORAGE CONDITIONS

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

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Bayer AG
51368 Leverkusen
Germany

12. MARKETING AUTHORISATION NUMBER

EU/1/95/003/005
EU/1/95/003/006
EU/1/95/003/007
EU/1/95/003/009
EU/1/95/003/010
EU/1/95/003/011
EU/1/95/003/012

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE**16. INFORMATION IN BRAILLE**

Betaferon

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

TITRATION PACK WITH 4x1 TRIPLE PACK (3 VIALS/3 PRE-FILLED SYRINGES), FOR FIRST 12 INJECTIONS/TREATMENT DAYS (INCLUDING BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

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

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 ml contains 250 microgram (8.0 million IU) interferon beta-1b when reconstituted.

3. LIST OF EXCIPIENTS

Excipients: Human albumin, mannitol

4. PHARMACEUTICAL FORM AND CONTENTS

**Titration pack
comprising 4 triple packs, each containing:**

- I. 3 Vials with powder for solution for injection**, each containing 300 microgram (9.6 million IU). After reconstitution, 1 ml contains 250 microgram (8.0 million IU) interferon beta-1b*.
- II. 3 Pre-filled syringes with solvent for reconstitution**, each containing 1.2 ml sodium chloride solution, 5.4 mg/ml.
- III. 3 Vial adapters with needles + 6 alcohol wipes**

*Betaferon is formulated to contain a calculated overfill of 20 %.

5. METHOD AND ROUTE OF ADMINISTRATION

For subcutaneous injection after reconstitution with 1.2 ml of solvent.
Single use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

After reconstitution, immediate use is recommended. In-use stability demonstrated for 3 hours at 2-8 °C.

9. SPECIAL STORAGE CONDITIONS

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

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Bayer AG
51368 Leverkusen
Germany

12. MARKETING AUTHORISATION NUMBER

EU/1/95/003/008

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY**15. INSTRUCTIONS ON USE**

Use yellow triple pack No. 1 for treatment days 1, 3 and 5
Use red triple pack No. 2 for treatment days 7, 9 and 11
Use green triple pack No. 3 for treatment days 13, 15 and 17
Use blue triple pack No. 4 for treatment days 19, 21 and 23

16. INFORMATION IN BRAILLE

Betaferon

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON OF THE TRIPLE PACK (3 VIALS/3 PFS) AS AN INTERMEDIATE PACK OF THE TITRATION PACK (WITHOUT BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

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

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 ml contains 250 microgram (8.0 million IU) interferon beta-1b when reconstituted.

3. LIST OF EXCIPIENTS

Excipients: Human albumin, mannitol

4. PHARMACEUTICAL FORM AND CONTENTS

Triple pack 1
1st dosage step (0.25 ml) for treatment days 1, 3, 5

Triple pack 2
2nd dosage step (0.5 ml) for treatment days 7, 9, 11

Triple pack 3
3rd dosage step (0.75 ml) for treatment days 13, 15, 17

Triple pack 4
4th dosage step (1.0 ml) for treatment days 19, 21, 23

Part of a titration pack. No individual sale.

3 Vials with powder: 300 microgram (9.6 m IU) per vial. When reconstituted 250 microgram/ml (8.0 m IU/ml) interferon beta-1b.

3 Pre-filled syringes with 1.2 ml solvent: sodium chloride solution, 5.4 mg/ml,

3 Vial adapters with needles + 6 alcohol wipes

5. METHOD AND ROUTE OF ADMINISTRATION

For subcutaneous injection after reconstitution with 1.2 ml of solvent.

Single use.

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

After reconstitution, immediate use is recommended. In-use stability demonstrated for 3 hours at 2-8 °C.

9. SPECIAL STORAGE CONDITIONS

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

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Bayer AG
51368 Leverkusen
Germany

12. MARKETING AUTHORISATION NUMBER

EU/1/95/003/008

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE (text for inside the lid)

Dear patient,

Triple pack 1 is designed to help you prepare the first 3 injections (days 1, 3 and 5).

Use **all** the solvent in the syringe to dissolve the Betaferon powder in the vial.

Then draw up solution **as far as the mark on the syringe:**

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

Discard the vial with the remaining solution.

Dear patient,

Triple pack 2 is designed to help you prepare the next 3 injections (days 7, 9 and 11).

Use **all** the solvent in the syringe to dissolve the Betaferon powder in the vial.

Then draw up solution **as far as the mark on the syringe:**

0.5 ml for the injections at day 7, 9 and 11 of therapy.

Discard the vial with the remaining solution.

Dear patient,

Triple pack 3 is designed to help you prepare the next 3 injections (days 13, 15 and 17).

Use **all** the solvent in the syringe to dissolve the Betaferon powder in the vial.

Then draw up solution **as far as the mark on the syringe:**

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

Discard the vial with the remaining solution.

Dear patient,

Triple pack 4 is designed to help you prepare the next 3 injections (days 19, 21 and 23).

Use **all** the solvent in the syringe to dissolve the Betaferon powder in the vial.

Then draw up solution **as far as the 1.0 ml mark on the syringe:**

1.0 ml for the injections at day 19, 21 and 23 of therapy.

Discard the vial with the remaining solution.

16. INFORMATION IN BRAILLE

Betaferon

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

LABEL OF PRE-FILLED SYRINGE (SOLVENT)

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

Solvent for reconstitution of Betaferon
1.2 ml sodium chloride solution 5.4 mg/ml

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1.2 ml

6. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

LABEL OF VIAL (BETAFERON)

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

Betaferon 250 microgram/ml, powder for solution for injection
interferon beta-1b Subcutaneous use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

After reconst. immediate use recommended. In-use stability demonstrated for 3 hours at 2-8 °C.

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

250 mcg (8 m IU) per ml after reconstitution

B. PACKAGE LEAFLET

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.

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:

- 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 [via the national reporting system listed in Appendix V](#). By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Betaferon

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

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

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

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

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

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

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:

België / Belgique / Belgien

Bayer SA-NV
Tél/Tel: +32-(0)2-535 63 11

България

Байер България ЕООД
Тел. +359 02 4247280

Česká republika

Bayer s.r.o.
Tel: +420 266 101 111

Danmark

Bayer A/S
Tlf: +45-45 23 50 00

Deutschland

Bayer Vital GmbH
Tel: +49-(0)214-30 513 48

Eesti

Bayer OÜ
Tel: +372 655 85 65

Ελλάδα

Bayer Ελλάς ΑΒΕΕ
Τηλ:+30 210 618 75 00

España

Bayer Hispania S.L.
Tel: +34-93-495 65 00

France

Bayer HealthCare
Tél (N° vert): +33-(0)800 87 54 54

Hrvatska

Bayer d.o.o.
Tel: +385-(0)1-6599 900

Ireland

Bayer Limited
Tel: +353 1 299 93 13

Ísland

Icepharma hf.
Sími: +354 540 80 00

Italia

Bayer S.p.A.
Tel: +39-02-397 81

Κύπρος

NOVAGEM Limited
Τηλ: +357 22 48 38 58

Latvija

SIA Bayer
Tel: +371 67 84 55 63

Lietuva

UAB Bayer
Tel. +370 5 23 36 868

Luxembourg / Luxemburg

Bayer SA-NV
Tél/Tel: +32-(0)2-535 63 11

Magyarország

Bayer Hungária Kft.
Tel.:+36-14 87-41 00

Malta

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

Nederland

Bayer B.V.
Tel: +31-(0)297-28 06 66

Norge

Bayer AS
Tlf. +47 23 13 05 00

Österreich

Bayer Austria Ges. m. b. H.
Tel: +43-(0)1-711 46-0

Polska

Bayer Sp. z o.o.
Tel.: +48-22-572 35 00

Portugal

Bayer Portugal, Lda.
Tel: +351-21-416 42 00

România

SC Bayer SRL
Tel: +40 21 528 59 00

Slovenija

Bayer d. o. o.
Tel.: +386-(0)1-58 14 400

Slovenská republika

Bayer, spol. s r.o.
Tel: +421 2 59 21 31 11

Suomi/Finland

Bayer Oy
Puh/Tel: +358-20 785 21

Sverige

Bayer AB
Tel: +46-(0)8-580 223 00

United Kingdom

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

This leaflet was last revised in

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



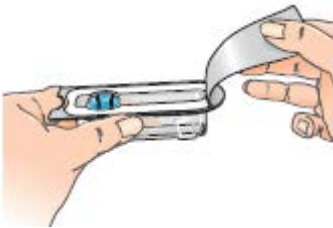
1 - Wash your hands thoroughly with soap and water before beginning this process.



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.



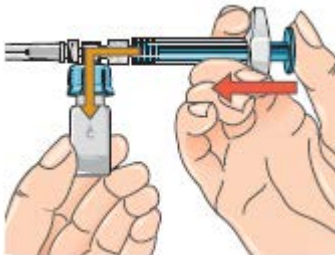
7 - Remove the blister pack from the vial adapter, holding the blister edges. Now you are ready to attach the pre-filled solvent syringe to the vial adapter.



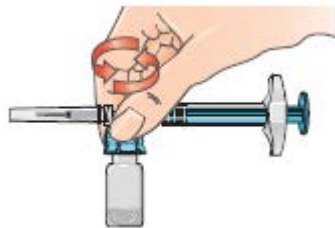
8 - Pick up the syringe. Be sure that the orange tip cap is firmly attached to the solvent syringe!
Remove the tip cap by twisting it off. Throw away the tip cap.



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.



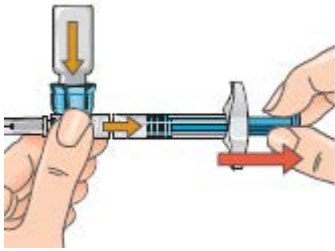
11 - With the syringe assembly still attached, swirl the vial around gently to completely dissolve the dry Betaferon powder.

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.**

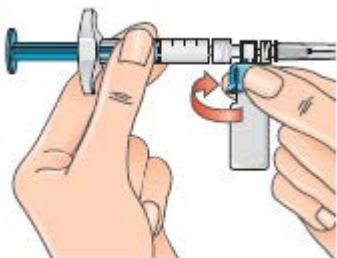


14 - After drawing up the solution turn the syringe assembly so that the needle is pointing up. This allows any air bubbles to rise to the top of the solution.

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.

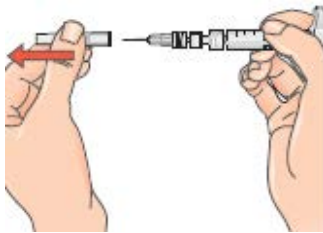
If, for some reason, you are not able to inject the Betaferon immediately, you can keep the reconstituted solution in the syringe in a refrigerator for up to 3 hours before using. Do not freeze the solution, and do not wait longer than 3 hours to inject it. If more than 3 hours pass, discard the reconstituted 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.

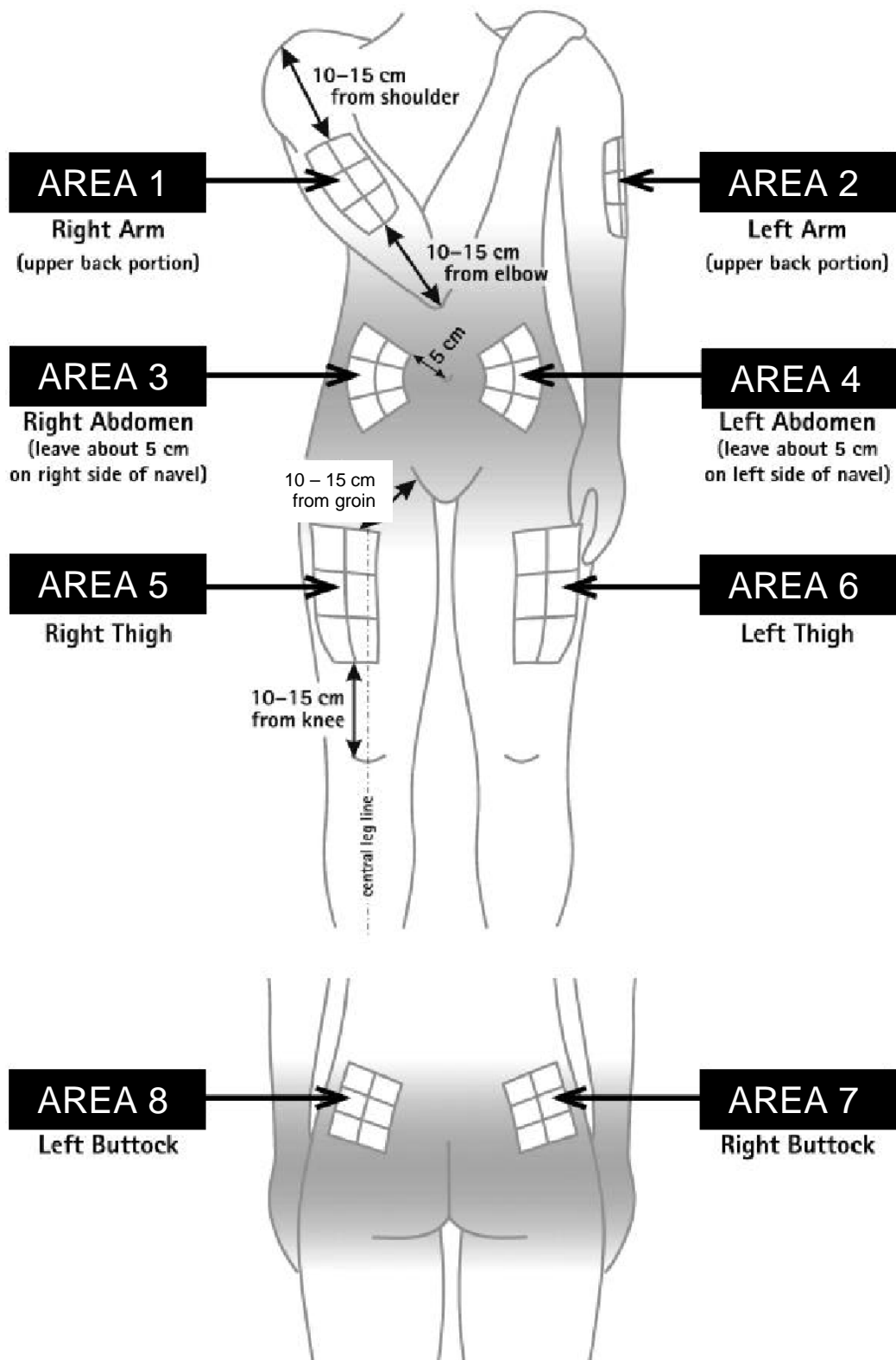
Rotation Schedule:

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

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	

Measurements: 10-15 cm from shoulder, 10-15 cm from elbow, 5 cm, 10-15 cm from groin, 10-15 cm from knee, central leg line.

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.