

## 1. NAME OF THE MEDICINAL PRODUCT

BETAFERON®

## 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 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

- Use in ambulatory patients with relapsing-remitting multiple sclerosis (RRMS) and relapsing progressive M.S. to reduce the frequency of clinical exacerbations.
- Treatment of secondary progressive (SP) form of multiple sclerosis.
- Treatment of patients who have experienced 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, including the presence of MRI abnormalities characteristic of M.S. and if they are determined to be at high risk of developing clinically definite multiple sclerosis.

### 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

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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.

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**

- Initiation of treatment in pregnancy (see section 4.6).
- 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

### 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  $\gamma$ -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) and Haemolytic anaemia (HA)

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. 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. Additionally, cases of HA not associated with TMA, including immune HA, have been reported with interferon beta products. Life-threatening and fatal cases have been reported. Cases of TMA and/or HA have been reported at various time points during treatment and may occur several weeks to several years after starting treatment with interferon beta.

If TMA and/or HA is diagnosed and a relationship to Betaferon is suspected, prompt treatment is required (in case of TMA 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 Pregnancy and breast-feeding**

Pregnancy

There is limited information on the use of Betaferon in pregnancy. Available data indicate that there may be an increased risk of spontaneous abortion. Initiation of treatment is contraindicated during pregnancy (see section 4.3).

Women of child-bearing potential

Women of child-bearing potential should take appropriate contraceptive measures. If the patient becomes pregnant or plans to become pregnant while using Betaferon, she should be informed of the potential hazards and discontinuation of therapy should be considered (see section 5.3). In patients with a high relapse rate before initiation of treatment, the risk of a severe relapse following discontinuation of Betaferon in the event of pregnancy should be weighed against a possible increased risk of spontaneous abortion.

Breast-feeding

It is not known whether interferon beta-1b is excreted in human milk. Because of the potential for serious adverse reactions in nursing infants a decision should be made on whether to discontinue breast-feeding or discontinue Betaferon therapy.

#### **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.

The most serious adverse reactions reported include thrombotic microangiopathy (TMA) and haemolytic anaemia (HA).

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)
<b>Infections and infestations</b>				
Infection	6% (3%)	13% (11%)	11% (10%)	14% (13%)
Abscess	0% (1%)	4% (2%)	4% (5%)	1% (6%)
<b>Blood and lymphatic system disorders</b>				
Lymphocyte count decreased ( $< 1,500/\text{mm}^3$ ) <sup>×</sup> <sup>△ °</sup>	79% (45%)	53% (28%)	88% (68%)	82% (67%)
Absolute neutrophil count decreased ( $< 1,500/\text{mm}^3$ ) <sup>×</sup> <sup>△ * °</sup>	11% (2%)	18% (5%)	4% (10%)	18% (5%)
White blood cell count decreased ( $< 3,000/\text{mm}^3$ ) <sup>×</sup> <sup>△ * °</sup>	11% (2%)	13% (4%)	13% (4%)	16% (4%)
Lymphadenopathy	1% (1%)	3% (1%)	11% (5%)	14% (11%)
<b>Metabolism and nutrition disorders</b>				
Blood glucose decreased ( $< 55 \text{ mg/dl}$ ) <sup>×</sup>	3% (5%)	27% (27%)	5% (3%)	15% (13%)
<b>Psychiatric disorders</b>				
Depression	10% (11%)	24% (31%)	44% (41%)	25% (24%)
Anxiety	3% (5%)	6% (5%)	10% (11%)	15% (13%)
<b>Nervous system disorders</b>				
Headache <sup>△</sup>	27% (17%)	47% (41%)	55% (46%)	84% (77%)
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%)
<b>Eye disorders</b>				

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)
Conjunctivitis	1% (1%)	2% (3%)	6% (6%)	12% (10%)
Abnormal vision <sup>^</sup>	3% (1%)	11% (15%)	11% (11%)	7% (4%)
<b>Ear and labyrinth disorders</b>				
Ear pain	0% (1%)	<1% (1%)	6% (8%)	16% (15%)
<b>Cardiac disorders</b>				
Palpitation *	1% (1%)	2% (3%)	5% (2%)	8% (2%)
<b>Vascular disorders</b>				
Vasodilatation	0% (0%)	6% (4%)	13% (8%)	18% (17%)
Hypertension <sup>o</sup>	2% (0%)	4% (2%)	9% (8%)	7% (2%)
<b>Respiratory, thoracic and mediastinal disorders</b>				
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%)
<b>Gastrointestinal disorders</b>				
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 <sup>^</sup>	5% (1%)	4% (6%)	10% (12%)	21% (19%)
Abdominal pain <sup>o</sup>	5% (3%)	11% (6%)	18% (16%)	32% (24%)
<b>Hepatobiliary disorders</b>				
Alanine aminotransferase increased (SGPT> 5 times baseline) <sup>x ^ * o</sup>	18% (5%)	14% (5%)	4% (2%)	19% (6%)
Aspartate aminotransferase increased (SGOT > 5 times baseline) <sup>x ^ * o</sup>	6% (1%)	4% (1%)	2% (1%)	4% (0%)
<b>Skin and subcutaneous tissue disorders</b>				
Skin disorder	1% (0%)	4% (4%)	19% (17%)	6% (8%)
Rash <sup>^ o</sup>	11% (3%)	20% (12%)	26% (20%)	27% (32%)
<b>Musculoskeletal and connective tissue disorders</b>				
Hypertonia <sup>o</sup>	2% (1%)	41% (31%)	57% (57%)	26% (24%)
Myalgia * <sup>o</sup>	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%)
<b>Renal and urinary disorders</b>				
Urinary retention	1% (1%)	4% (6%)	15% (13%)	
Urinary protein positive (> 1+) <sup>x</sup>	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%)
<b>Reproductive system and breast disorders</b>				
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%)

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)
Impotence	1% (0%)	7% (4%)	10% (11%)	2% (1%)
<b>General disorders and administration site conditions</b>				
Injection site reaction (various kinds) <sup>^ * ° §</sup>	52% (11%)	78% (20%)	89% (37%)	85% (37%)
Injection site necrosis <sup>* °</sup>	1% (0%)	5% (0%)	6% (0%)	5% (0%)
Flu-like symptoms <sup>&amp; ^ * °</sup>	44% (18%)	61% (40%)	43% (33%)	52% (48%)
Fever <sup>^ * °</sup>	13% (5%)	40% (13%)	29% (24%)	59% (41%)
Pain	4% (4%)	31% (25%)	59% (59%)	52% (48%)
Chest pain <sup>°</sup>	1% (0%)	5% (4%)	15% (8%)	15% (15%)
Peripheral oedema	0% (0%)	7% (7%)	21% (18%)	7% (8%)
Asthenia <sup>*</sup>	22% (17%)	63% (58%)	64% (58%)	49% (35%)
Chills <sup>^ * °</sup>	5% (1%)	23% (7%)	22% (12%)	46% (19%)
Sweating <sup>*</sup>	2% (1%)	6% (6%)	10% (10%)	23% (11%)
Malaise <sup>*</sup>	0% (1%)	8% (5%)	6% (2%)	15% (3%)
<sup>x</sup> Laboratory abnormality <sup>^</sup> Significantly associated with Betaferon treatment for patients with first event suggestive of MS, p < 0.05 <sup>*</sup> Significantly associated with Betaferon treatment for RRMS, p < 0.05 <sup>°</sup> Significantly associated with Betaferon treatment for SPMS, p < 0.05 <sup>§</sup> 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 <sup>&amp;</sup> "Flu-like symptom complex" denotes flu syndrome and/or a combination of at least two AEs from fever, chills, myalgia, malaise, sweating. <sup>#</sup> During the BENEFIT follow-up study, no change in the known risk profile of Betaferon was observed.				

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 (≥ 1/10) <sup>1</sup>	Common (≥ 1/100 to < 1/10) <sup>1</sup>	Uncommon (≥ 1/1,000 to < 1/100) <sup>1</sup>	Rare (≥ 1/10,000 to < 1/1,000) <sup>1</sup>	Frequency not known
Blood and lymphatic system disorders		Anaemia	Thrombocytopenia	Thrombotic microangiopathy <sup>5</sup> including thrombotic thrombocytopenic purpura/ haemolytic uraemic syndrome <sup>3</sup>	Haemolytic anaemia <sup>2, 5</sup>

System Organ Class	Very common ( $\geq 1/10$ ) <sup>1</sup>	Common ( $\geq 1/100$ to $< 1/10$ ) <sup>1</sup>	Uncommon ( $\geq 1/1,000$ to $< 1/100$ ) <sup>1</sup>	Rare ( $\geq 1/10,000$ to $< 1/1,000$ ) <sup>1</sup>	Frequency not known
Immune system disorders				Anaphylactic reactions	Capillary leak syndrome in pre-existing monoclonal gammopathy <sup>2</sup>
Endocrine disorders		Hypothyroidism		Hyperthyroidism, Thyroid disorders	
Metabolism and nutrition disorders		Weight increased, Weight decreased	Blood triglycerides increased	Anorexia <sup>2</sup>	
Psychiatric disorders		Confusional state	Suicide attempt (see also section 4.4), Emotional lability		
Nervous system disorders			Convulsion		
Cardiac disorders		Tachycardia		Cardiomyopathy <sup>2</sup>	
Respiratory, thoracic and mediastinal disorders				Bronchospasm <sup>2</sup>	Pulmonary arterial hypertension <sup>4</sup>
Gastrointestinal disorders				Pancreatitis	
Hepatobiliary disorders		Blood bilirubin increased	Gamma-glutamyl-transferase increased, Hepatitis	Hepatic injury (including hepatitis), Hepatic failure <sup>2</sup>	
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) <sup>2,3</sup>		
Reproductive system and breast disorders		Menorrhagia			

<sup>1</sup> 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  $< 1/10,000$ ).

<sup>2</sup> ADRs derived only during post-marketing

<sup>3</sup> Class label for interferon beta products (see section 4.4).

<sup>4</sup> Class label for interferon products, see below Pulmonary arterial hypertension.

<sup>5</sup> life-threatening and/or fatal cases have been reported.

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.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form:

<https://sideeffects.health.gov.il/>

## **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  $\geq 6$  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	Placebo	Imme- diate Betaferon 250 mcg	Delayed Betaferon 250 mcg	Imme- diate Betaferon 250 mcg	Delayed Betaferon 250 mcg

	n=292	n=176	n=292	n=176	n=292	n=176
Number of patients completed the trial phase	271 (93%)	166 (94%)	249 (85%)	143 (81%)	235 (80%)	123 (70%)
<b>Primary efficacy variables</b>						
<b>Time to CDMS</b>						
<b>Kaplan-Meier estimates</b>	28%	45%	37%	51%	46%	57%
<b>Risk reduction</b>	47% versus placebo		41% versus delayed Betaferon		37% versus delayed Betaferon	
<b>Hazard ratio with 95% confidence interval</b>	HR = 0.53 [0.39, 0.73]		HR = 0.59 [0.42, 0.83]		HR = 0.63 [0.48, 0.83]	
<b>log-rank test</b>	p < 0.0001		p = 0.0011		p = 0.0027	
Betaferon prolonged the time to CDMS by 363 days, from 255 days in the placebo group to 618 days in the Betaferon group (based on the 25th percentiles)						
<b>Time to McDonald MS</b>						
<b>Kaplan-Meier estimates</b>	69%	85%	No primary endpoint		No primary endpoint	
<b>Risk reduction</b>	43% versus placebo					
<b>Hazard ratio with 95% confidence interval</b>	HR = 0.57 [0.46, 0.71]					
<b>log-rank test</b>	p < 0.00001					
<b>Time to confirmed EDSS progression</b>						
<b>Kaplan-Meier estimates</b>	No primary endpoint		16%	24%	25%	29%
<b>Risk reduction</b>			40% versus delayed Betaferon		24% versus delayed Betaferon	
<b>Hazard ratio with 95% confidence interval</b>			HR = 0.60 [0.39, 0.92]		HR = 0.76 [0.52, 1.11]	
<b>log-rank test</b>			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 ml·min<sup>-1</sup>·kg<sup>-1</sup> and 5 hours, respectively.

Betaferon injections given every other day do not lead to serum level increases, and the pharmacokinetics do 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**

The expiry date of the product is indicated on the packaging materials.

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**

Store below 30°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 12 or 15 single packs, each containing 1 vial with powder, 1 pre-filled syringe with solvent, 1 vial adapter with needle, 2 alcohol wipes.

Not all pack sizes may be marketed.

### **6.6 Special precautions for disposal and other handling of the product**

Reconstitution

To reconstitute lyophilised interferon beta-1b for injection, connect the vial adapter with 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 micrograms 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.

**Manufactured by:**

Bayer AG, Müllerstrasse 178, Berlin, Germany

**Registration Holder:**

Bayer Israel Ltd, 36 Hacharash St., Hod Hasharon 45240

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