PRODUCT INFORMATION

BETAFERON® Single use pack (AUST R 83309)

NAME OF THE MEDICINE

BETAFERON is interferon beta-1b (rbe), 8 million IU (0.25 mg).
CAS registry no: 145155-23-3

DESCRIPTION

1 mL of the reconstituted solution for injection contains 8 million IU (0.25 mg) of interferon beta-1b. 1 mL of solution for injection contains 5.4 mg sodium chloride.

Interferon beta-1b is a purified, sterile lyophilised protein that has 165 amino acids and an approximate molecular weight of 18,500 daltons. It is produced by recombinant DNA techniques from a strain of *Escherichia coli* that bears a genetically engineered plasmid containing a modified human interferon beta gene.

Interferon beta-1b differs structurally from natural human interferon beta by the presence of serine instead of cysteine in position 17, lack of methionine in position 1 and absence of carbohydrate moieties.

BETAFERON is presented as a sterile lyophilised white to off-white cake or powder.

Excipients

Human albumin and mannitol.

Solvent for solution for injection: clear colourless liquid

Excipients

Sodium chloride and water for injection.

PHARMACOLOGY

Pharmacodynamics

Pharmacotherapeutic group: Cytokines, Interferons

ATC Code: L03AB08

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 generally species-restricted and therefore, the most pertinent pharmacologic information on interferon beta-1b is derived from studies of human cells in culture or in human *in vivo* studies.

BETAFERON has been shown to possess both antiviral and immunoregulatory activities. The mechanisms by which interferon beta-1b exerts its actions in multiple sclerosis (MS) are not clearly understood. However, it is known that the biological response-modifying properties of interferon beta-1b are mediated through its interaction 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.

**Pharmacokinetics**

Because serum concentrations of interferon beta-1b are low or not detectable following subcutaneous administration of 8 million IU (0.25 mg) or less of interferon beta-1b, pharmacokinetic information in patients with MS receiving the recommended dose of interferon beta-1b is not available.

**Absorption**

Following single and multiple daily subcutaneous administration of 16 million IU (0.5 mg) interferon beta-1b to healthy volunteers, interferon beta-1b concentrations in serum were generally below 100 IU/mL. Peak serum interferon beta-1b concentrations occurred between 1 to 8 hours, with a mean peak interferon concentration in serum of 40 IU/mL. Bioavailability, based on a total dose of 16 million IU (0.5 mg) interferon beta-1b given as two subcutaneous injections at different sites, was approximately 50%.

After intravenous administration of interferon beta-1b in a dosage range of 0.2 million IU (0.0006 mg) to 64 million IU (2.0 mg), similar pharmacokinetic profiles were obtained from healthy volunteers and from patients with diseases other than MS. In patients receiving single intravenous doses of up to 64 million IU (2.0 mg), increases in serum concentrations were dose proportional. Mean serum clearance values of up to 28.9 mL/min.kg\(^{-1}\) were observed.

**Elimination**

Mean terminal elimination half-life and steady-state volume of distribution were estimated to be at most 4.3 hours and 2.88 L/kg. Three-times-a-week intravenous dosing for 2 weeks resulted in no accumulation of interferon beta-1b in the serum of patients. Pharmacokinetic parameters after single and multiple intravenous doses of interferon beta-1b were comparable.

Following every other day subcutaneous administration of 0.25 mg (8 million IU) of interferon beta-1b in healthy volunteers, biologic response marker levels (neopterin, \(\beta_2\)-microglobulin and the immunosuppressive cytokine, IL-10) increased significantly above baseline levels within 6 to 12 hours after the first BETAFERON dose. Biologic response marker levels peaked between 40 and 124 hours, and remained above baseline throughout the seven day (168 hour) study period. The relationship between serum interferon beta–1b levels or the levels of induced biologic response markers to the mechanism by which BETAFERON exerts its effects in MS is unknown.
CLINICAL TRIALS

Relapsing-remitting multiple sclerosis

BETAFFERON was shown to reduce the frequency and severity of clinical relapses, to reduce the number of MS related hospitalisations and steroid usage and to prolong the exacerbation-free time in patients with both relapsing-remitting multiple sclerosis (EDSS 0 - 5.5) and secondary progressive multiple sclerosis (EDSS 3.0 – 6.5).

Furthermore, BETAFFERON has a significant beneficial effect on disease burden and activity as measured by magnetic resonance imaging (MRI); an increase in MRI disease burden has been demonstrated to correlate with an increase in disability as measured by expanded disability status scale (EDSS).

Secondary progressive multiple sclerosis

Patients with secondary progressive disease receiving BETAFFERON showed a delay of up to 12 months in time to progression of disability including time to severely disabling stages, i.e. patients becoming wheelchair bound. This delay in disability occurred in patients with or without relapses and at all levels of disability investigated (EDSS 3 - 6.5).

Single clinical event suggestive of multiple sclerosis

One multi-centred, randomised, placebo-controlled, double-blind, clinical efficacy and safety study (BENEFIT) was performed in patients with a single clinical demyelinating event suggestive of MS and at least two clinically silent magnetic resonance imaging (MRI) lesions characteristic of MS. The study enrolled patients within 60 days after the onset of a single clinical event suggestive of MS, based on the appearance of a new neurological abnormality which had to be present for at least 24 hours. The T2-weighted brain MRI scan had to show at least two clinically silent lesions with a size of at least 3 mm, at least one of which had to be ovoid or periventricular or infratentorial. Patients were aged 18 to 45 years with an EDSS of < 5.0. Patients with monofocal or multifocal onset of the disease were included (i.e. patients with clinical evidence of a single or at least two lesions, respectively, of the central nervous system). Patients with any disease other than multiple sclerosis that could better explain the signs and symptoms 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 BETAFFERON to evaluate the effects of immediate versus delayed start of BETAFFERON-treatment, comparing patients initially randomised to BETAFFERON (“immediate treatment group”) or to placebo (“delayed treatment group”). Patients and investigators remained blinded to the initial treatment allocation.

The two primary efficacy variables were time to onset of clinically definite MS (CDMS), and time to onset of MS according to McDonald diagnostic criteria. Clinically definite MS was reached if the patient experienced a relapse of the disease, or a sustained progression of ≥ 1.5 points on the EDSS scale as compared to the lowest EDSS obtained during the screening on day 1 reaching a total EDSS
score of ≥ 2.5. Multiple sclerosis according to the McDonald criteria was reached if, in addition to the single clinical demyelinating event, both dissemination in space and dissemination in time had been established.

Patients selected for the study were randomized to treatment with either 0.25 mg (8 million IU) BETAFERON (n=292) or placebo (n=176) self-administered subcutaneously every second day for a treatment duration of up to 2 years.

In the placebo-controlled phase, BETAFERON delayed the progression from the first clinical event to CDMS in a statistically significant and clinically meaningful manner compared with placebo, corresponding to a risk reduction of 47% (hazard ratio = 0.53; 95% confidence interval [0.39, 0.73], p<0.0001). A post-hoc analysis adjusting for standard baseline covariates revealed a risk reduction by 50%. Within two years, CDMS occurred in 45% of the placebo group compared to 28% of the BETAFERON group (Kaplan-Meier estimates). 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 25th percentiles).

BETAFERON also statistically significantly delayed the progression to MS according to the McDonald criteria compared with placebo, corresponding to a risk reduction of 43% (hazard ratio = 0.57; 95% confidence interval [0.46, 0.71], p<0.00001). In the first six months, a diagnosis of MS according to the McDonald criteria was made in 51% of placebo and 28% of BETAFERON patients, and after two years, the respective incidences were 85% and 69% (Kaplan-Meier estimates).

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 randomised to BETAFERON (“immediate treatment group”) or to placebo (“delayed treatment group”). Patients and investigators remained blinded to the initial treatment allocation. The two analyses at three and five years include integrated data of the placebo-controlled and the follow-up phase for the first three years and the entire five year observation period, respectively.

Immediate BETAFERON-treatment delayed the progression from the first clinical event to CDMS in a statistically significant and clinically meaningful manner. At three years, the risk for CDMS was 51% in the delayed treatment group compared to 37% in the immediate treatment group (log rank p = 0.0011). At the end of the five year observation period, the risk for CDMS was 57% in the delayed treatment group and 46% in the immediate treatment group (log rank p = 0.0027) (Kaplan-Meier estimates – see Figure 1). The majority of patients from the original placebo-group were treated with BETAFERON from the end of the second year.
At three years the risk (Kaplan-Meier estimates – see Figure 2) for disability progression (as measured by EDSS progression) was 24% in the delayed treatment group and 16% in the immediate treatment group (log rank p = 0.0218). Over five years the risk (Kaplan-Meier estimates) for disability progression was not statistically significantly different (log rank p = 0.177) between delayed (29%) and immediate (25%) treatment groups.
Two MRI-derived parameters, the cumulative number of newly active lesions and the change in T2 lesion volume, were analysed as secondary efficacy variables. The cumulative number of newly active lesions up to end of study was statistically significantly lower in the BETAFERON group when non-annualised (median number of newly active lesions was 4.0 for BETAFERON and 7.0 for placebo) values were considered ($p = 0.00602$). The T2 lesion volume reduction up to the last scan was not statistically significantly different between the groups.

In a questionnaire assessing health-related quality of life as reported by the patient (Functional Assessment of MS), scores remained high and stable throughout the five years, significant differences between the two treatment groups could not be demonstrated.

**INDICATIONS**

BETAFERON is indicated for

- the treatment of patients with a single clinical event suggestive of multiple sclerosis and at least two clinically silent magnetic resonance imaging (MRI) lesions characteristic of multiple sclerosis, if alternative diagnoses have been excluded,

- the treatment of ambulatory patients with relapsing-remitting multiple sclerosis (MS) characterised by at least two attacks of neurologic dysfunction over a two year period followed by complete or incomplete recovery,

- the reduction of frequency and severity of clinical relapses, and for the slowing of progression of disease in patients with secondary progressive multiple sclerosis.

**CONTRAINDICATIONS**

BETAFERON is contraindicated in patients with a history of hypersensitivity to natural or recombinant interferon beta or to any of the excipients.

**PRECAUTIONS**

**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.

Serious hypersensitivity reactions (rare but severe acute reactions such as bronchospasm, anaphylaxis, urticaria) may occur. If reactions are severe, interferon beta-1b should be discontinued and appropriate medical intervention instituted. Other moderate to severe adverse experiences may require modifications of the interferon beta-1b dosage regimen or even discontinuation of the agent.

**Gastrointestinal disorders**

In rare cases, pancreatitis was observed with BETAFERON use, often associated with hypertriglyceridaemia.
Depression and suicide

Patients to be treated with interferon beta-1b should be informed that depression and suicidal ideation may be a side effect of the treatment and should report these symptoms immediately to the prescribing physician. In rare cases these symptoms may result in a suicide attempt. Patients exhibiting depression and suicidal ideation should be monitored closely and cessation of therapy should be considered.

In the study with patients with a single demyelinating event suggestive of MS and in the study with patients with secondary progressive multiple sclerosis, there were no significant differences between BETAFERON treated patients and placebo treated patients for depression and suicidal ideation. However, because it cannot be excluded that BETAFERON treatment may be associated with depression and suicides in individual patients, BETAFERON should be administered with caution to patients with previous or current depressive disorders or suicidal ideation. Cessation of BETAFERON therapy should be considered if such events develop during therapy.

Nervous System disorders

Seizures

BETAFERON should be administered with caution to patients with a history of seizures. BETAFERON should be withdrawn from patients who develop seizures while on medication until the cause of the seizure is investigated. If it is determined that BETAFERON is not the cause of the seizure, treatment can be reinitiated.

This product contains human albumin, a derivative of human blood. Based on effective product manufacturing processes, it carries an extremely remote risk for transmission of viral diseases. A theoretical risk for transmission of Creutzfeldt-Jacob Disease (CJD) is also considered extremely remote.

Haemolymphatic system

As therapy with interferons can lead to abnormal laboratory findings, it is proposed that, apart from the laboratory tests usually required for monitoring MS patients, regular checks of complete blood cell counts, with differential white blood cell counts, and platelet counts be carried out following the introduction of BETAFERON therapy, and then periodically thereafter in the absence of clinical symptoms.

Patients who develop neutropaenia should be monitored closely for the development of fever or infection.

Patients with anaemia, thrombocytopaenia, leukopaenia (alone or in combination) may require more extensive monitoring of complete blood counts, with differential and platelet counts.

Endocrine function

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

Asymptomatic elevations of serum transaminases, in most cases mild and transient, occurred very commonly in patients treated with BETAFERON during clinical trials. Rare cases of severe hepatic injury, including cases of hepatic failure have been reported.

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 co-morbid 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, including liver function tests (e.g. AST (SGOT), ALT (SGPT) and \(\gamma\)-GT), which are recommended at regular intervals following the introduction of BETAFERON therapy, and then periodically thereafter in the absence of clinical symptoms.

Withdrawal of BETAFERON should be considered if the levels significantly increase or if they are associated with clinical symptoms suggesting the development of hepatitis e.g. 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 function

In patients with renal impairment, renal function should be monitored carefully when such patients receive BETAFERON therapy.

Thrombotic microangiopathy

Cases of thrombotic microangiopathy, manifested as thrombotic thrombocytopenic purpura and haemolytic uraemic syndrome have been reported with interferon beta therapy, including fatal cases (see ADVERSE EFFECTS). Monitoring of early symptoms in all patients is recommended e.g. new onset hypertension, impaired renal function and thrombocytopenia. Prompt treatment is required and discontinuation of interferon is recommended.

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 therapies (see ADVERSE EFFECTS). 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 interferon should be considered.
**Cardiac disorders**

BETAFERON should be used with caution in patients with pre-existing significant cardiac disease such as congestive heart failure, coronary artery disease or arrhythmias. These patients should be monitored for worsening of their cardiac condition. This applies particularly during initiation of treatment with BETAFERON, where flu-like symptoms, commonly associated with beta interferons, exert cardiac stress through fever, chills and tachycardia. This may aggravate cardiac symptoms in patients with pre-existing significant cardiac disease. Such patients should be closely observed for worsening of their cardiac disease during therapy with BETAFERON.

During the post-marketing period very rare reports have been received of worsening of cardiac status in patients with pre-existing significant cardiac disease, temporally 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.

**Skin and appendages**

Injection site necrosis (ISN) has been reported in patients using BETAFERON (see ADVERSE EFFECTS). 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 their 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.

**Carcinogenesis, Mutagenesis and Impairment of Fertility**

Interferon beta-1b was inactive in a bacterial gene mutation assay, and in a short term assay for mammalian cell transformation *in vitro*. Long term *in vivo* studies for tumourigenic potential have not been carried out.
Studies in rhesus monkeys at doses up to 10.7 million IU/kg/day SC showed no effects on menstrual cycle or hormone profiles, however, there have been no animal studies investigating effects on fertility. It is not known whether BETAFERON can affect human reproductive capacity.

Preclinical Safety Data

Although acute toxicity studies have not been carried out, an experimental primate study using daily intravenous and subcutaneous administration did not reveal any untoward acute effects of treatment. This study showed a potential for interferon beta-1b treatment to elicit transient pyrogenic and haematological effects, including neutropaenia and thrombocytopaenia. Pronounced thrombocytopaenia or anaemia was seen in some pregnant experimental primates after daily treatment with high doses of interferon beta-1b (8 million IU/kg and above). The long term toxicity of interferon beta-1b has not been investigated in any experimental species.

Based on experiments using other interferons, a potential risk of impaired male and female fertility cannot be ruled out.

Specific testing for contact sensitivity was not carried out, but delayed type hypersensitivity reactions specific for interferon beta-1b were not seen in experimental primates after daily intravenous or subcutaneous administration. However, serum anti-interferon beta-1b antibodies were measurable in these animals.

Use in Pregnancy

Pregnancy Category D.

BETAFERON was not teratogenic in rhesus monkeys at doses up to 13.3 million IU/kg/day SC, but demonstrated an abortifacient activity when administered at doses ranging from 0.89 to 24 million IU/kg/day. It is not known whether interferon beta-1b can cause fetal harm when administered to a pregnant woman or can affect human reproductive capacity. Spontaneous abortions have been reported in subjects with MS in controlled clinical trials. Therefore, women of child-bearing potential should take appropriate contraceptive measures. If the patient becomes pregnant or plans to become pregnant while taking interferon beta-1b, she should be informed of the potential hazards and it should be recommended to discontinue therapy.

Use in Lactation

It is not known whether interferon beta-1b is excreted in the milk of animals or humans. Because of the potential for serious adverse reactions to interferon beta-1b in infants being breast-fed a decision should be made whether nursing or the drug should be discontinued.

Use in Children

Efficacy and safety of BETAFERON has not been investigated in children and adolescents less than 18 years of age.
Interaction with Other Medicines

No formal drug interaction studies have been carried out with BETAFERON, the effect of BETAFERON on drug metabolism in MS patients is unknown.

Corticosteroid or ACTH treatment of relapses for periods of up to 28 days has been well tolerated in patients receiving BETAFERON. However, in the clinical trials, patients receiving BETAFERON had a significantly reduced steroid usage compared with placebo patients.

Due to the lack of clinical experience in MS patient’s use of BETAFERON together with immunomodulators other than corticosteroids or ACTH is not recommended.

Interferons have been reported to cause a down regulation of hepatic cytochrome P450-dependent enzymes in humans and animals. Caution should be exercised when BETAFERON is administered in combination with drugs that have a narrow therapeutic index and are largely dependent on the hepatic cytochrome P450 system for clearance. Caution should be exercised with any co-medication which has an effect on the haematopoetic system.

Influence on Laboratory Tests

At the recommended dose, leukopaenia (lymphopaenia, neutropaenia), thrombocytopaenia, anaemia or elevated SGPT, SGOT, γ-GT may be seen.

ADVERSE EFFECTS

Experience with interferon beta-1b in patients with MS is limited, consequently adverse events with low incidence may not yet have been observed. Table 1 below lists the adverse experiences reported at an incidence of ≥ 2% by 124 relapsing remitting MS patients receiving 8 million IU of BETAFERON in multicentre clinical trials conducted in the United States and Canada. The adverse events reported in the secondary progressive study (360 patients) were consistent with the known side effect profile; the most frequently reported adverse events reported in this study are shown in Table 2 below.

Injection site reactions occurred frequently after administration of BETAFERON. Redness, swelling, discoloration, inflammation, pain, hypersensitivity, necrosis, and non-specific reactions were significantly associated with 8 million IU BETAFERON treatment. Lymphadenopathy has also been reported. The incidence rate of injection site reactions usually decreased over time.

Flu-like symptom complex (fever, chills, arthralgia, headache or myalgia, malaise, or sweating) has been seen frequently. The incidence rate of the symptoms decreased over time. Generally, dose titration is recommended at the start of treatment (see DOSAGE AND ADMINISTRATION). Flu like symptoms may also be reduced by administration of non steroidal anti-inflammatory drugs.

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.
Serum Neutralising Antibodies

As with all therapeutic proteins, there is a potential for immunogenicity. Serum samples in controlled clinical trials were collected every 3 months (in the study of patients with a single clinical event suggestive of MS every 6 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 titers; of these patients, between 43% to 55% converted to a stable antibody negative status (based on two consecutive negative titers) during the subsequent observational period of the respective study.

No consistent attenuating effects on clinical outcomes, have been demonstrated related to the presence of neutralising antibodies, across studies, endpoints, different statistical approaches and varying definitions of neutralising antibody positive status. Adverse events have not been associated with the development 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 five year period. Within the study period of five years, the development of neutralising activity was not 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.

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.

Table 1: Adverse Reactions and Laboratory Abnormalities Reported in Multicentre Trials (United States & Canada) in relapsing remitting patients

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Placebo n = 123</th>
<th>INFB-1b 0.25 mg (8 million IU) n = 124</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Body as a Whole</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Injection site reaction *</td>
<td>37%</td>
<td>85%</td>
</tr>
<tr>
<td>Headache</td>
<td>77%</td>
<td>84%</td>
</tr>
<tr>
<td>Fever *</td>
<td>41%</td>
<td>59%</td>
</tr>
<tr>
<td>Flu-like symptom complex *</td>
<td>56%</td>
<td>76%</td>
</tr>
<tr>
<td>Pain</td>
<td>48%</td>
<td>52%</td>
</tr>
<tr>
<td>Asthaenia *</td>
<td>35%</td>
<td>49%</td>
</tr>
<tr>
<td>Chills *</td>
<td>19%</td>
<td>46%</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>24%</td>
<td>32%</td>
</tr>
<tr>
<td>Malaise *</td>
<td>3%</td>
<td>15%</td>
</tr>
<tr>
<td>Generalised oedema</td>
<td>6%</td>
<td>8%</td>
</tr>
<tr>
<td>Pelvic pain</td>
<td>3%</td>
<td>6%</td>
</tr>
<tr>
<td>Injection site necrosis *</td>
<td>0%</td>
<td>5%</td>
</tr>
<tr>
<td>Cyst</td>
<td>2%</td>
<td>4%</td>
</tr>
<tr>
<td>Necrosis</td>
<td>0%</td>
<td>2%</td>
</tr>
<tr>
<td>Suicide attempt</td>
<td>0%</td>
<td>2%</td>
</tr>
<tr>
<td>Adverse Reaction</td>
<td>Placebo n = 123</td>
<td>INFB-1b 0.25 mg (8 million IU) n = 124</td>
</tr>
<tr>
<td>-------------------------------------------------------</td>
<td>------------------</td>
<td>----------------------------------------</td>
</tr>
<tr>
<td><strong>Cardiovascular System</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Migraine</td>
<td>7%</td>
<td>12%</td>
</tr>
<tr>
<td>Palpitation *</td>
<td>2%</td>
<td>8%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2%</td>
<td>7%</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>3%</td>
<td>6%</td>
</tr>
<tr>
<td>Peripheral vascular disorder</td>
<td>2%</td>
<td>5%</td>
</tr>
<tr>
<td>Haemorrhage</td>
<td>1%</td>
<td>3%</td>
</tr>
<tr>
<td><strong>Digestive System</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>29%</td>
<td>35%</td>
</tr>
<tr>
<td>Constipation</td>
<td>18%</td>
<td>24%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>19%</td>
<td>21%</td>
</tr>
<tr>
<td>Gastrointestinal disorder</td>
<td>3%</td>
<td>6%</td>
</tr>
<tr>
<td><strong>Endocrine System</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Goiter</td>
<td>0%</td>
<td>2%</td>
</tr>
<tr>
<td><strong>Haematological and Lymphatic System</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymphocytes less than 1500/mm³ *</td>
<td>67%</td>
<td>82%</td>
</tr>
<tr>
<td>ANC &lt; 1500/mm³ *</td>
<td>6%</td>
<td>18%</td>
</tr>
<tr>
<td>WBC &lt; 3000/mm³ *</td>
<td>5%</td>
<td>16%</td>
</tr>
<tr>
<td>Lymphadenopathy</td>
<td>11%</td>
<td>14%</td>
</tr>
<tr>
<td><strong>Metabolic and Nutritional Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SGPT &gt; 5 times baseline *</td>
<td>6%</td>
<td>19%</td>
</tr>
<tr>
<td>Glucose &lt; 55 mg/dL</td>
<td>13%</td>
<td>15%</td>
</tr>
<tr>
<td>Total bilirubin &gt; 2.5 times baseline</td>
<td>2%</td>
<td>6%</td>
</tr>
<tr>
<td>Urine protein &gt; 1+</td>
<td>3%</td>
<td>5%</td>
</tr>
<tr>
<td>SGOT &gt; 5 times baseline *</td>
<td>0%</td>
<td>4%</td>
</tr>
<tr>
<td>Weight gain</td>
<td>0%</td>
<td>4%</td>
</tr>
<tr>
<td>Weight loss</td>
<td>2%</td>
<td>4%</td>
</tr>
<tr>
<td><strong>Musculoskeletal System</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myalgia *</td>
<td>28%</td>
<td>44%</td>
</tr>
<tr>
<td>Myasthenia</td>
<td>10%</td>
<td>13%</td>
</tr>
<tr>
<td><strong>Nervous System</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>28%</td>
<td>35%</td>
</tr>
<tr>
<td>Hypertonia</td>
<td>24%</td>
<td>26%</td>
</tr>
<tr>
<td>Anxiety</td>
<td>13%</td>
<td>15%</td>
</tr>
<tr>
<td>Nervousness</td>
<td>5%</td>
<td>8%</td>
</tr>
<tr>
<td>Somnolence</td>
<td>3%</td>
<td>6%</td>
</tr>
<tr>
<td>Confusion</td>
<td>2%</td>
<td>4%</td>
</tr>
<tr>
<td>Speech disorder</td>
<td>1%</td>
<td>3%</td>
</tr>
<tr>
<td>Convulsion</td>
<td>0%</td>
<td>2%</td>
</tr>
<tr>
<td>Hyperkinesia</td>
<td>0%</td>
<td>2%</td>
</tr>
<tr>
<td>Amnesia</td>
<td>0%</td>
<td>2%</td>
</tr>
<tr>
<td>Adverse Reaction</td>
<td>Placebo n = 123</td>
<td>INFB-1b 0.25 mg (8 million IU) n = 124</td>
</tr>
<tr>
<td>---------------------------</td>
<td>-----------------</td>
<td>----------------------------------------</td>
</tr>
<tr>
<td><strong>Respiratory System</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sinusitis</td>
<td>26%</td>
<td>36%</td>
</tr>
<tr>
<td>Dyspnoea *</td>
<td>2%</td>
<td>8%</td>
</tr>
<tr>
<td>Laryngitis</td>
<td>2%</td>
<td>6%</td>
</tr>
<tr>
<td><strong>Skin and Appendages</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sweating *</td>
<td>11%</td>
<td>23%</td>
</tr>
<tr>
<td>Alopecia</td>
<td>2%</td>
<td>4%</td>
</tr>
<tr>
<td><strong>Special Senses</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conjunctivitis</td>
<td>10%</td>
<td>12%</td>
</tr>
<tr>
<td>Abnormal vision</td>
<td>4%</td>
<td>7%</td>
</tr>
<tr>
<td><strong>Urogenital System</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dysmenorrhoea</td>
<td>11%</td>
<td>18%</td>
</tr>
<tr>
<td>Intermenstrual spotting *</td>
<td>8%</td>
<td>17%</td>
</tr>
<tr>
<td>Metrorrhagia</td>
<td>8%</td>
<td>15%</td>
</tr>
<tr>
<td>Cystitis</td>
<td>4%</td>
<td>8%</td>
</tr>
<tr>
<td>Breast pain</td>
<td>3%</td>
<td>7%</td>
</tr>
<tr>
<td>Menorrhagia</td>
<td>3%</td>
<td>6%</td>
</tr>
<tr>
<td>Urinary urgency</td>
<td>2%</td>
<td>4%</td>
</tr>
<tr>
<td>Fibrocystic breast</td>
<td>1%</td>
<td>3%</td>
</tr>
<tr>
<td>Breast neoplasm</td>
<td>0%</td>
<td>2%</td>
</tr>
</tbody>
</table>

* Significantly associated with interferon beta-1b treatment.

Table 2: Frequently reported adverse events in the secondary progressive study

<table>
<thead>
<tr>
<th>Adverse reaction</th>
<th>Placebo n=358</th>
<th>INFB-1b 0.25 mg (8 million IU) n=360</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Body as a whole</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asthenia</td>
<td>88.5%</td>
<td>96.4%</td>
</tr>
<tr>
<td>Flu syndrome *</td>
<td>56.4%</td>
<td>60.0%</td>
</tr>
<tr>
<td>Fever *</td>
<td>37.2%</td>
<td>59.2%</td>
</tr>
<tr>
<td>Pain</td>
<td>13.1%</td>
<td>39.4%</td>
</tr>
<tr>
<td>Back pain</td>
<td>20.7%</td>
<td>23.3%</td>
</tr>
<tr>
<td>Chills*</td>
<td>21.8%</td>
<td>23.3%</td>
</tr>
<tr>
<td><strong>Injection site</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Injection site inflammation*</td>
<td>7.3%</td>
<td>21.9%</td>
</tr>
<tr>
<td>Injection site reaction*</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Musculoskeletal system</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myasthenia</td>
<td>55.3%</td>
<td>61.9%</td>
</tr>
<tr>
<td>Myalgia*</td>
<td>37.2%</td>
<td>36.4%</td>
</tr>
<tr>
<td><strong>Nervous system</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>93.9%</td>
<td>93.6%</td>
</tr>
<tr>
<td>Neuropathy**</td>
<td>39.7%</td>
<td>45.6%</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>39.1%</td>
<td>33.3%</td>
</tr>
<tr>
<td>****</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Betaferon PI - Single Use Pack Version
<table>
<thead>
<tr>
<th>Adverse reaction</th>
<th>Placebo n=358</th>
<th>INFB-1b 0.25 mg (8 million IU) n=360</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abnormal gait</td>
<td>33.2%</td>
<td>33.6%</td>
</tr>
<tr>
<td>Muscular hypertonia*</td>
<td>27.4%</td>
<td>37.8%</td>
</tr>
<tr>
<td>Depression</td>
<td>28.8%</td>
<td>24.4%</td>
</tr>
<tr>
<td>Ataxia</td>
<td>22.1%</td>
<td>18.9%</td>
</tr>
<tr>
<td><strong>Respiratory system</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rhinitis</td>
<td>53.1%</td>
<td>50.8%</td>
</tr>
<tr>
<td><strong>Skin and appendages</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash*</td>
<td>34.1%</td>
<td>38.9%</td>
</tr>
<tr>
<td><strong>Urogenital system</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>55.9%</td>
<td>51.1%</td>
</tr>
</tbody>
</table>

*Significantly associated with IFNB-1b treatment (p < 0.05)

** "Neuropathy” was used in the study as the HARTS term for recording MS symptoms

Subject count for each individual adverse event term. Subjects who had more than one adverse event are thus counted more than once. The table does not count multiple occurrences of the same event in one patient.

Table 3: Adverse Events and Laboratory Abnormalities reported in the BENEFIT study (single clinical event suggestive of multiple sclerosis).

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Placebo n=176</th>
<th>BETAFERON n=292</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections and infestations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infection</td>
<td>3%</td>
<td>6%</td>
</tr>
<tr>
<td>Abscess</td>
<td>1%</td>
<td>0%</td>
</tr>
<tr>
<td><strong>Blood and lymphatic system disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymphocyte count decreased (&lt;1500/mm³)</td>
<td>45%</td>
<td>79%</td>
</tr>
<tr>
<td>Absolute neutrophil count decreased (&lt;1500/mm³)</td>
<td>2%</td>
<td>11%</td>
</tr>
<tr>
<td>White blood cell count decreased (&lt;3000/mm³)</td>
<td>2%</td>
<td>11%</td>
</tr>
<tr>
<td>Lymphadenopathy</td>
<td>1%</td>
<td>1%</td>
</tr>
<tr>
<td><strong>Metabolism and nutrition disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood glucose decreased (&lt;55 mg/dL)</td>
<td>5%</td>
<td>3%</td>
</tr>
<tr>
<td><strong>Psychiatric disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td>11%</td>
<td>10%</td>
</tr>
<tr>
<td>Anxiety</td>
<td>5%</td>
<td>3%</td>
</tr>
<tr>
<td><strong>Nervous system disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>17%</td>
<td>27%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>4%</td>
<td>3%</td>
</tr>
<tr>
<td>Insomnia</td>
<td>4%</td>
<td>8%</td>
</tr>
<tr>
<td>Migraine</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>17%</td>
<td>16%</td>
</tr>
<tr>
<td><strong>Eye disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conjunctivitis</td>
<td>1%</td>
<td>1%</td>
</tr>
<tr>
<td>Abnormal vision ^</td>
<td>1%</td>
<td>3%</td>
</tr>
<tr>
<td><strong>Ear and labyrinth disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ear pain</td>
<td>1%</td>
<td>0%</td>
</tr>
<tr>
<td>Medical Condition</td>
<td>Incidence 1</td>
<td>Incidence 2</td>
</tr>
<tr>
<td>--------------------------------------------------------</td>
<td>-------------</td>
<td>-------------</td>
</tr>
<tr>
<td><strong>Cardiac disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Palpitation</td>
<td>1%</td>
<td>1%</td>
</tr>
<tr>
<td><strong>Vascular disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vasodilatation</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0%</td>
<td>2%</td>
</tr>
<tr>
<td><strong>Respiratory, thoracic and mediastinal disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper respiratory infection</td>
<td>19%</td>
<td>18%</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>6%</td>
<td>4%</td>
</tr>
<tr>
<td>Cough increased</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>2%</td>
<td>4%</td>
</tr>
<tr>
<td>Constipation</td>
<td>1%</td>
<td>1%</td>
</tr>
<tr>
<td>Nausea</td>
<td>4%</td>
<td>3%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1%</td>
<td>5%</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>3%</td>
<td>5%</td>
</tr>
<tr>
<td><strong>Hepatobiliary disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alanine aminotransferase increased (SGPT &gt;5 times baseline)</td>
<td>5%</td>
<td>18%</td>
</tr>
<tr>
<td>Aspartate aminotransferase increased (SGOT &gt;5 times baseline)</td>
<td>1%</td>
<td>6%</td>
</tr>
<tr>
<td><strong>Skin and subcutaneous tissue disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin disorder</td>
<td>0%</td>
<td>1%</td>
</tr>
<tr>
<td>Rash</td>
<td>3%</td>
<td>11%</td>
</tr>
<tr>
<td><strong>Musculoskeletal and connective tissue disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertonia</td>
<td>1%</td>
<td>2%</td>
</tr>
<tr>
<td>Myalgia</td>
<td>8%</td>
<td>8%</td>
</tr>
<tr>
<td>Myasthenia</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>Back pain</td>
<td>7%</td>
<td>10%</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>3%</td>
<td>6%</td>
</tr>
<tr>
<td><strong>Renal and urinary disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinary retention</td>
<td>1%</td>
<td>1%</td>
</tr>
<tr>
<td>Urinary protein positive (&gt;1+)</td>
<td>26%</td>
<td>25%</td>
</tr>
<tr>
<td>Urinary frequency</td>
<td>1%</td>
<td>1%</td>
</tr>
<tr>
<td>Urinary incontinence</td>
<td>1%</td>
<td>1%</td>
</tr>
<tr>
<td>Urinary urgency</td>
<td>1%</td>
<td>1%</td>
</tr>
<tr>
<td><strong>Reproductive system and breast disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dysmenorrhoea</td>
<td>0%</td>
<td>2%</td>
</tr>
<tr>
<td>Menstrual disorder</td>
<td>2%</td>
<td>1%</td>
</tr>
<tr>
<td>Metrorrhagia</td>
<td>0%</td>
<td>2%</td>
</tr>
<tr>
<td>Impotence</td>
<td>0%</td>
<td>1%</td>
</tr>
<tr>
<td><strong>General disorders and administration site conditions</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Injection site reaction (various kinds) ^§</td>
<td>11%</td>
<td>52%</td>
</tr>
<tr>
<td>Injection site necrosis</td>
<td>0%</td>
<td>1%</td>
</tr>
<tr>
<td>Flu-like symptoms ^</td>
<td>18%</td>
<td>44%</td>
</tr>
<tr>
<td>Fever ^</td>
<td>5%</td>
<td>13%</td>
</tr>
<tr>
<td>Pain</td>
<td>4%</td>
<td>4%</td>
</tr>
<tr>
<td>Chest pain</td>
<td>0%</td>
<td>1%</td>
</tr>
<tr>
<td>Peripheral oedema</td>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
</table>
Asthenia  |  17%  |  22%  
Chills*  |  1%  |  5%  
Sweating  |  1%  |  2%  
Malaise  |  1%  |  0%  

*Significantly associated with BETAFERON treatment for patients with first event suggestive of MS, p < 0.05
§ 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 and flu like symptom complex denotes flu syndrome and/or a combination of at least two AEs from fever, chills, myalgia, malaise, sweating.

Post marketing information

Anecdotal evidence from post marketing experience suggests that systemic flu-like symptoms can be substantially suppressed by the concomitant administration of paracetamol or ibuprofen.

The following adverse reactions have been reported at the approximate frequencies (not necessarily implicating a causal relationship) indicated below:

<table>
<thead>
<tr>
<th>Frequentity</th>
<th>Reporting Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very Common</td>
<td>≥ 1/10</td>
</tr>
<tr>
<td>Common</td>
<td>≥ 1/100 and &lt;1/10</td>
</tr>
<tr>
<td>Uncommon</td>
<td>≥1/1000 and &lt;1/100</td>
</tr>
<tr>
<td>Rare</td>
<td>≥1/10 000 and &lt;1/1000</td>
</tr>
<tr>
<td>Very rare</td>
<td>&lt;1/10 000</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Body System</th>
<th>Reporting Rate</th>
<th>Adverse Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and lymphatic</td>
<td>Uncommon</td>
<td>Anaemia</td>
</tr>
<tr>
<td>system disorders</td>
<td></td>
<td>Thrombocytopaenia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Leukopaenia</td>
</tr>
<tr>
<td></td>
<td>Rare</td>
<td>Lymphadenopathy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Thrombotic microangiopathy</td>
</tr>
<tr>
<td>Immune system disorders</td>
<td>Rare</td>
<td>Anaphylactic reactions</td>
</tr>
<tr>
<td>Endocrine disorders</td>
<td>Rare</td>
<td>Hyperthyroidism</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hypothyroidism</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Thyroid disorder</td>
</tr>
<tr>
<td>Metabolism and nutrition</td>
<td>Rare</td>
<td>Anorexia</td>
</tr>
<tr>
<td>disorders</td>
<td></td>
<td>Triglyceride increased</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Weight decrease</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Weight increase</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>Uncommon</td>
<td>Depression</td>
</tr>
<tr>
<td></td>
<td>Rare</td>
<td>Confusion</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Anxiety</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Emotional lability</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Suicide attempt</td>
</tr>
<tr>
<td>Body System</td>
<td>Reporting Rate</td>
<td>Adverse Reaction</td>
</tr>
<tr>
<td>-------------------------------------</td>
<td>----------------</td>
<td>-------------------------------------------------------</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Rare</td>
<td>Convulsion</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dizziness</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>Rare</td>
<td>Cardiomyopathy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tachycardia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Palpitation</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Uncommon</td>
<td>Hypertension</td>
</tr>
<tr>
<td></td>
<td>Very rare</td>
<td>Vasodilation</td>
</tr>
<tr>
<td>Respiratory, thoracic and</td>
<td>Rare</td>
<td>Bronchospasm</td>
</tr>
<tr>
<td>mediastinal disorders</td>
<td></td>
<td>Dyspnoea</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Uncommon</td>
<td>Nausea</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Vomiting</td>
</tr>
<tr>
<td></td>
<td>Rare</td>
<td>Pancreatitis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Diarrhoea</td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td>Uncommon</td>
<td>Alanine aminotransferase increased</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Aspartate amino transferase increased</td>
</tr>
<tr>
<td></td>
<td>Rare</td>
<td>Hepatic injury (including hepatitis)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Blood bilirubin increased</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gamma glutamyl transferase increased</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue</td>
<td>Uncommon</td>
<td>Alopecia</td>
</tr>
<tr>
<td>disorders</td>
<td></td>
<td>Urticaria</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pruritus</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Rash</td>
</tr>
<tr>
<td></td>
<td>Rare</td>
<td>Skin discolouration</td>
</tr>
<tr>
<td>Musculoskeletal, connective tissue</td>
<td>Uncommon</td>
<td>Myalgia</td>
</tr>
<tr>
<td>and bone disorders</td>
<td></td>
<td>Hypertonia</td>
</tr>
<tr>
<td></td>
<td>Rare</td>
<td>Arthralgia</td>
</tr>
<tr>
<td></td>
<td>Not known</td>
<td>Drug-induced lupus erythematosus</td>
</tr>
<tr>
<td>Renal disorders</td>
<td>Uncommon</td>
<td>Nephrotic syndrome</td>
</tr>
<tr>
<td>Reproductive system</td>
<td>Rare</td>
<td>Menstrual disorder</td>
</tr>
</tbody>
</table>
Body System | Reporting Rate | Adverse Reaction
---|---|---
disorders | Very rare | Menorrhagia

General disorders and administration site conditions | Very common | Flu-like symptoms*, chills*, fever*, injection site reaction*, injection site inflammation*, injection site pain*

Common | Injection site necrosis*

Rare | Malaise

Chest pain

Sweating

* frequencies based on clinical trials

Capillary leak syndrome in pre-existing monoclonal gammopathy and hepatic failure have been reported in post-marketing surveillance. The frequency cannot be estimated from the available data and is therefore unknown.

**DOSAGE AND ADMINISTRATION**

**General**

Treatment with interferon beta-1b should be initiated under the supervision of a physician experienced in the treatment of multiple sclerosis. There are follow-up data under controlled clinical trial conditions for patients with relapsing–remitting MS for up to five years and for patients with secondary progressive MS for up to 3 years.

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

Inspect the reconstituted product visually before use. The reconstituted product is colourless to light yellow and slightly opalescent to opalescent. Discard the product if it contains particulate matter or is discoloured. The reconstituted solution contains 8 million IU (0.25 mg) of interferon beta-1b per mL.

After reconstitution, draw 1.0 mL from the vial into the syringe for administration of 0.25 mg BETAFERON. Remove the vial with the vial adapter from the pre-filled syringe by twisting the vial and then pulling it down, away from the syringe before injection. For dose titration at the start of treatment, draw the respective volume as given in Table A. Proceed to inject appropriate volume of injection. Discard any unused reconstituted solution.

To reduce microbiological hazard, the reconstituted solution should be used as soon as practicable after reconstitution. If storage is necessary, hold at 2°C to 8°C for not more than 3 hours.
In the absence of compatibility studies, this medicinal product should not be mixed with other medicinal products.

**Relapsing-remitting multiple sclerosis**

For relapsing-remitting multiple sclerosis, the recommended dose of BETAFERON (interferon beta-1b) is 8 million IU (0.25 mg) contained in 1 mL of reconstituted solution, injected subcutaneously every other day.

Treatment should start as soon as the definite diagnosis of relapsing-remitting multiple sclerosis has been made and the patient has had at least two exacerbations in the previous two years. In case there are fewer than two relapses during the last two years the decision should be made on an individual basis; the treating physician should inform the patient on the possible risk and benefit of a treatment with interferon beta-1b and decide with him/her whether he/she would be willing to accept possible side effects and inconveniences that might be related to the treatment with interferon beta-1b.

For relapsing-remitting MS, the available data for up to five years suggest sustained treatment efficacy of BETAFERON over the whole time period.

**Secondary progressive multiple sclerosis**

For secondary progressive multiple sclerosis, the recommended dose of BETAFERON (interferon beta-1b) is 8 million IU (0.25 mg) contained in 1 mL of reconstituted solution, injected subcutaneously every other day.

Treatment should start as soon as the definite diagnosis of secondary progressive multiple sclerosis has been made. For secondary progressive MS, efficacy for a period of two years with limited data for a period of up to three years of treatment has been demonstrated under controlled clinical trial conditions.

According to the results of the clinical studies the treatment should last at least two years. The follow-up studies in relapsing remitting patients indicate a persistence of the treatment effect until the end of four to five years. Since the statement on the efficacy after four to five years is based on a small number of patients, a decision for long-term treatment should be made on an individual basis by the treating physician.

**Single clinical event suggestive of multiple sclerosis**

For a single clinical event suggestive of multiple sclerosis, dose titration is recommended at the start of treatment.

Patients should be started at 2 million IU (0.0625 mg) contained in 0.25 mL of solution subcutaneously every other day, and increased slowly to a dose of 8 million IU (0.25 mg) contained in 1.0 mL of solution every other day. The titration period may be adjusted according to individual tolerability.

In the BENEFIT study in patients with a single clinical event, dosage was increased as shown in Table A.
Table A: Schedule for dose titration*

<table>
<thead>
<tr>
<th>treatment day</th>
<th>dose</th>
<th>volume</th>
</tr>
</thead>
<tbody>
<tr>
<td>1, 3, 5</td>
<td>0.0625 mg (2 million IU)</td>
<td>0.25 mL</td>
</tr>
<tr>
<td>7, 9, 11</td>
<td>0.125 mg (4 million IU)</td>
<td>0.5 mL</td>
</tr>
<tr>
<td>13, 15, 17</td>
<td>0.1875 mg (6 million IU)</td>
<td>0.75 mL</td>
</tr>
<tr>
<td>&gt;19</td>
<td>0.25 mg (8 million IU)</td>
<td>1.0 mL</td>
</tr>
</tbody>
</table>

*Titration scheme as used in the BENEFIT study in patients with a single clinical event suggestive of multiple sclerosis.

At the present time it is not known how long the patient should be treated for. In patients with a single clinical event suggestive of multiple sclerosis, data suggest efficacy over a period of five years.

OVERDOSAGE

Interferon beta-1b has been given without serious adverse events compromising vital functions to adult cancer patients at individual doses as high as 5.5 mg (176 million IU) i.v. three times a week. There have been no reported cases of accidental overdose.

In cases of overdose, it is advisable to contact the Poisons Information Centre (131126) for recommendations on the management and treatment of overdosage.

PRESENTATION AND STORAGE CONDITIONS

3 mL clear glass vial with a 13 mm butyl rubber stopper and aluminium overseal containing powder for solution for injection.

Each BETAFERON vial is provided with a separate 2.25 mL pre-filled syringe of diluent, containing 1.2 mL of sterile sodium chloride solution (0.54% w/v). Each vial contains 0.3 mg (9.6 million IU) of interferon beta-1b at a calculated overfill of 20% allowing extraction of the nominal content of 8 million IU (0.25 mg) in 1 mL after reconstitution with 1.2 mL of diluent.

Multipack comprising 15 single use packs, each containing 1 BETAFERON vial with powder, 1 pre-filled syringe with diluent, 1 vial adapter with needle, and 2 alcohol wipes.

Shelf-life and Storage

- of the product as packaged for sale: 24 months at store below 25 °C
- after reconstitution according to directions: up to 3 hours at 2 to 8 °C

NAME AND ADDRESS OF THE SPONSOR

Bayer Australia Limited
ABN 22 000 138 714
875 Pacific Highway
Pymble, NSW 2073

POISON SCHEDULE OF THE MEDICINE
S4, PRESCRIPTION ONLY MEDICINE

DATE OF FIRST INCLUSION IN THE ARTG
9 August 2002

DATE OF MOST RECENT AMENDMENT
21 August 2015

® Registered trademark of the Bayer Group, Germany