

Data Sheet

BETAFERON[®]

Recombinant Interferon beta-1b 0.25 mg (8.0 million IU) per mL when reconstituted.

Presentation

Lyophilisate and solvent for solution for injection.

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

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 and solvent for solution for injection. 1 mL solution for injection contains 5.4 mg sodium chloride.

Uses

Actions

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 biological activities. The activities of interferon beta-1b are generally 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.

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 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- γ 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.

Pharmacokinetics

BETAFERON serum levels were followed in patients and volunteers by means of a non-specific bioassay. Following subcutaneous administration of the recommended dose of 8 million IU (0.25 mg) or less of interferon beta-1b, serum concentrations of interferon beta-1b are low or not detectable. Pharmacokinetic information in patients with MS receiving the recommended dose of BETAFERON is therefore not available.

Absorption

Following subcutaneous injection of 0.5 mg of interferon beta-1b to healthy volunteers, maximum serum levels of about 40 IU/mL were found 1-8 hours after dosing. In this study, the absolute bioavailability of subcutaneously administered BETAFERON was estimated at approximately 50%. From various studies with intravenous administration of interferon beta-1b, mean clearance and disposition half-life from serum were estimated to be at most 30 mL/min/kg and 5 hours, respectively.

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.

Every other day BETAFERON injections do not lead to serum level increases and pharmacokinetics do not seem to change during therapy.

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, β 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 elevated above baseline throughout the 7 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.

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 characterised by at least two attacks of neurological dysfunction over a two year period followed by complete or incomplete recovery.
- the reduction of frequency and severity of clinical relapses and for slowing the progression of disease in patients with secondary progressive multiple sclerosis

Clinical Trials

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 expanded disability status scale (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 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 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 randomised to treatment with either 0.25 mg (8 million IU) BETAFFERON (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, BETAFFERON delayed the progression from the first clinical event to clinically definite MS 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 BETAFFERON group (Kaplan-Meier estimates). BETAFFERON prolonged the time to CDMS by 363 days, from 255 days in the placebo group to 618 days in the BETAFFERON group (based on 25th percentiles).

BETAFFERON 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 BETAFFERON 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 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 pre-planned 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 BETAFFERON-treatment delayed the progression from the first clinical event to CDMS in a statistically significant and clinically meaningful manner, corresponding to a risk reduction of 41% (Hazard Ratio = 0.59, 95% CI (0.42, 0.83), $p = 0.0011$) over three years and 37% over five years. At three years, CDMS had occurred in 51% of the delayed treatment group compared to 37% of the immediate treatment group (Kaplan-Meier estimates – see Figure 1). At five years, 57% of the delayed treatment group and 46% of the immediate treatment group were diagnosed with CDMS. This effect was observed even though the majority of patients from the original placebo-group were treated with BETAFFERON at least from the second year onwards.

Immediate BETAFFERON-treatment reduced risk for confirmed disability progression by 40% (Hazard Ratio = 0.60, 95% CI (0.39-0.92), $p = 0.022$) as compared to delayed start of treatment. Over three years EDSS progression occurred in 24% of the patients in the delayed treatment group compared to 16% of the patients in the immediate treatment group (see Figure 2).

At three years immediate BETAFFERON-treatment as compared to a delayed start of treatment reduced the risk for confirmed disability progression by 40% (statistically significant). Over five years the risk reduction (24%) was no longer statistically significant. Disability progression had occurred in 29% of the delayed treatment group compared to 25% of the early treatment group.

Figure 1. Kaplan-Meier Curve for "Time to Clinically Definite MS"

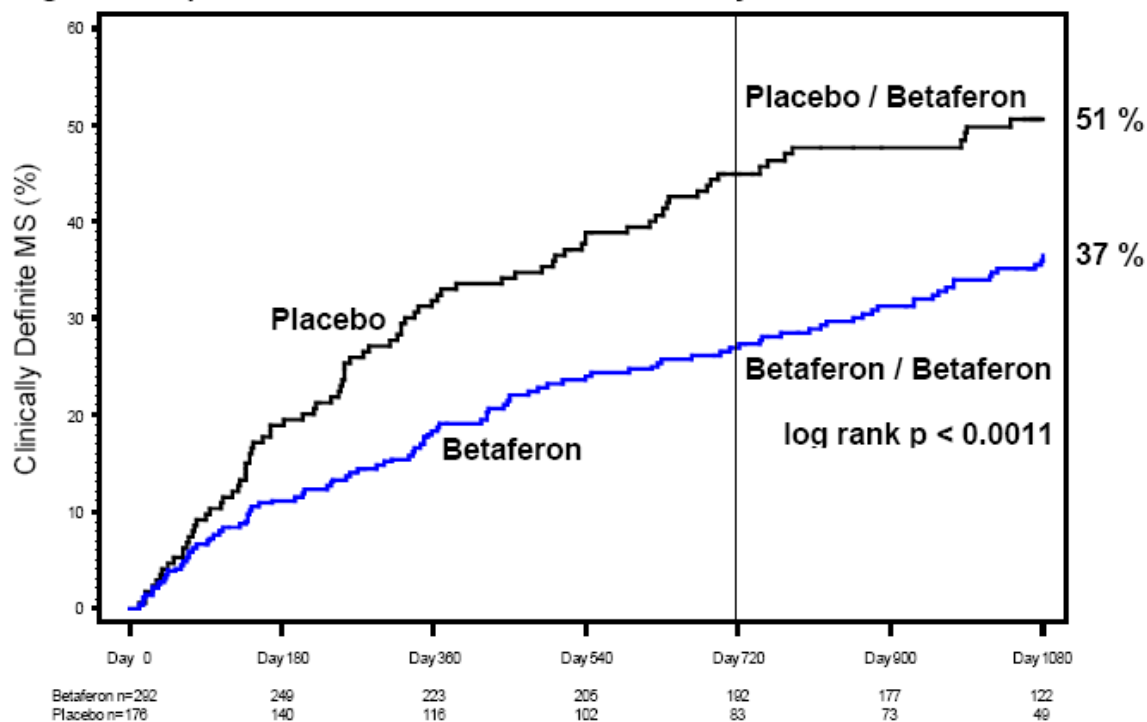
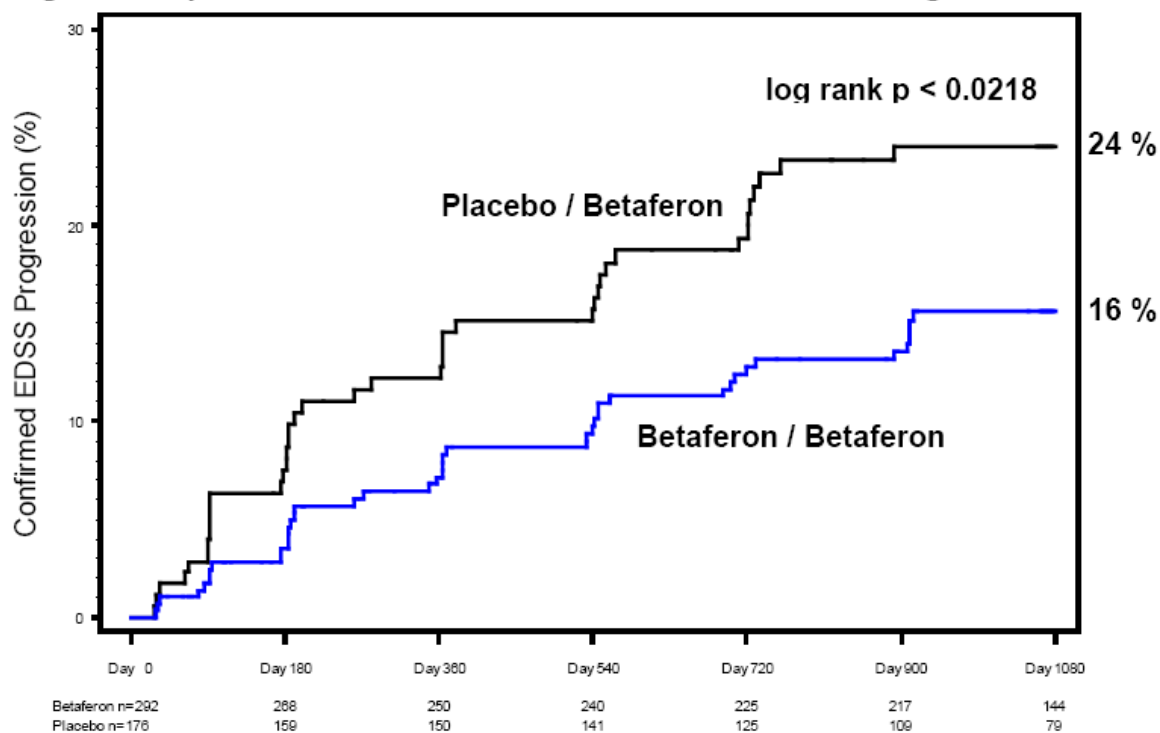


Figure 2. Kaplan-Meier Curve for "Time to Confirmed EDSS Progression"



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 BETA FERON group, irrespective of whether annualised (median number of newly active lesions was 1.34 for BETA FERON and 3.16 for placebo), or non-annualised (median number of newly active lesions was 2.0 for

BETAFERON and 4.0 for placebo) values were considered ($p < 0.0001$ for both analyses). The non-annualised T2 lesion volume reduction up to the last scan was statistically significantly higher in the BETAFERON group (median change – 206.0 mm³ for BETAFERON vs – 93.00 mm³ for placebo; $p = 0.0498$, but not for the annualised values (median change – 119.70 mm³ for BETAFERON vs – 57.54 mm³ for placebo; $p = 0.1906$).

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.

Relapsing-remitting multiple sclerosis

BETAFERON was shown to reduce the frequency and severity of clinical relapses, to reduce the number of MS related hospitalisations and steroid usage 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, BETAFERON 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 BETAFERON 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).

Both relapsing-remitting and secondary progressive multiple sclerosis patients receiving BETAFERON showed a reduction in frequency (30%) and severity of clinical relapses, as well as a prolongation of the relapse-free interval. The number of hospitalisations and steroid usage due to disease was reduced.

Furthermore, in both relapsing-remitting and secondary progressive multiple sclerosis BETAFERON demonstrated a significant beneficial effect on disease burden as measured by T2-weighted MRI scans and on newly active lesions as measured by six weekly MRIs in relapsing-remitting MS and by monthly contrast medium (Gd-DTPA) enhanced T1 weighted MRIs (months 1-6 and 19-24) in secondary-progressive MS. An increase in MRI disease burden has been demonstrated to correlate with an increase in disability as measured by expanded disability status scale.

Dosage and Administration

Treatment with BETAFERON 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 multiple sclerosis for up to 5 years and for patients with secondary progressive multiple sclerosis for up to 3 years. Non-controlled follow up data for patients with secondary progressive MS exist for up to 4.5 years.

The recommended dose of BETAFERON is 0.25 mg (8 million IU), contained in 1 mL of the reconstituted solution (see “Instructions for Use and Handling”), to be injected subcutaneously every other day.

Efficacy and safety of BETAFERON were not investigated systematically in children and adolescents under 18 years of age.

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 (0.25mg) 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 the table below.

Table A: **Schedule for dose titration***

Treatment Day	Dose	Volume
1, 3, 5	0.0625 mg (2 million IU)	0.25 mL
7, 9, 11	0.125 mg (4 million IU)	0.5 mL
13, 15, 17	0.1875 mg (6 million IU)	0.75 mL
>19	0.25 mg (8 million IU)	1.0 mL

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

In patients with a single clinical event suggestive of multiple sclerosis, efficacy has been demonstrated over a period of five years.

Relapsing-remitting Multiple Sclerosis

For relapsing-remitting multiple sclerosis the recommended dose of BETAFERON (interferon beta-1b) is 0.25 mg (8 million IU), contained in 1 mL of the reconstituted solution to be 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 5 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 0.25 mg (8 million IU), contained in 1 mL of the reconstituted solution to be 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.

At the present time it is not known for how long the patient should be treated. Efficacy for a period of up to three years of treatment has been demonstrated in a controlled clinical trial.

Contraindications

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

BETAFERON is also contraindicated during pregnancy and in patients with decompensated liver disease or with epilepsy not adequately controlled by treatment.

Warnings and Precautions

Immune System Disorders

The administration of cytokines to patients with 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, BETAFERON 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 hypertriglyceridemia.

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, as it cannot be excluded that BETAFERON treatment may be associated with depression and suicide in individual patients, BETAFERON should be administered with caution to patients with previous or current depressive disorders or suicidal ideation.

Nervous System Disorders

This product contains human albumin, a derivative of human blood. Based on effective donor screening and product manufacturing processes, it carries an extremely remote risk for transmission of viral diseases. A theoretical risk for transmission of Creutzfeldt-Jakob Disease (CJD) also is considered extremely remote. No cases of transmission of viral diseases or CJD have ever been identified for albumin.

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.

Laboratory Tests

In addition to those laboratory tests normally required for monitoring patients with multiple sclerosis, complete blood and differential white blood cell counts, platelet counts, and blood chemistries, including liver function tests (e.g. AST (SGOT), ALT (SGPT) and γ -GT), are recommended prior to initiation and at regular intervals (one, three and six months) following introduction of BETAFERON therapy, and then periodically thereafter in the absence of clinical symptoms. Thyroid function tests are recommended regularly in patients with a history of thyroid dysfunction or as clinically indicated. Patients with anaemia, thrombocytopenia, leukopaenia (alone or in combination) may require more intensive monitoring of complete blood cell 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.

Hepatobiliary 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 and transplant have been reported during post-marketing safety surveillance.

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 and 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 γ -GT), which are recommended at regular intervals following the introduction of BETAIFERON therapy, and then periodically thereafter in the absence of clinical symptoms.

Withdrawal of BETAIFERON 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 function.

Renal function

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

Cardiac Disorders

BETAIFERON should be used with caution in patients with pre-existing significant cardiac disease such as congestive heart failure, coronary artery disease or arrhythmias. While there is no evidence of a direct cardiotoxic potential for BETAIFERON, these patients should be monitored for worsening of their cardiac condition. This applies particularly during initiation of treatment with BETAIFERON, 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 BETAIFERON.

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 BETAIFERON therapy. Rare cases of cardiomyopathy have been reported: if this occurs and a relationship to BETAIFERON is suspected, treatment should be discontinued.

Administration Site Conditions

Injection site necrosis (ISN) has been reported in patients using BETAIFERON. 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, is 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 with injections of BETAIFERON.

If the patient has multiple lesions, BETAIFERON should be discontinued until healing has occurred.

Patients with single lesions may continue on BETAIFERON provided the necrosis is not too extensive, as some patients have experienced healing of injection site necrosis whilst on BETAIFERON.

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 auto-injector. In the pivotal study of patients with a single clinical event suggestive of multiple sclerosis an auto-injector 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 self-administration by the patient should be reviewed periodically especially if injection site reactions have occurred.

Preclinical Safety Data

No acute toxicity studies have been carried out. As rodents do not react to human interferon beta, risk assessment was based on repeated dose studies carried out with rhesus monkeys.

Transitory hyperthermia was observed, as well as a significant transient rise in lymphocytes and a significant transient decrease in thrombocytes and segmented neutrophils. No long-term studies have been conducted.

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.

In one single genotoxicity study (Ames test), no mutagenic effect has been observed. An *in vitro* cell transformation test gave no indication of tumourigenic potential.

Pregnancy and Lactation

Use in Pregnancy

Pregnancy category D. (Medicines which have caused, are suspected to cause or may have expected to cause, an increased incidence of human foetal malformations or irreversible damage. These medicines may also have adverse pharmacological effects).

It is not known whether BETAFERON can cause foetal 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.

Recombinant human interferon beta-1b was not teratogenic in studies with 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. Therefore, BETAFERON is contraindicated during pregnancy and women of childbearing potential should take appropriate contraceptive measures. If the patient becomes pregnant or plans to become pregnant while taking BETAFERON, 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 human milk. Because of the potential for serious adverse reactions to BETAFERON 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. However, limited data suggest that the safety profile in adolescents from 12 to 16 years of age receiving 250 microgram BETAFERON subcutaneously every other day is similar to that seen in adults.

There is only limited information on the use of BETAFERON in children under 12 years of age and, therefore, BETAFERON should not be administered to this age group.

Effects on Ability to Drive and Use Machines

This has not been investigated.

Central nervous system-related adverse events associated with the use of BETAFERON, although unlikely, may have an influence on the ability to drive and use machines in susceptible patients.

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 $\geq 2\%$ 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 (e.g. redness, swelling, discolouration, inflammation, pain, hypersensitivity, necrosis, and non-specific reactions) occurred frequently after administration of BETAFERON. The incidence rate of injection site reactions usually decreased over time. The use of auto-injectors may reduce the intensity and frequency of skin reactions.

Inflammation and pain at the injection site is very common. Redness, swelling, discoloration, hypersensitivity, necrosis and non-specific reactions were significantly associated with 0.25 mg (8 million IU) BETAFERON treatment. The occurrence of necrosis at the injection site is common. Lymphadenopathy has also been reported. The incidence rate of injection site reactions usually decreased over time.

Flu-like symptom complex has been seen frequently. This includes fever and chills which are very common, myalgia which is uncommon, malaise and sweating which occur rarely and headache and arthralgia. The incidence rate of the symptoms decrease over time. Generally, dose titration is recommended at the start of treatment in order to increase tolerability to BETAFERON (see Dosage and Administration). Flu-like symptoms may also be reduced by administration of non steroidal inflammatory medicines.

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.

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

Adverse Reaction	Placebo n = 123	Interferon beta-1b 0.25 mg (8 million IU) n = 124
Body as a Whole		
Injection site reaction*	37%	85%
Headache	77%	84%
Fever*	41%	59%
Flu-like symptom complex*	56%	76%
Pain	48%	52%
Asthaenia*	35%	49%
Chills*	19%	46%
Abdominal pain	24%	32%
Malaise*	3%	15%
Generalized oedema	6%	8%
Pelvic pain	3%	6%
Injection site necrosis*	0%	5%
Cyst	2%	4%
Necrosis	0%	2%
Suicide attempt	0%	2%
Cardiovascular System		
Migraine	7%	12%
Palpitation*	2%	8%
Hypertension	2%	7%
Tachycardia	3%	6%
Peripheral vascular disorder	2%	5%
Haemorrhage	1%	3%
Digestive System		
Diarrhoea	29%	35%
Constipation	18%	24%
Vomiting	19%	21%
Gastrointestinal disorder	3%	6%
Endocrine System		
Goitre	0%	2%
Haematological and Lymphatic System		
Lymphocytes less than 1500/mm ³ *	67%	82%
ANC < 1500/mm ³ *	6%	18%
WBC < 3000/mm ³ *	5%	16%
Lymphadenopathy	11%	14%

Adverse Reaction	Placebo n = 123	Interferon beta-1b 0.25 mg (8 million IU) n = 124
Metabolic and Nutritional Disorders SGPT > 5 times baseline* Glucose < 55 mg/dL Total bilirubin > 2.5 times baseline Urine protein > 1+ SGOT > 5 times baseline* Weight gain Weight loss	6% 13% 2% 3% 0% 0% 2%	19% 15% 6% 5% 4% 4% 4%
Musculoskeletal System Myalgia* Myasthenia	28% 10%	44% 13%
Nervous System Dizziness Hypertonia Anxiety Nervousness Somnolence Confusion Speech disorder Convulsion Hyperkinesia Amnesia	28% 24% 13% 5% 3% 2% 1% 0% 0% 0% 0%	35% 26% 15% 8% 6% 4% 3% 2% 2% 2%
Respiratory System Sinusitis Dyspnoea* Laryngitis	26% 2% 2%	36% 8% 6%
Skin and Appendages Sweating* Alopecia	11% 2%	23% 4%
Special Senses Conjunctivitis Abnormal vision	10% 4%	12% 7%
Urogenital System Dysmenorrhoea Intermenstrual spotting* Metrorrhagia Cystitis Breast pain Menorrhagia Urinary urgency Fibrocystic breast Breast neoplasm	11% 8% 8% 4% 3% 3% 2% 1% 0%	18% 17% 15% 8% 7% 6% 4% 3% 2%

* Significantly associated with interferon beta-1b treatment.

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

Adverse reaction	Placebo n = 358	Interferon beta-1b 0.25 mg (8 million IU) n = 360
Body as a whole*	88.5%	96.4%
Asthaenia	56.4%	60.0%
Flu syndrome*	37.2%	59.2%
Fever*	13.1%	39.4%
Pain	20.7%	23.3%
Back pain	21.8%	23.3%
Chills*	7.3%	21.9%
Injection site*	19.8%	77.5%
Injection site inflammation*	4.2%	50.0%
Injection site reaction*	10.3%	43.6%
Musculoskeletal system	55.3%	61.9%
Myasthaenia	37.2%	36.4%
Myalgia*	8.9%	22.8%
Nervous system	93.9%	93.6%
Headache	39.7%	45.6%
Neuropathy**	39.1%	33.3%
Paresthaesia	37.4%	32.2%
Abnormal gait	33.2%	33.6%
Muscular hypertonia*	27.4%	37.8%
Depression	28.8%	24.4%
Ataxia	22.1%	18.9%
Respiratory system	53.1%	50.8%
Rhinitis	29.9%	25.6%
Skin and appendages	34.1%	38.9%
Rash*	10.6%	21.4%
Urogenital system	55.9%	51.1%
Urinary tract infection	22.6%	18.9%

*Significantly associated with interferon beta-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).

Adverse Reaction	Placebo n = 176	BETAFERON n = 292
Infections and infestations Infection Abscess	3% 1%	6% 0%
Blood and lymphatic system disorders Lymphocyte count decreased (<1500/mm ³) [^] Absolute neutrophil count decreased (<1500/mm ³) [^] White blood cell count decreased (<3000/mm ³) [^] Lymphadenopathy	45% 2% 2% 1%	79% 11% 11% 1%
Metabolism and nutrition disorders Blood glucose decreased (<55 mg/dL)	5%	3%
Psychiatric disorders Depression Anxiety	11% 5%	10% 3%
Nervous system disorders Headache [^] Dizziness Insomnia Migraine Paresthesia	17% 4% 4% 2% 17%	27% 3% 8% 2% 16%
Eye disorders Conjunctivitis Abnormal vision [^]	1% 1%	1% 3%
Ear and labyrinth disorders Ear pain	1%	0%
Cardiac disorders Palpitation	1%	1%
Vascular disorders Vasodilatation Hypertension	0% 0%	0% 2%
Respiratory, thoracic and mediastinal disorders Upper respiratory infection Sinusitis Cough increased Dyspnoea	19% 6% 2% 0%	18% 4% 2% 0%
Gastrointestinal disorders		

Adverse Reaction	Placebo n = 176	BETAFERON n = 292
Diarrhoea Constipation Nausea Vomiting [^] Abdominal pain	2% 1% 4% 1% 3%	4% 1% 3% 5% 5%
Hepatobiliary disorders Alanine aminotransferase increased (SGPT >5 times baseline) [^] Aspartate aminotransferase increased (SGOT >5 times baseline) [^]	5% 1%	18% 6%
Skin and subcutaneous tissue disorders Skin disorder Rash [^]	0% 3%	1% 11%
Renal and urinary disorders Urinary retention Urinary protein positive (>1+) Urinary frequency Urinary incontinence Urinary urgency	1% 26% 1% 1% 1%	1% 25% 1% 1% 1%
Reproductive system and breast disorders Dysmenorrhoea Menstrual disorder Metrorrhagia Impotence	0% 2% 0% 0%	2% 1% 2% 1%
General disorders and administration site conditions Injection site reaction (various kinds) ^{^ §} Injection site necrosis Flu-like symptoms [^] Fever [^] Pain Chest pain Peripheral oedema Asthma Chills [^] Sweating Malaise	11% 0% 18% 5% 4% 0% 0% 17% 1% 1% 1%	52% 1% 44% 13% 4% 1% 0% 22% 5% 2% 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.

During the third year of the BENEFIT study, no change of the known risk profile of BETAFERON was observed

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:

Very common	≥ 1/10		
Common	≥ 1/100	to	< 1/10
Uncommon	≥ 1/1 000	to	< 1/100
Rare	≥ 1/10 000	to	< 1/1 000
Very rare	< 1/10 000		

Adverse Events and Laboratory Abnormalities

Body System	Reporting Rate	Adverse Reaction
Blood and Lymphatic System Disorders	Uncommon	Anaemia, Thrombocytopaenia, Leukopaenia
	Rare	Lymphadenopathy
Immune System Disorders	Rare	Anaphylactic reactions
Endocrine Disorders	Rare	Hyperthyroidism, Hypothyroidism, Thyroid dysfunction
Metabolism and Nutrition Disorders	Rare	Triglyceride increase Anorexia, Weight increase Weight decrease
Psychiatric Disorders	Uncommon	Depression
	Rare	Confusion, Anxiety, Emotional lability, Suicide attempt
Nervous System Disorders	Rare	Convulsion, Dizziness
Cardiac Disorders	Rare	Cardiomyopathy, Tachycardia, Palpitation
Vascular Disorders	Uncommon	Hypertension

	Very rare	Vasodilatation
Respiratory Disorders	Rare	Bronchospasm, Dyspnoea
Gastrointestinal Disorders	Uncommon	Nausea, Vomiting,
	Rare	Pancreatitis Diarrhoea
Hepatobiliary Disorders	Uncommon	ALT increase, AST increase
	Rare	Hepatic injury (including Hepatitis) Gamma GT increase, Blood Bilirubin increase
Skin and Subcutaneous Tissue Disorders	Uncommon	Alopaecia, Urticaria, Pruritus, Rash
	Rare	Skin discolouration,
Musculoskeletal Disorders	Uncommon	Myalgia, Hypertonia,
	Rare	Arthralgia
Reproductive system disorders	Rare	Menstrual disorder
	Very rare	Menorrhagia
General Disorders and Administration Site Conditions	Very common	Flu-like symptoms ^o , Chills ^o , Fever ^o , Injection site reaction ^o , Injection site inflammation ^o , Injection site pain ^o
	Common	Injection site necrosis
	Rare	Chest pain, Malaise, Sweating

^o 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.

Immunogenicity

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 titres; 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.

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) and time to confirmed EDSS progression and relapse rate.

No consistent attenuating effects on clinical outcomes, including MRI findings, 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.

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.

Interactions

No formal drug interaction studies have been carried out with BETAFERON. The effect of alternate-day administration of 0.25 mg (8 million IU) 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 interferon beta-1b had a significantly reduced steroid usage compared with placebo patients. Due to the lack of clinical experience in MS patients, the use of interferon beta-1b 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 medicinal products that have a narrow therapeutic index and are largely dependent on the hepatic cytochrome P450 system for clearance, e.g. anti-epileptics. Caution should be exercised with any co-medication, which has an effect on the hematopoietic system.

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.

Pharmaceutical Precautions

Instructions for Use/Handling

- 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 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 solution for injection.

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.

Detailed instructions for the self-injection procedure can be found in the Consumer Medicine Information. For auto-injection, please refer to the manufacturer's instructions for use of the auto-injector.

- Inspection Prior To Use

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

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.

Storage Conditions:

- Before reconstitution, store at or below 25 °C.
- After reconstitution, store at 2 - 8 °C for up to 3 hours.

Shelf Life:

- As packaged for sale, 24 months starting from the date of sterile filtration of the formulated bulk solution
- After reconstitution according to the directions: up to 3 hours at 2 - 8 °C.

Medicine Classification

Prescription Medicine

Package Quantities

BETAFERON is presented as a 3 mL clear glass vial containing powder for solution for injection with 13 mm black chlorinated butyl rubber stopper and aluminium overseal.

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.

The multipack comprises 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.

Further Information

List of Excipients

Lyophilisate: human albumin, mannitol

Solvent: sodium chloride, water for injection

Store all medicines properly and keep them out of reach of children.

Name and Address

Bayer New Zealand Limited
3 Argus Place
Hillcrest
North Shore
AUCKLAND 0627

Free phone: 0800 233 988

Date of Preparation

09 August 2010