ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

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

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

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

For the full list of excipients, see section 6.1.

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

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection.

Sterile white to off-white powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Betaferon is indicated for the treatment of

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

4.2 Posology and method of administration

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

Posology

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

Paediatric population
No formal clinical trials or pharmacokinetic studies have been conducted in children or adolescents. However, limited published data suggest that the safety profile in adolescents from 12 to 16 years of age receiving Betaferon 8.0 million IU subcutaneously every other day is similar to that seen in adults. There is no information on the use of Betaferon in children under 12 years of age. Therefore Betaferon should not be used in this population.

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

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

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

Table A: Schedule for dose titration*

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

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

The optimal dose has not been fully clarified.

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

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

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

Method of administration

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

4.3 Contraindications

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

4.4 Special warnings and precautions for use

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

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

Gastrointestinal disorders
In rare cases, pancreatitis was observed with Betaferon use, often associated with hypertriglyceridemia.

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

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

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

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

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

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

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

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

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

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

Cardiac disorders
Betaferon should also be used with caution in patients who suffer from pre-existing cardiac disorders. Patients with pre-existing significant cardiac disease, such as congestive heart failure, coronary artery disease or arrhythmia, should be monitored for worsening of their cardiac condition, particularly during initiation of treatment with Betaferon.
While Betaferon does not have any known direct-acting cardiac toxicity, symptoms of the flu-like syndrome associated with beta interferons may prove stressful to patients with pre-existing significant cardiac disease. During the post-marketing period very rare reports have been received of worsening of cardiac status in patients with pre-existing significant cardiac disease temporarily associated with the initiation of Betaferon therapy.

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

Thrombotic microangiopathy (TMA) and Haemolytic anaemia (HA)
Cases of thrombotic microangiopathy, manifested as thrombotic thrombocytopenic purpura (TTP) or haemolytic uraemic syndrome (HUS), including fatal cases, have been reported with interferon beta products. Early clinical features include thrombocytopenia, new onset hypertension, fever, central nervous system symptoms (e.g. confusion, paresis) and impaired renal function. Laboratory findings suggestive of TMA include decreased platelet counts, increased serum lactate dehydrogenase (LDH) due to haemolysis and schistocytes (erythrocyte fragmentation) on a blood film. Therefore if clinical features of TMA are observed, further testing of blood platelet levels, serum LDH, blood films and renal function is recommended.
Additionally, cases of HA not associated with TMA, including immune HA, have been reported with interferon beta products. Life-threatening and fatal cases have been reported. Cases of TMA and/or HA have been reported at various time points during treatment and may occur several weeks to several years after starting treatment with interferon beta.
If TMA and/or HA is diagnosed and a relationship to Betaferon is suspected, prompt treatment is required (in case of TMA considering plasma exchange) and immediate discontinuation of Betaferon is recommended.

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

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

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

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

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

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

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

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

Immunogenicity

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

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

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

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

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

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

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

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

Excipients

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

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

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

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

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

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

4.6 Fertility, pregnancy and lactation

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

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

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

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

Betaferon can be used during breast-feeding.

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

4.7 Effects on ability to drive and use machines

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

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

4.8 Undesirable effects

Summary of the safety profile
At the beginning of treatment adverse reactions are common but in general they subside with further treatment. The most frequently observed adverse reactions are a flu-like symptom complex (fever, chills, arthralgia, malaise, sweating, headache, or myalgia), which is mainly due to the pharmacological effects of the medicinal product, and injection site reactions. Injection site reactions occurred frequently after administration of Betaferon. Redness, swelling, discolouration, inflammation, pain, hypersensitivity, infection, necrosis and non-specific reactions were significantly associated with 250 microgram (8.0 million IU) Betaferon treatment.
The most serious adverse reactions reported include thrombotic microangiopathy (TMA) and haemolytic anaemia (HA).

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

Tabulated list of adverse reactions
The following adverse event listing is based on reports from clinical trials and from the post-marketing surveillance *(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))* of Betaferon use.
The most appropriate MedDRA term is used to describe a certain reaction and its synonyms and related conditions.

Table 1: Adverse drug reactions (ADRs) based on reports from clinical trials and identified during post-marketing surveillance (*frequencies - where known - calculated based on pooled clinical trial data)*

System Organ Class	**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)**	**Frequency not known**
Blood and lymphatic system disorders	Lymphocyte count decreased (< 1500/mm^3) [e], White blood cell count decreased (< 3000/mm^3) [e], Absolute neutrophil count decreased (< 1500/mm^3)[e]	Lymphadenopathy, Anaemia	Thrombocytopenia	Thrombotic microangiopathy[d] including thrombotic thrombocytopenic purpura/ haemolytic uraemic syndrome[b]	Haemolytic anaemia[a, d]
Immune system disorders				Anaphylactic reactions	Capillary leak syndrome in pre-existing monoclonal gammopathy[a]
Endocrine disorders		Hypothyroidism		Hyperthyroidism, Thyroid disorders	
Metabolism and nutrition disorders		Weight increased, Weight decreased	Blood triglycerides increased	Anorexia[a]	
Psychiatric disorders		Confusional state	Suicide attempt (see also section 4.4), Emotional lability		Depression, Anxiety
Nervous system disorders	Headache, Insomnia		Convulsion		Dizziness

System Organ Class	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)	Frequency not known
Cardiac disorders		Tachycardia		Cardiomyopathy[a]	Palpitation
Vascular disorders		Hypertension			Vasodilatation
Respiratory, thoracic and mediastinal disorders		Dyspnoea		Bronchospasm[a]	Pulmonary arterial hypertension[c]
Gastrointestinal disorders	Abdominal pain			Pancreatitis	Nausea, Vomiting, Diarrhoea
Hepatobiliary disorders	Alanine aminotransferase increased (ALAT > 5 times baseline)[e]	Aspartate aminotransferase increased (ASAT > 5 times baseline)[e], Blood bilirubin increased	Gamma-glutamyl-transferase increased, Hepatitis	Hepatic injury, Hepatic failure[a]	
Skin and subcutaneous tissue disorders	Rash, Skin disorder	Urticaria, Pruritus, Alopecia	Skin discolouration		
Musculoskeletal and connective tissue disorders	Myalgia, Hypertonia, Arthralgia				Drug-induced lupus erythematosus
Renal and urinary disorders	Urinary urgency		Nephrotic syndrome, Glomerulosclerosis (see section 4.4)[a, b]		
Reproductive system and breast disorders		Menorrhagia, Impotence, Metrorrhagia			Menstrual disorder
General disorders and administration site conditions	Injection site reaction (various kinds[f]), Flu-like symptoms (complex [g]), Pain, Fever, Chills, Peripheral oedema, Asthenia	Injection site necrosis, Chest pain, Malaise			Sweating

System Organ Class	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)	Frequency not known

[a] *ADRs derived only during post-marketing*
[b] *Class label for interferon beta products (see section 4.4).*
[c] *Class label for interferon products, see below Pulmonary arterial hypertension.*
[d] *life-threatening and/or fatal cases have been reported.*
[e] *laboratory abnormality*
[f] *'Injection site reaction (various kinds)' comprises all adverse events occurring at the injection site (except injection site necrosis), e.g. the following terms: injection site atrophy, injection site edema, injection site haemorrhage, injection site hypersensitivity, injection site infection, injection site inflammation, injection site mass, injection site pain and injection site reaction.*
[g] *Flu-like symptom complex' denotes flu syndrome and/or a combination of at least two Adverse Events from fever, chills, myalgia, malaise, sweating.*

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

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via:

United Arab Emirates (UAE):
Pharmacovigilance & Medical Device section
Tel: 80011111 / +971 42301000
Email: pv@mohap.gov.ae
Website: www.mohap.gov.ae
P.O.Box 1853 Dubai

Egypt:
Egyptian Pharmaceutical Vigilance Centre
Hotline: 15301
Email: pv.followup@edaegypt.gov.eg
Website: www.edaegypt.gov.eg

Oman:
Tel: +968 - 2444 1999
Fax: +968 - 24602287
Email: pharma-vigil@moh.gov.om
Website: www.moh.gov.om

Jordan:
Tel: +962-6-5632000
JFDA email : jpc@jfda.jo
JFDA website: www.jfda.jo
http://primaryreporting.who-umc.org/JO

Kuwait:
Drug &Food Control, Ministry of Health
Tel.: +965-24811532 Fax: +965-24811507
Email : Adr_reporting@moh.gov.kw
Website: http://eservices.moh.gov.kw/SPCMS/DrugCmp.aspx

Other Countries:
Please contact the relevant competent authority

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

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

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

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

Clinical efficacy and safety

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

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

One of the two studies demonstrated a statistically significant delay in the time to disability progression (Hazard Ratio = 0.69, 95% confidence interval (0.55, 0.86), p=0.0010, corresponding to a 31% risk reduction due to Betaferon) and in the time to becoming wheelchair bound (Hazard Ratio = 0.61, 95% confidence interval (0.44, 0.85), p=0.0036, corresponding to a 39% risk reduction due to Betaferon) in patients who received Betaferon. This effect continued over the observation period of up to 33 months. The treatment effect occurred in patients at all levels of disability investigated and independent of relapse activity.
In the second trial of Betaferon in secondary progressive multiple sclerosis, no delay in the time to disability progression was observed. There is evidence that the patients included in this study had overall less active disease than in the other study in secondary progressive multiple sclerosis.

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

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

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

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

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

Table 2: Primary efficacy results of the BENEFIT and the BENEFIT Follow-up study

	Year 2 results Placebo-controlled phase		**Year 3 results Open-label follow-up**		**Year 5 results Open-label follow-up**	
	Betaferon 250 mcg n=292	**Placebo n=176**	**Imme-diate Betaferon 250 mcg n=292**	**Delayed Betaferon 250 mcg n=176**	**Imme-diate Betaferon 250 mcg n=292**	**Delayed Betaferon 250 mcg n=176**

Number of patients completed the trial phase	271 (93%)	166 (94%)	249 (85%)	143 (81%)	235 (80%)	123 (70%)
Primary efficacy variables						
Time to CDMS						
Kaplan-Meier estimates	28%	45%	37%	51%	46%	57%
Risk reduction **Hazard ratio with 95% confidence interval** **log-rank test**	47% versus placebo HR = 0.53 [0.39, 0.73] p < 0.0001 Betaferon prolonged the time to CDMS by 363 days, from 255 days in the placebo group to 618 days in the Betaferon group (based on the 25th percentiles)		41% versus delayed Betaferon HR = 0.59 [0.42, 0.83] p = 0.0011		37% versus delayed Betaferon HR = 0.63 [0.48, 0.83] p = 0.0027	
Time to McDonald MS						
Kaplan-Meier estimates	69%	85%	No primary endpoint		No primary endpoint	
Risk reduction **Hazard ratio with 95% confidence interval** **log-rank test**	43% versus placebo HR = 0.57 [0.46, 0.71] p < 0.00001					
Time to confirmed EDSS progression						
Kaplan-Meier estimates	No primary endpoint		16%	24%	25%	29%
Risk reduction **Hazard ratio with 95% confidence interval** **log-rank test**			40% versus delayed Betaferon HR = 0.60 [0.39, 0.92] p = 0.022		24% versus delayed Betaferon HR = 0.76 [0.52, 1.11] p=0.177	

In the placebo-controlled phase, Betaferon delayed the progression from the first clinical event to CDMS in a statistically significant and clinically meaningful manner. The robustness of the treatment

effect was also shown by the delay of progression to multiple sclerosis according to McDonald criteria (Table 2).

Subgroup analyses according to baseline factors demonstrated evidence of efficacy on progression to CDMS in all subgroups evaluated. The risk for progression to CDMS within 2 years was higher in monofocal patients with at least 9 T2-lesions or Gd-enhancement on brain MRI at baseline. In multifocal patients, the risk for CDMS was independent from MRI findings at baseline, indicating a high risk for CDMS because of the dissemination of the disease based on clinical findings. For the time being there is no well-established definition of a high risk patient, although a more conservative approach is to accept at least nine T2 hyperintense lesions on the initial scan and at least one new T2 or one new Gd-enhancing lesion on a follow-up scan taken at least 1 month after the initial scan. In any case, treatment should only be considered for patients classified as high risk.
Therapy with Betaferon was well accepted as indicated by a high rate of trial completion (93% in the Betaferon group). To increase tolerability of Betaferon, a dose titration was applied and non-steroidal anti-inflammatory drugs were administered at start of therapy. Moreover, an autoinjector was used by the majority of patients throughout the study.

In the open-label follow-up phase, the treatment effect on CDMS was still evident after 3 and 5 years (Table 2) even though the majority of patients from the placebo-group were treated with Betaferon at least from the second year onwards. EDSS progression (confirmed increase in EDSS of at least one point compared to baseline) was lower in the immediate treatment group (Table 2, significant effect after 3 years, no significant effect after 5 years). The majority of patients in both treatment groups had no disability progression over the 5-year period. Robust evidence for benefit on this outcome parameter could not be demonstrated for 'immediate' treatment. No benefit, attributable to immediate Betaferon treatment, in quality of life (as measured by FAMS - Functional Assessment of MS: Treatment Outcomes Index) was seen.

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

5.2 Pharmacokinetic properties

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

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

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

5.3 Preclinical safety data

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

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

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

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients:

Vial (with powder for solution for injection):
Human albumin
Mannitol

Solvent (sodium chloride solution 5.4 mg/ml (0.54% w/v)):
Sodium chloride
Water for injection

6.2 Incompatibilities

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

6.3 Shelf life

2 years.

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

6.4 Special precautions for storage

Do not store above 30°C.
Do not freeze.

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

6.5 Nature and contents of container

Vial (with powder for solution for injection):
3 ml clear vial (type I glass) with a butyl rubber stopper (type I) and aluminum overseal and

Solvent (with sodium chloride solution 5.4 mg/ml (0.54% w/v)):
2.25 ml pre-filled syringe (type I glass) with 1.2 ml solvent.

Pack sizes
- Pack with 5 single packs, each containing 1 vial with powder, 1 pre-filled syringe with solvent, 1 vial adapter with needle, 2 alcohol wipes or
- Pack with 15 single packs, each containing 1 vial with powder, 1 pre-filled syringe with solvent, 1 vial adapter with needle, 2 alcohol wipes or
- Pack with 14 single packs, each containing 1 vial with powder, 1 pre-filled syringe with solvent, 1 vial adapter with needle, 2 alcohol wipes or

- Pack with 12 single packs, each containing 1 vial with powder, 1 pre-filled syringe with solvent, 1 vial adapter with needle, 2 alcohol wipes or
- 2-month pack with 2x14 single packs, each containing 1 vial with powder, 1 pre-filled syringe with solvent, 1 vial adapter with needle, 2 alcohol wipes or
- 3-month pack with 3x14 single packs, each containing 1 vial with powder, 1 pre-filled syringe with solvent, 1 vial adapter with needle, 2 alcohol wipes or
- 3-month pack with 3x15 single packs, each containing 1 vial with powder, 1 pre-filled syringe with solvent, 1 vial adapter with needle, 2 alcohol wipes or
- Titration pack for dose titration with 4 differently coloured and numbered triple packs:
  - yellow, with number "1"(treatment days 1, 3 and 5; 0.25-ml syringe marking),
  - red, with number "2" (treatment days 7, 9 and 11; 0.5-ml syringe marking),
  - green, with number "3" (treatment days 13, 15 and 17; 0.75-ml syringe marking),
  - blue, with number "4" (treatment days 19, 21 and 23; 0.25, 0.5, 0.75 and 1-ml syringe marking)

  Each triple pack contains 3 vials with powder, 3 pre-filled syringes with solvent, 3 vial adapters with pre-attached needle and 6 alcohol wipes.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Reconstitution:
To reconstitute lyophilized interferon beta-1b for injection, connect the vial adapter with the attached needle on the vial. Connect the pre-filled syringe with solvent to the vial adapter and inject the 1.2 ml of the solvent (sodium chloride solution, 5.4 mg/ml (0.54% w/v)) into the Betaferon vial. Dissolve the powder completely without shaking.
After reconstitution, draw 1.0 ml from the vial into the syringe for the administration of 250 microgram Betaferon. For the dose titration at the start of treatment, draw the respective volume as given in section 4.2.

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

Inspection prior to use
Inspect the reconstituted product visually before use. The reconstituted product is colourless to light yellow and slightly opalescent to opalescent.

Discard the product before use if it contains particulate matter or is discoloured.

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

7. MARKETING AUTHORISATION HOLDER

Bayer AG
51368 Leverkusen
Germany

8. MARKETING AUTHORISATION NUMBERS

EU/1/95/003/005
EU/1/95/003/006
EU/1/95/003/007
EU/1/95/003/008

EU/1/95/003/009
EU/1/95/003/010
EU/1/95/003/011
EU/1/95/003/012

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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

10. DATE OF REVISION OF THE TEXT

12/2022