SCIENTIFIC DISCUSSION

This module reflects the initial scientific discussion for the approval of Betaferon. This scientific discussion has been updated until 9 January 2003. For information on changes after this date please refer to module 8B

1. Introduction

Multiple sclerosis (MS) is a common, non-traumatic cause of neurologic dysfunction in young adults, and is the commonest disabling neurological disease of young people in the northern temperate zones. The highest prevalence is in Northern Europe (> 200/100,000 in Scotland). The estimated number of newly diagnosed cases in Europe is more than 10,000 per year. The median age of onset is 33 years. Multiple sclerosis is usually categorised on the basis of clinical manifestations as benign (15-20%), primarily progressive, relapsing-remitting and secondary progressive disease (60-75%).
Clinically, MS occurs in two basic forms:

A progressive loss of function, e.g. leg weakness, known as *primary progressive MS.* It is the least common type, comprising 10-14% of patients, more frequent in men and has onset in the 5th and 6th decade.

Most patients with MS present with a relapsing-remitting course. They have a disease course characterised by attacks of neurologic dysfunction (exacerbations or relapses) that are followed by complete or incomplete recovery, which are called remissions. It is commoner in females and has a maximum incidence in the early 30s. Some never develop significant disability (the *benign* form RRMS) - about 15% of all patients. However, about 70% of the RRMS patients develop increasing deficit after initial relatively benign relapses. Whilst some of the progression is due to a gradual accumulation of deficit consequent upon incomplete recovery from relapses, much of the progression follows a more insidious, continuous decline with or without superimposed relapses, known as *secondary progressive* MS.

Therapy for MS falls into 3 main categories: symptomatic therapy, treatment of the acute relapse, and attempts to favourably alter the natural history of the disease by reducing relapse rate and progression.

Effective symptomatic treatments are available to alleviate common symptoms such as spasticity, bladder disturbances, sexual dysfunction, ataxia pain, and weakness. Acute relapses are often treated with corticosteroids. While substantial advances have been made in these first two areas, attempts to alter the course of the disease have been largely unsuccessful until recently.

Based on the hypothesis that immunologic dysregulation underlies MS, a large number of trials of immunomodulating therapy have been conducted. The pivotal trials with interferon beta-1b in relapsing-remitting MS have shown that the frequency and severity of clinical relapses in ambulatory patients can be significantly reduced. In a study, in the secondary progressive form of multiple sclerosis, interferon beta-1b slowed progression of disease and reduced the frequency of clinical relapses.

The mechanisms of action of interferon beta-1b in multiple sclerosis are not known, but plausible explanations have been proposed.

The biological actions of interferon beta-1b comprise antiviral activity, modulation of cytokine production/activity (e.g. inhibition of IFNγ, IL-1, TNFα, upregulation of TGFß expression), and alteration of dysregulated T cell function in multiple sclerosis.

2. Chemical, pharmaceutical and biological aspects

Betaferon is presented as a sterile lyophilised powder in 3 ml vials containing 0.30 mg interferon beta-1b, together with human albumin and dextrose. A diluent of 0.54% sodium chloride solution is supplied for reconstitution. Reconstituted solution contains 0.25 mg interferon beta-1b (8 MIU) per ml.

A shelf life of 18 months (for Betaferon in vial) and 36 months (for sodium chloride solution in pre-filled syringe) has been approved. The product should be stored at 2-8°C.

The holder of the marketing authorisation is Schering AG. The product is packed and released for sale in the EU by the holder of the marketing authorisation, Schering AG.

The active ingredient in Betaferon is interferon beta-1b (pINN). Interferon beta-1b is a human recombinant interferon beta in which the native cysteine is replaced by serine at position 17, lacks methionine in position 1 and carbohydrate moieties, and is produced in E. coli cells.

The E. coli production strain contains the gene for interferon beta-1b, which was derived from the human gene for interferon beta by site directed mutagenesis on a recombinant plasmid. In order to avoid any risks associated with material of bovine origin in the manufacturing process for Betaferon, a modified process for the generation of the Working Cell Bank has been established, in which a soya bean extract is used. The strain is grown in a minimal salt/glucose medium using standard fermentation techniques. The cells are harvested, disrupted and homogenised. Interferon beta-1b is isolated by extraction with butanol from the inclusion bodies obtained after centrifugation of the homogenated cells. It is purified by two successive size exclusion chromatography steps and is finally formulated with human serum albumin and dextrose and then lyophilised. After formulation the bulk product is filtered through two filters.

The results of batch analyses suggested that specification limits could be tightened and the applicant has agreed to this. The specification for moisture content has been tightened accordingly. The revised specifications and analytical methods proposed are considered adequate to ensure quality and consistency of the active ingredient and the finished product and all questions on quality raised during the assessment of the application have been answered to the satisfaction of the CPMP.

Chemical, pharmaceutical and biological documentation provided post-authorisation

The Company submitted additional chemical, biological and pharmaceutical information according to the specific obligations and follow up measures defined by the CPMP.

The Company provided full data on development programme and has performed extensive studies on the purity and by-products resulting in variations introducing new methods and amending specifications. The current manufacturing process has proved to produce a product with consistent quality, which has extensive clinical data.

Clarification was required regarding the monitoring of the possible modification of an excipient.
The data provided showed an improved and more robust stability profile.

The Company applied for a new pharmaceutical form of Betaferon, in which the solvent vial is replaced with a pre-filled syringe in two pack sizes:

15 vials containing interferon beta-1b and 15 pre-filled syringes containing solvent

5 vials containing interferon beta-1b and 5 pre-filled syringes containing solvent

The company justifies this proposed change for the convenience of the patients, particularly disabled patients. The use of the pre-filled syringe is expected to reduce the complexity of reconstitution of the lyophilised drug. The Company has therefore decided to replace on the market the presentations with the solvent vial for the presentations with the solvent in pre-filled syringes.

The assessment of this application is based on the assessment report of the original dossier submitted, updated in the light of new data and analyses provided by the applicant.

To support the new pharmaceutical form “pre-filled syringe” for the solvent, the applicant submitted full Part II information for this new presentation.

No new data concerning toxico-pharmacological aspects and clinical aspects were submitted.

The obligations and follow up measures have been satisfactorily fulfilled by the MAH.

Manufacturing plants and inspection status

Manufacturer of active substance:

Boehringer Ingelheim Austria, A-1121 Vienna, Dr.-Boehringer-Gasse 5-11, Austria.

Authorisation delivered by Magistrat der Stadt Wien, on 30 May 1985.

Authorisation delivered by the Bundesministerium für Gesundheit und Konsumentenschutz, Wien on 30 January 1995.

Chiron Corporation, 4560 Horton Street, Emeryville CA, USA.

The Chiron manufacturing plant was subject to EU inspection on 11-12 May 1995.

Manufacturer of solvent:

B. Braun Medical S.A., Huelma 5, Poligono Industrial los Olivares, 23009 Jaen, Spain

Vetter Pharma-Fertigung GmbH & Co. KG, Schuetzenstrasse 99/101, D-88212 Ravensburg, Germany.

Authorisation delivered by Regierungpräsidium, Tübingen, on 5 August 1996.

GMP Certificate delivered by Regierungpräsidium, Tübingen, on 19 June 1996.

Manufacturer of the dosage form:

–Boehringer Ingelheim Pharma KG, Birkendorfer Str. 65, D- 88397 Biberach an der Riss, Germany.

GMP Certificate delivered by Regierungpräsidium, Tübingen, on 5 March 1992.

GMP Certificate delivered by Regierungpräsidium, Tübingen, on 3 February 1995.

Chiron Corporation, 4560 Horton Street, Emeryville CA, USA.

The Chiron manufacturing plant was subject to EU inspection on 11-12 May 1995

Manufacturer responsible for batch release in the European Economic Area:

Schering Aktiengesellschaft, D-13342 Berlin, Germany

GMP certificate issued by Senatsverwaltung für Gesundheit und Soziales, Berlin. Schering Aktiengesellschaft, Germany is the marketing authorisation holder of the medicinal product Betaferon.

3. Toxico-pharmacological aspects

The mechanism of action of Interferon beta 1-b in multiple sclerosis is not known, but plausible explanations have been proposed.

The biological actions of interferon beta-1b include antiviral activity, modulation of cytokine production/activity, e.g. inhibition of IFN, IL-1, and TNF**,** upregulation of TGFß expression, and alteration of dysregulated T cell function in multiple sclerosis.

The preclinical pharmacokinetics of interferon beta-1b have been characterised in the African Green Monkey by measuring interferon beta-1b serum levels after intravenous, intramuscular and subcutaneous administration of the drug. Peak concentrations and AUC values were shown to increase after multiple dosing. However, no accumulation of interferon beta-1b in serum was observed when dosing frequency was less than once per day.

The species specificity and antigenicity of the test compound influenced toxicological evaluation. Risk assessment was based on subacute studies in monkeys, in which typical interferon effects such as transient hyperthermia and transient haematological alterations were observed. Owing to specific antibody formation, no chronic studies were performed.

Embryotoxicity studies revealed an abortive potential known to be characteristic for interferons.

As exogeneously administered proteins are unlikely to interact with cellular DNA, genotoxicity testing was limited to the Ames test and a short-term in vitro transformation assay, showing negative results.

During the centralised procedure, questions regarding the preclinical characterisation were answered comprehensively so that no issues were left open.

4. Clinical aspects

Pharmacodynamics

The clinical pharmacodynamics evaluation of Betaferon is based on one study in healthy volunteers and is completed by data derived from pilot and phase III studies where also testing for antigenicity was carried out.

From the study conducted in healthy volunteers biological markers (neopterin, beta-2 microglobulin and 2-5A synthetase) were used to compare biological responses after single versus every-other-day dosing. There was a dose dependent elevation of cellular 2-5A synthetase ($p < 0.0001$). The maximum response occurred at 24 h post-administration. Thereafter, the enzyme level decreased steadily, however, at the end of the study period (72 h post-administration), the elevation from baseline was still significant. There is no information on the therapeutic effect of Betaferon in MS compared with either the biological effect and/or serum levels.

Pharmacokinetics

Serum concentrations of interferon beta- 1 b are low or not detectable following subcutaneous administration of 0.25 mg (8 MIU) or less of Betaferon. As pharmacokinetic information in patients with MS receiving the recommended dose of Betaferon is not available, a new pharmacokinetic assay is under development.

The pharmacokinetics of Betaferon has been investigated after intravenous administration in healthy volunteers and in patients with non-neurological disease. Following intravenous injection of 0.5 mg (16 MIU, new standard) of Betaferon to healthy volunteers, serum activities rapidly decreased in two phases with mean half-lives of 0.42 and 4.35 hours. Essentially similar results were obtained in patients with non-neurologic disease at various dosages. The elimination half-life ranged between 2-5 hours. Mean clearance rates were estimated to be at most 30 $ml \cdot min^{-1} \cdot kg^{-1}$.

Maximum serum levels of about 40 $IU \cdot ml^{-1}$ were found 1-8 hours after subcutaneous injection of 0.5 mg (16 MIU) interferon beta-1b.

Clinical Efficacy

Efficacy in relapsing remitting multiple sclerosis

An overall summary of the main efficacy results is provided in the following table:

	placebo n=112	1.6 MIU[x] n=111	8 MIU[xx] n=115	overall p value
Primary				
Annual exacerbation rate	1.27	1.17[$]	0.84[***,++]	0.0001
90 % CI	1.12-1.43	1.03-1.33	0.72-0.97	
No. subjects exacerbation free	18	23	36[**]	0.019
Secondary				
Median days to:				
- first exacerbation	153	180	295[*,+]	0.030
- second exacerbation	503	556	>762[**,+]	0.015
(MRI) mean total lesion area in mm^2 : baseline	2611	2750	2392	
Mean change at endpoint[1]	509.1	200.1	-100[***,+]	0.0002
Mean EDSS[a)]				
- baseline	2.9	2.9	3.0	0.827
- last value	3.1	3.0	2.9	0.518
Mean Scripps				
- baseline	80.4	81.0	81.0	0.872
- endpoint	80.3	80.7	81.8	0.181

[a)] Kurtzke Expanded Disability Status Scale (EDSS)

[*] $p < 0.05$, 8 MIU vs placebo

[**] $p < 0.01$, 8 MIU vs placebo

[***] $p < 0.005$, 8 MIU vs placebo

[+] $p < 0.05$, 8 MIU vs 1.6 mIU

[++] $p < 0.01$, 8 MIU vs 1.6 mIU

[$] $p < 0.05$, 1.6 MIU vs placebo

[x] new standard - equivalent to 9 MIU old standard

[xx] new standard - equivalent to 45 MIU old standard

[1] The cohort subject to frequent MRI scanning showed a reduction of active lesions (= new, recurring, and enhancing lesions) by 59% (mean), new lesions were reduced by 62%.

The following endpoints were considered in the evaluation of the efficacy of Betaferon in relapsing remitting multiple sclerosis:

Reduction in Relapse Rate

In an analysis which examined the types of relapses observed, it was shown that the most impressive relapse reductions involved systems likely to be most disabling functionally, particularly the cerebellar and pyramidal systems, as well as the brainstem and the bladder.

It was concluded that the reduction of the relapses was not of trivial clinical or social consequence.

The reduction of relapse rate and relapse severity resulted in a reduction of steroid use, a mainstay of relapse therapy.

A major benefit of the reduction in relapse rate is derived from the fact that not all patients recover fully from a relapse, i.e. incomplete remission is one means by which disability accumulates.

The number of hospitalisations for MS was substantially reduced, providing further evidence that some of the relapses were indeed significant and that there was a saving in terms of handicap by the administration of interferon beta-1b.

Disability

Disability, a secondary endpoint in the interferon beta-1b trial, is extremely important from a clinical viewpoint. The data do not show a significant favourable effect over a two-year period on disability as assessed by the Scripps score or the EDSS. Given the relatively short duration of study and the small change in the EDSS in the placebo group, it was not possible to show a large beneficial effect upon disability even at 3 years. (see also section 6)

Disease Burden

Disease burden as measured by magnetic resonance imaging (MRI) was a surrogate endpoint in the clinical trials of interferon beta-1b, and was intended to provide additional evidence that patients benefit from treatment with IFN ß-1b. After three years of treatment, disease burden as measured by MRI was slightly reduced in the group receiving the therapeutic dose of interferon beta-1b, while it increased by about 20% in the placebo group. The group differences increased progressively with time, and gradually with dosage. However, it has not yet been proven that disease burden as measured by MRI demonstrates the disease process accurately, or that there is a correlation with disability.

During review, additional questions were raised regarding the safety and efficacy implications of serum NA seen to develop in a significant proportion of patients receiving Betaferon therapy.

During the formal hearing held at the CPMP meeting on 16 May 1995, the company presented proposals for additional post-approval studies to further elucidates the effects of serum NA on clinical safety and efficacy.

The chemistry and pharmaceutical data submitted in the application were judged sufficient to support product quality, pending clarification on specific issues.

After considerable dialogue, the preclinical data presented were judged to be sufficient to prove safety in view of the limited applicability of standard toxicological approaches to evaluating the effect of species-specific bioactive proteins.

The therapeutic efficacy of interferon beta-1b at a dose of 8 MIU given subcutaneously on alternate days outweighs any adverse events likely to occur.

These data were judged sufficient for approval on the light of the current scientific knowledge.

Efficacy in secondary progressive multiple sclerosis (data submitted post-authorisation)

As part of the clinical specific obligations set out by the CPMP and agreed upon by the MAH additional data were to be provided as follows:

The Company submitted a report of the study conducted in Europe on the Secondary Progressive form of Multiple Sclerosis (SPMS). The data submitted to support the variation application for the extension of the indication to include Secondary Progressive Multiple Sclerosis (SPMS), are the results of a prospectively planned interim analysis in a Phase III study in 718 patients suffering from the secondary progressive form of multiple sclerosis. The study was a double-blind placebo-controlled multicentre study. The study was designed to evaluate the safety and efficacy of 8 MIU interferon beta-1b given subcutaneously on alternate days for up to 3 years to outpatients with SPMS.

The trial was a 3 year randomised multi-centre double blind placebo controlled study. Sample size was determined on the assumptions that the proportion of patients with confirmed progression in the placebo group would be 50% at 3 years, and that a treatment difference of 12.5% was to be detected – considering one prospectively planned efficacy interim analysis and taking drop-outs into account.

An interim analysis of efficacy was prospectively planned to be conducted after all patients had completed at least 2 years of treatment. An independent Advisory Board reviewed results. The interim analysis of data up to November 20, 1997 led to a recommendation to terminate the study, based on evidence of efficacy as defined prospectively by a level of significance of p=0.0133 for the primary endpoint in the ITT (Intention To Treat) population (n=718). The interim analysis relates to the safety and efficacy results, comprising data for all patients up to 24 months, plus all data available from the third year of the study for Kurtzke Expanded Disability Status Scale (EDSS), relapses and safety at the interim cut off date.

The primary efficacy variable was the time to a confirmed increase by 1 point on the EDSS from baseline if the entry score was 3.0 to 5.5, or 0.5 points on the EDSS if the baseline score was 6.0 or The increased score had to be maintained for 3 months before progression was confirmed.

Secondary and Tertiary Efficacy Variables were:

1. Proportion of patients with confirmed progression.
2. Time to becoming wheelchair bound (EDSS 7.0).
3. EDSS at endpoint.
4. Reduction of relapse rate where relapses were defined as
   - new neurological abnormality or the reappearance of a previous neurological abnormality
   - lasting more than 24 hours

   in a patient who
   - had been stable, was improving or slowly progressing in the previous 30 days.
   - and in whom there was no infection, fever or withdrawal of steroid medication at the time of the relapse.

A relapse was considered verified if evaluated by a Clinician within 14 days of its occurrence. Only verified relapses were used in these analyses.

The *results* of the study can be summarised as follows: Compared with placebo, patients (baseline EDSS 3 to 6.5) receiving Betaferon showed a statistically significant delay in time (several months) to progression of multiple sclerosis. The treatment effect occurred in patients with and without relapses and at all levels of disability investigated (patients with mild disease and those unable to walk were not studied). Patients receiving Betaferon also showed a statistically significant delay in the time

(several months) to become wheelchair-bound when compared with placebo. Secondary progressive multiple sclerosis patients receiving Betaferon showed a reduction in frequency (30%) of clinical relapses. There is no evidence of an effect of Betaferon on the duration of exacerbations. Details are presented in the following tables and figures.

Table 1: Summary of primary and secondary efficacy results in the ITT population (n=718)

Endpoint		Placebo (n=358)	IFNß-1b (n=360)	p-value
Time to confirmed progression [1)]				**0.0008**
Estimated survival rates [2)]:	Year 1	0.71	0.81	0.0031
	Year 2	0.53	0.65	0.0012
	Month 33	0.47	0.58	0.0015
Time to becoming wheelchair-bound [2)]				**0.0133**
Estimated survival rates [2)]:	Year 1	0.90	0.96	0.0129
	Year 2	0.81	0.89	0.0094
	Month 36	0.66	0.77	0.0133
Mean annual relapse rate [3)]		0.64	0.44	**0.0002**

Mantel-Haenszel test for covariance adjusted logrank scores with covariance adjustment for baseline EDSS and stratification adjustment for centre (non-parametric analysis of covariance)

Mantel-Cox logrank test with stratification adjustment for baseline EDSS category

Mantel-Haenszel test with covariance adjustment for relapses in 2 years prior to study and stratification adjustment for centre.

Figure 1: Life-table estimate – Time to confirmed progression

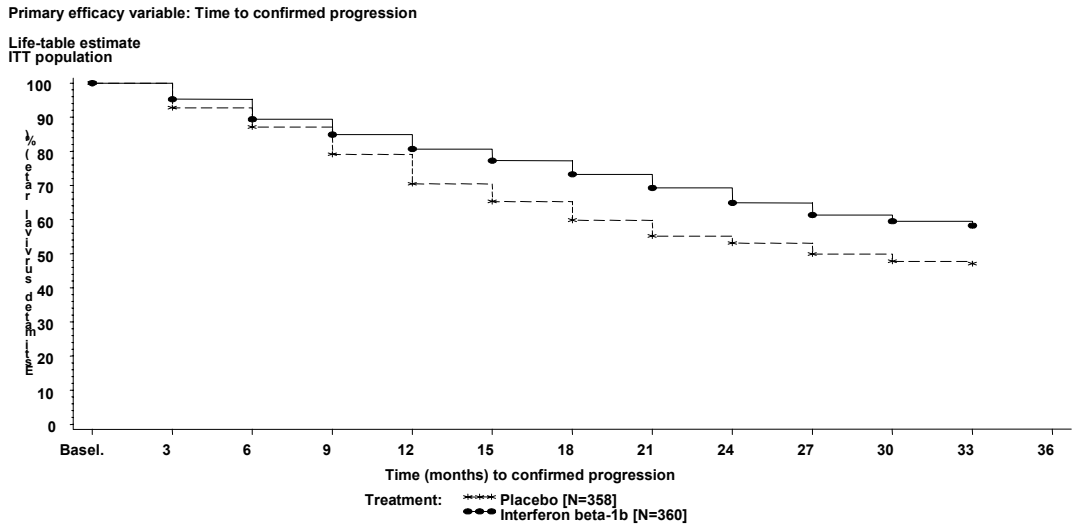


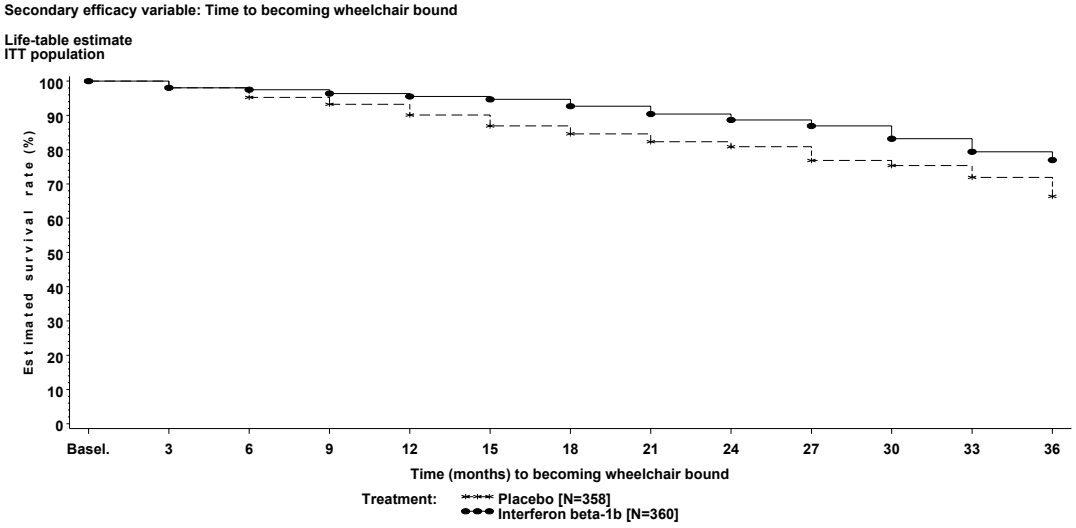
Table 2: Summary of tertiary and additional efficacy results in the ITT population (n=718)

Endpoints	Placebo (n=358)	IFNß-1b (n=360)	p-value
Proportion of patients with confirmed EDSS increase:			
Patients lost to follow-up counted as progressed (ITT-A analysis) [1, 2)]	55.0%	44.2%	0.0056
Proportion of patients with confirmed EDSS increase (ITT-B analysis) [1, 2)]	49.7%	38.9%	0.0048
Additional analysis: Proportion of patients becoming wheelchair-bound	24.6%	16.7%	0.0277

Efficacy variables included in the review of the interim data set of the independent Advisory Board

Mantel-Haenszel test with stratification adjustment for baseline EDSS

Figure 2: Life-table estimate – Time to becoming wheelchair bound



Clinical safety

Clinical safety in relapsing remitting multiple sclerosis

At the time of the submission of the dossier, a total of 3067 patients received Betaferon in 73 studies of whom 407 participated in the MS studies. Data are provided from patients with a variety of conditions, and who were treated with interferon beta-1b at dosages of up to 28 MIU daily (160 MIU of the old WHO standard).

Four hundred and seven patients with MS have been assessed for adverse events, 277 received IFN and 130 placebo. Interferon beta-1b injections at a dosage of 8 MIU or less in patients with MS caused short-lived fever, myalgia, and malaise; events lessened over the first 3-6 months. Local inflammatory reactions at the site of the injection were common and, in a proportion of patients, necrosis was reported at the injection site. Injection site necrosis may occur at single or multiple injection sites, sometimes leading to scar formation.

Other serious adverse events were observed during the treatment with Betaferon, even though they were not unequivocally related to interferon beta-1b administration like convulsions and attempted suicide.

Among laboratory abnormalities observed during the treatment with Betaferon, reversible leukopenia as well as elevated SGOT and SGPT were a frequent occurrence.

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.

Clinical safety in secondary-progressive multiple sclerosis (data submitted post-authorisation)
Clinically relevant laboratory abnormalities occurred rarely and for the most part were evenly distributed among placebo and IFNB-1b treated patients. As expected, IFNB-1b-treatment was significantly associated with elevations of transaminases and decreased values for leukocytes, neutrophils and lymphocytes. Toxicity grades 3 and 4 were rare for transaminase elevations, as were hematologic parameters, being associated with active treatment for lymphopenia only (placebo patients 7.5% vs. IFNB-1b patients 21.7%).

Serious adverse events*: m*ost of the SAEs reported during the study were MS-related. Non-MS related SAEs were comparably distributed between treatment groups in all body systems with the exception of injection site events (0 placebo patients vs. 8* (2.2%) IFNB-1b patients). Four patients died during the study, 3 of which were in the IFNB-1b group. One patient in each treatment group committed suicide. Of the other two deaths in the IFNB-1b group, one patient died of bronchopneumonia with lung oedema, and another of pulmonary embolism.

Muscular hypertonia was reported significantly more often in the IFNB-1b group (37.8% patients) than in the placebo group (27.4% patients).

Other significant adverse events: injection site necrosis was reported in 4.7% of patients receiving IFNB-1b, consistent with previously reported frequencies of this event. Flu-like symptom complex (fever, chills, myalgia, malaise or sweating) has been seen frequently. The incidence rate of the symptoms decreased over time. There were 5 suicide attempts in the placebo group* (1.4%) and 3 suicide attempts in the IFNB-1b group (0.8%) (Including one patient in either group, who committed suicide). Neither the AE/SAE evaluations nor the MADRS (Montgomery Asberg Depression Rating Scale) scores indicated any elevated risk of IFNB-1b to develop depression or have suicidal thoughts.

Persistence of effect

The persistence of effect in patients with Remitting Relapsing Multiple Sclerosis was not satisfactorily addressed by the information available at marketing authorisation. The CPMP agreed that it might be addressed by data generated in the third year of treatment in the two studies in SPMS (secondary progressive multiple sclerosis). For secondary progressive multiple sclerosis efficacies for a period of two years with limited data for a period of up to three years of treatment have been demonstrated under controlled clinical-trial conditions. With respect to the NAB status following discontinuation of therapy, it was considered that the SPMS study might supply useful information. The CPMP requested that patients should be followed up to 1 year after the study has been completed, and the analysis should include evaluation of NAB titre as a continuous variable and relation to multiple endpoints explored.

Serum Neutralising Activity in relapsing remitting MS

Relapsing-remitting multiple sclerosis patients treated with interferon beta-1b was monitored for the development of serum neutralising activity (NA). Neutralising activity was defined as the ability of patient sera to reverse or neutralise the antiviral effect of interferon beta-1b, protecting cells in culture from being killed by viral infection. This assay method shows significant variability, with many patients being only transiently positive despite continued treatment with interferon beta-1b. If positive is defined as two consecutive positive values, typically 3 months apart, 65% of patients were negative when tested subsequently. Over three years, 35% of patients receiving recommended doses of interferon beta- 1b were found to have NA at two or more consecutive observations.

The primary analysis of efficacy was based on the 2-year data set. Patients receiving 8 MIU of interferon beta-1b showed no difference in the relapse rate between the NA-positive and the NA-negative groups when relapse rates from baseline to years 1 and 2 were considered. When the data are

* One patient not included in frozen database.

examined at 6-monthly intervals, a trend is evident in the period from 19-24 months suggesting a higher relapse rate in patients with NA compared to those without.

In an additional analysis of patients with two consecutive positive titres in the 3-year database, this trend is confirmed and the difference becomes significant in the 19-24 months period.

It can be seen that the relapse rate was significantly higher in the NA-positive patients up to 30 months, but then this difference was lost for the final 6 months (31-36 months).

It is noted that there was a correspondingly lower relapse rate in the NA-negative group during these periods.

However, the greater effect seen in the negative group was camouflaged in the common analysis of both groups, leading to an underestimation of the efficacy of the drug.

Analysis of the percentage change of the total lesion area as detected by MRI done at yearly intervals showed no significant difference and no trend was seen between the NA-positive and the NA-negative subjects in any of the three years. In contrast, there is a suggestion that the numbers of new lesions and enlarging lesions are greater in the NA-positive patients than the NA-negative patients. With respect to the new lesions, these differences are not quite significant but, interestingly, the enlarging lesions are significantly more frequent after the first year in the positive group.

There was no evidence of increased frequency of any adverse events in patients who developed NA. Indeed, there is some indication that the flu-like symptoms commonly seen after interferon administration may be less frequent in patients who develop NA.

This development of NA is associated with a reduction in clinical efficacy as measured by relapse rate, becoming evident at 19-24 months; however high titres of NA within individual patients do not appear to be associated with any evidence of worsening compared to the baseline.

Neutralising Antibodies (data submitted post-authorisation)

A new, sensitive and reliable assay has been developed after the marketing authorisation was granted, for the determination of neutralising activity.

Using this new assay it has been shown that the neutralising antibodies against the recombinant interferon beta-1b also interact with endogenous interferon beta albeit to a lesser extent.

The original analyses of NA effects did not take into consideration the relapse rate before becoming NA positive, further analyses have, therefore, recently been performed, which adjusted for possible time trends over the course of the trial. Definitions for NA positivity were the same as for the original analysis and were based on data obtained from the recently developed MxA neutralisation activity assay and on the full 5-year data set.

The results based on the 5 years of available longitudinal data from the pivotal trial and its extension did not support an unequivocal conclusion that in individual patients the change from an NA negative to an NA positive status is associated with a diminished effectiveness of interferon beta-1b.

Autoimmunity (data submitted post-authorisation)

In order to evaluate a possible association of increased risk of autoimmune-mediated disease, following discussions with experts, it was recommended to re-analyse pooled data of the two pivotal studies in RRMS and SPMS. All possible instances of autoimmune disease should be identified. The sample size was considered to provide a sufficient study power to assess whether there is an important associated risk of Betaferon treatment with regard to autoimmune-mediated disease. After completion and unblinding the data of the currently ongoing North American trial in SPMS could also be included in such an analysis. In addition, data will become available from an open-label study.

For the 4th annual re-assessment, the MAH submitted analyses regarding autoantibodies of sera from the European SPMS study. The study included 718 patients with SPMS participating in a randomised, double blind placebo controlled evaluation of hepatic function, thyroid function and assessment of a wide range of AAbs. The submitted data provide re-assurance over a 24- month period that no clinically relevant adverse effect on autoimmune function has been detected in the patient population studied.

Postmarketing Experience

According to Commission Regulation (EEC) 2309/93 and to the specific obligations stated in Annex II.C of the Commission Decision of 30 November 1995 and in chapter II of the CPMP Assessment Report (CPMP/213/95), the Marketing Authorisation Holder submitted during the concerned period the requested Periodic Safety Update Reports (PSURs) and line listings. The evaluation of this data is presented in this section.

Interferon beta-1b has been registered in the USA since July 1993 under the trade name Betaseron for use in ambulatory patients with relapsing-remitting multiple sclerosis to reduce the frequency of clinical exacerbations. Since registration, over 40,000 patients have been treated with the product in the USA. Apart from the USA and the EU (November 1995), Betaferon is currently authorised in a number of other countries including Canada, Australia, New Zealand, South Africa, and several Asian and Latin American countries.

Based on the analysis of post-approval drug experience reports and on the Periodic Safety Update Reports submitted at six-month intervals, as part of the drug surveillance program to be carried out in line with the existing EU legislation, further information has been accrued.

The SPC and PL texts have been updated and extended to include additional information on possible injection site necrosis, drug induced hepatitis, thrombocytopenia with profound decreases in platelet count in rare cases with recommendations to minimise such reactions.

Since the second annual re-assessment changes to the safety sections of the SPC were proposed and were the subject of positive opinion by CPMP:

- addition of statements on cardiomyopathy and on the development of capillary leak syndrome in patients with monoclonal gammopathy to section 4.4 of the SPC
- addition of cardiomyopathy to section 4.8 of the SPC
- addition of muscular hypertonia to Section 4.8 of the SPC
- Section 4.8 Undesirable effects
  "... Rare cases of thyroid dysfunction (hyper- as well as hypothyroidism) associated with the use of Betaferon have been reported."

There was said to be no increased frequency of listed reactions during the review period.

There were no reports of drug interaction, overdose or abuse. No negative effects of long-term treatment were identified.

Since the third annual re-assessment changes to the safety sections of the SPC were proposed and were the subject of positive opinion by CPMP:

- Addition of dyspnoea and lymphadenopathy to section 4.8 of the SPC

5. Overall conclusions and benefit/risk balance

Multiple sclerosis is a serious neurological disease affecting the central nervous system including the spinal cord, resulting in significant morbidity as well as progressive disability in many afflicted individuals. The underlying aetiology is not clearly understood.

All currently available therapeutic interventions are non-specific and largely symptomatic in nature.

Because of the significant unmet clinical need for specific treatment for multiple sclerosis, the initial Betaferon application-containing results from two pivotal studies with 372 patients was accepted is support of the therapeutic indication for the treatment of Relapsing-Remitting Multiple Sclerosis.

The CPMP Members have, during the first review process, agreed that the application contains adequate clinical data to support clinical safety and efficacy, allowing a positive recommendation for marketing approval for the treatment of Relapsing-Remitting Multiple Sclerosis.

The MA Holder has stipulated several pharmaceutical and clinical follow-up measures as requiring action: most of the pharmaceutical follow-up measures were satisfactorily fulfilled and some required additional studies.

With regard to the clinical specific obligations, the decision to stop the trial in patients with SPMS was supported by the evidence presented. The CPMP and the European Commission approved the SPMS indication for the use of Betaferon after submission of the dossier and full review of all data. The Company will also submit a report of the study conducted in the USA / Canada on the secondary progressive form of multiple sclerosis.

In view of the specific obligations on neutralising antibodies all patients from the studies in secondary progressive MS should be followed up irrespective of early termination in order to provide further long-term data on NAB in relation to safety and efficacy.

Additional data was provided after authorisation relevant to pharmaceutical and biological aspects as well as clinical aspects.

The SPC and PIL have been amended to reflect the additional clinical safety evaluations carried out by the CPMP within the assessment of the PSURs submitted and of various applications for variations to the terms of the marketing authorisation.

On the basis of additional clinical efficacy data submitted post-authorisation the CPMP recommended the extension of the indication to include Secondary Progressive Multiple Sclerosis (SPMS). The European Commission issued a corresponding decision on 26 January 1999. On the basis of the additional efficacy and safety data provided, the benefit/risk profile for Betaferon remained in favour of the drug in the context of the serious condition being treated.

The CPMP re-assessed annually the benefit risk profile of Betaferon on the basis of the information generated during the first five years of marketing of Betaferon. At the meeting on 14 December 2000, the CPMP, having reviewed the fifth annual reassessment and the compliance with the specific obligations submitted by the Marketing Authorisation Holder, considered that the MAH has made progress in fulfilling all outstanding obligations and most of the follow-up measures. Since all specific obligations as agreed between the Applicant and the CPMP on 12 July 1995 have been fulfilled, there are no remaining grounds for the Marketing Authorisation to be kept under exceptional circumstances. On 14 December 2000, the CPMP recommended therefore that the Marketing Authorisation for Betaferon would be released from the status “under exceptional circumstances”. At that moment, however, efficacy in SPMS based on the outcome of the North American SPMS study was under review in a separate type II variation procedure (see section 6).

6. Revision of the indication following results of the NA SPMS study (submitted post – authorisation)

Betaferon was granted an EU authorisation in November 1995 under exceptional circumstances for the indication of relapsing-remitting MS for “ the reduction of frequency and degree of severity of clinical relapses in ambulatory patients (i.e. patients who are able to walk unaided), characterised by at least two attacks of neurological dysfunction over the preceding two year period, followed by complete or incomplete recovery. 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 exacerbations, on symptoms in between exacerbations, or of the progression of the disease. There is also no evidence of an effect on disability in relapsing-remitting multiple sclerosis”.

As part of the specific obligations the Company was requested to submit a report of the study conducted in Europe (a) and in the USA/Canada (b) on the secondary progressive form of multiple sclerosis: (a) Double -blind, placebo-controlled multicenter study to evaluate the safety and efficacy of 8 MIU Interferon beta-1b vs placebo. (b) Double-blind, placebo controlled multicenter study to evaluate the safety and efficacy of two doses of Intereron beta-1b (8MIU per dose; 4.9 MIU/m2 body surface areas). Both studies had been terminated early, the former due to efficacy, the latter due to futility considerations.

Following the results of the European study Betaferon was granted an extension of the indication in secondary progressive multiple sclerosis for:
" slowing progression of disease and for the reduction of frequency of clinical relapses. Compared with placebo, patients receiving Betaferon showed a statistically significant delay in time to progression of multiple sclerosis. The treatment effect occurred in patients with and without relapses and at all levels of disability investigated (patients with mild disease and those unable to walk were not studied). Patients receiving Betaferon also showed a statistically significant delay in the time to become wheelchair-bound when compared with placebo. See also Section 5.1 "Pharmacodynamic properties". Secondary progressive multiple sclerosis patients receiving Betaferon showed a reduction in frequency (30%) of clinical relapses. There is no evidence of an effect of Betaferon on the duration of exacerbations.

The present variation has been submitted in the context of the clinical obligation related to the North American (NA) clinical study in SPMS. Based on the results of this study the MAH proposed to clarify the existing SPMS indication for Betaferon by adding:
"in patients with active disease. Active disease is evidenced by concurrent relapses or pronounced neurological deterioration (EDSS>1.0 points in the previous 2 years."

The NA study failed to show any significant differences between Betaferon and placebo with respect to efficacy in terms of slowing progression of disability in SPMS. As the design of the EU and NA studies were very similar, an attempt have been made by the MAH to provide an explanation. In the submission of this variation various issues were raised relating to differences in patient populations between the EU and NA studies. NA patients are older and have disease of longer duration. Rates of progression in the placebo-treated patients were significantly different between the two studies, however it was not clear if these differences would account for the conflicting results.

At the request of the CPMP, the MAH has provided a formal meta-analysis of the efficacy of Betaferon in SPMS with respect to time to progression of disability. In general, the meta-analysis has been performed using appropriate statistical methodology. The magnitude of the effect of Betaferon treatment was clearly higher in the EU study. However, compared with placebo, a statistically significant effect was observed for the licensed 8 MIU dose of IFNB when data from the two studies was pooled. Given the highly significant and clinically relevant results of the EU-SPMS study, combined with the significant result from the meta-analysis, it seems clear that Betaferon has some efficacy in this condition.

In the clinically defined subgroups of patients with relapses and/or changes in EDSS>1, there is no evidence of lack of homogeneity across the studies. However, a non-significant p-value when testing for a difference does not confirm that no difference exists. These analyses cannot therefore be interpreted as confirmatory evidence that no heterogeneity exists in these subgroups. For each subgroup, these statistical tests should be used alongside clinical judgement of the differences between the hazard ratios observed in each trial.

Analyses according to prior disease activity are supportive of a greater effect in patients with a higher disease activity as defined by relapse and EDSS criteria independently.

The meta-analysis confirmed the effects of Betaferon on time to progression of disability as being heterogeneous in the two SPMS trials but offers no explanation for this heterogeneity in terms of baseline covariates.

Since both studies were terminated early, the EU due to attained efficacy endpoints and the NA due to futility considerations, the MAH was asked to consider potential bias. It appears that the possibility of bias does exist with the early termination of the 2 studies, however, such bias would be small. Therefore, it is doubted that the meta-analysis has been unduly affected. In particular, because the potential biases in the two studies were in different directions, the test for homogeneity of the treatment effect in the meta-analysis is conservative.

The MAH was asked to justify the inclusion of EDSS-based criteria in addition to relapse-based criteria in identifying SPMS patients suitable for treatment with Betaferon.

A summary of differences between the EU and NA SPMS studies, including a table comparing baseline and demographic characteristics and summary statistics and figures of on-study disease activity for patients on placebo were presented. Post hoc subgroup analyses are presented on the NA and EU SPMS trials separately to investigate the effect of pre-trial disease activity on efficacy outcome. The subgroups are formed according to frequency of relapses and progression of EDSS > 1 in the two years prior to study.

There is no evidence to suggest that change in EDSS is not a useful predictor of efficacy and some of these explanatory analyses suggest it probably is useful. It would appear that the use of relapse and EDSS criteria to identify disease activity and likelihood of a clinical response to Betaferon in SPMS patients is justified and can be reflected in the authorised indication.

There was no convincing evidence of efficacy in patients without relapses who are still progressing (EDSS>1). The CPMP was also concerned about the lack of effect of Betaferon on disease progression in SPMS. These concerns were endorsed by the CPMP Ad Hoc group on beta interferons, which met on 28 May 2001. In their response document, the MAH has provided data from the existing plus additional post-hoc analyses in sub-groups of patients according to relapse rates and EDSS criteria. Based on these data the MAH concluded that in their view:

- Pronounced pre-study EDSS progression is a relevant modified of treatment response
- Sub-groups selected for the relapse-related disease activity at baseline as defined by total relapses, >=2 relapses, and exactly 1 relapse do not differ with regards to "prediction" treatment response
- There is insufficient evidence to limit the criteria defining "active disease" to "relapses" only
- Progression is related to baseline disease activity as shown by EDSS progression in the prior 2 years (observation in the placebo groups)

The data provided show consistently in all analyses that relapse activity of >=2 in 2 years does not materially differ from 1 relapse in 2 years in terms of correlation with response rate; confidence intervals for hazard ratios for such comparisons are all very similar.
Based on the data provided it is concluded that

- Presence of relapses correlates to the likelihood of effect but the latter appears to be independent of exact number of relapses
- Patients with 1 relapse and EDSS progression > 1 point may respond
- Patients with no relapses are unlikely to respond, irrespective of EDSS

The analyses presented do appear to indicate trends for predicting treatment response based both on relapses and changes in EDSS. However, because of the retrospective nature of these analyses and the unclear rationale concerning the role of the EDSS, the data are not considered sufficiently convincing to be included in section 4.1 of the SPC. Following discussions at the CPMP the statement "or pronounced neurological deterioration (EDSS > 1 point or > 0.5 for EDSS > = 6) within the last 2 years." was deleted from the indication (4.1 of the SPC) and a suitable statement was considered based on the above findings regarding patients with relapses as well as EDSS increase in the previous two years of >1 point (or >0.5 point for EDSS >=6), for inclusion in section 5.1 of the Betaferon SPC.

The indication for Betaferon was modified as follows:

- "Betaferon is indicated for the treatment of patients with relapsing remitting multiple sclerosis and 2 or more relapses within the last 2 years. Betaferon is also indicated for patients with secondary progressive multiple sclerosis with active disease, evidenced by relapses.