SCIENTIFIC DISCUSSION

I This module reflects the initial scientific discussion and scientific discussion on procedures, which have been finalised before 1 March 2004. For scientific information on procedures after this date, please refer to module 8B.

1. Introduction

Multiple sclerosis (MS) is characterised by chronic patchy inflammation of the CNS with demyelination and gliosis (scarring). Although the aetiology of the disorder is unknown, immunology abnormalities are considered to be important in its pathogenesis.
The characteristics of the clinical course of MS may be classified into four categories:

a) Relapsing/remitting form (approximately 65% of the patients) with attacks of neurologic dysfunction attributable to central nervous system plaques that resolve over weeks to months.

b) Relapsing/progressive form (about 15% of the patients) who have clinical exacerbations of the neurologic dysfunction with residual disability;

c) A chronic progressive form from onset.

d) A silent form, in which the disease remains inactive for years after one or two exacerbations with or without residual disability.

These clinical categories are not fixed and patients may change from category during the course of their disease.

Therapy for MS can be symptomatic treatment, treatment of the acute relapse, and therapy 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.

Treatment for reducing the frequency of exacerbations has been based so far on the use of immuno-suppressants; corticoids and ACTH have not proven to be efficacious.

Interferons, a family of naturally occurring proteins, are cytokines that mediate antiviral, antiproliferative and immunomodulatory activities.

It is unknown if these mechanisms of action of the interferons mediate the therapeutic effect in multiple sclerosis because the pathophysiology of multiple sclerosis itself is not yet well known.

Rebif contains recombinant interferon beta-1a, which is a glycoprotein with the same primary structure as that of natural human interferon beta.

Rebif is formulated as solution for injection in 1 ml glass pre-filled syringes. Rebif is available in two strengths: 22 micrograms and 44 micrograms. The recommended posology of Rebif is 44 micrograms given three times per week by subcutaneous injection. Rebif 22 micrograms, also given three times per week by subcutaneous injection, is recommended for patients who cannot tolerate the higher dose in view of the treating specialist. (see section 4.2 of SPC). For Rebif 44 micrograms see sections 6, 7 of this document.

Rebif is indicated for the treatment of patients with multiple sclerosis and with 2 or more relapses within the last two years. Efficacy has not been demonstrated in patients with secondary progressive multiple sclerosis without ongoing relapsing activity.

Treatment should be initiated under supervision of a physician experienced in the treatment of the disease.

2. Chemical, pharmaceutical, and biological aspects

Composition of the product

Rebif is available in two strengths (22 and 44 µg) and is presented in liquid form as solution for injection, with human serum albumin (HSA), mannitol and sodium acetate as auxiliary substances. HSA is added as a stabiliser and to prevent adsorption to glass or plastic tubing.

Rebif is provided as 0.5 ml solution for injection, in Type I glass (Ph.Eur.) 1 ml pre-filled syringes with bromobutyl plunger stoppers (Ph. Eur.). The product is available as a package of 1, 3 or 12 individual doses.

Method of preparation

Rebif is typically manufactured in the 10L - 75 L scale. With the exception of the filling step, which is performed at ambient temperature, the manufacture of the finished product is performed at 2-8°C.

Adequate tests are utilised for in-process control during formulation and filling of the product. The test schedules include determinations of pH, bio-burden, extractable volume as well as tests to control the integrity of filters used for sterile filtration.

The procedures used for preparation of excipient solution as well as compounding, sterile filtration, and filling of the product are satisfactorily validated.

Control of starting material

Specifications and routine tests of the active substance

Each production batch of the active substance is tested according to the intermediate specifications for:

Identity i.e. SDS-PAGE, N-terminal amino acid sequence, peptide map, RP-HPLC, carbohydrate map, and iso-electric point.

Purity

a) clarity, coloration and pH, which are tested according to Ph. Eur.

b) degradation, aggregation, and by-products (RP-HPLC, SE-HPLC, and SDS-PAGE)

c) impurities, DNA, host cell derived proteins, residual solvents (ELISA, GLC, IE-HPLC)

d) microbial contamination (Ph. Eur.) and endotoxins (LAL)

Potency, i.e. content of interferon-ß (RP-HPLC), activity (cytopathic effect).

All non *Ph. Eur.* methods have been satisfactorily validated and the specifications according to which the tests are performed are justified by batch data as well as data obtained in clinical trials.

Development genetics

Recombinant IFN-ß is produced in dehydrofolate reductase (DHFR) deficient Chinese Hamster Ovary (CHO) cells transfected with two plasmids, one carrying the interferon coding region, the other the sequences encoding mouse DHFR. Both plasmids are integrated into the host cell genome. The DHFR gene acts as a marker for the selection of transfected cells, but is also required to allow for methotrexate treatment and amplification of the cloned sequences.

Cell Bank System

Inconsistencies in the documentation on the history of the producer cell line identified in the primary submission were clarified in time of the processes, and data was submitted showing genetic and phenotypic stability of the Interferon-ß producing cell line. The consistency of the fermentation process was shown for a time that exceeds the time period used in production.

Production

Cell culture and harvesting of crude Interferon-ß is carried out in bioreactors and supported by growth-promoting microcarriers. Relevant in-process testing controls the propagation of the working seed, the seeds, the cells in bioreactors as well as the harvest. All raw materials used during fermentation are of acceptable quality.

Purification

The filtered and pooled crude harvests are purified by affinity chromatography, ion exchange chromatography, reversed-phase liquid chromatography and size exclusion chromatography. Three ultrafiltration or microfiltration steps are also included in the down-stream process.

Characterisation

The fermentation and purification procedures give an end product with consistent quality and characteristics from batch to batch. The active substance has a primary amino acid structure consistent with that of Interferon-ß obtained from human fibroblasts as confirmed by full amino acid sequencing. There is one potential N-glycosylation site on Interferon-ß and evidence was presented that carbohydrate chain is linked to Asn-80. The carbohydrate side chain structure was analysed by LC separation followed by FAB-MS analysis.

The microheterogeneity of the purified product was studied using Western Blotting and iso-electric focusing. The presence of degradation products was monitored by RP-HPLC and formation of aggregates/oligomers was measured by SE-HPLC.

The secondary structure was studied by identification of the disulphide bond between Cys31 and Cys141 by peptide mapping after enzymatic digestion.

Using both bioassay and immunoassay methods consistent specific activity of Interferon-ß bulk batches was demonstrated.

Control of the finished product

During the evaluation process, acceptable limits for the control test routine to be carried out were established.

Stability

The stability of the finished product is monitored in real-time studies. The approved shelf-life is **24** months. In addition to analyses of general features, parameters such as content (RP-HPLC), antiviral activity and sterility are studied. Furthermore, new methods were developed for monitoring contamination with dimers/oligomers as well as oxidised forms of Interferon-ß in the presence of HSA.

Follow-up measures to be fulfilled by the marketing authorisation holder

The company, after having been consulted, agreed to meet the commitment to submit to the EMEA within the defined timeframe, further information requested by the CPMP on chemical and pharmaceutical aspects. (Undertaking signed from Ares-Serono (Europe) Ltd, dated 16 December 1997).

Manufacturing authorisations/inspection status

The EU inspector team has inspected the manufacturer responsible for the production of the active substance, Interpharm laboratories Ltd, Science-Based Industrial Park, Kiryat Weizmann, 76110, Ness-Ziona Israel, on 23-24 July 1997 with a favourable outcome. An additional alternative manufacturer for the active substance, Laboratoires Serono S.A. Vevey, Switzerland, was authorised by Decision C(2001)567. The EU inspector team has inspected this Swiss site on 27-29 November 2000 with a favourable outcome.

The Serono site at Bari, Italy, responsible for batch release in the EEA, has been inspected during the assessments of Gonal-F and no further inspections are considered necessary. Manufacturing Authorisation issued on 14 January 1995 by the Ministero Della Sanita', Direzione Generale del Servizio Farmaceutico, Via della Civiltà' Romana 7, Roma Italia

Vetter Pharma - Fertigung GmbH & Co, Schützenstrasse 99/101, 88212 Ravensburg in Germany: is the manufacturer responsible for operations from formulation to packaging. Manufacturing authorisation was issued on 10 May 1991 by the Regierungspräsidium Tübingen, Konrad-Adenauer-Strasse 20, D-7400 Tübingen. . Industria Farmaceutica Serono SpA, Zona Industriale di Modugno, Bari, Italy has also been approved as an additional alternative manufacturer for operations from formulation to packaging pursuant to a variation approved on 17 August 2001.

3. Toxico-pharmacological aspects

Pharmacodynamics

A number of published studies detailing antiviral; antiproliferative and immunomodulatory effects of hIFN-beta were submitted to support the concept of interferon-beta therapy in multiple sclerosis. Very few of the published studies, however, involved the administration of Rebif. Subsequent to the first assessment, the applicant submitted data on the in vitro comparison of Rebif and native hIFN-β in terms of antiviral activity using the WISH/VSV cytopathic effect inhibition assay. A corresponding comparison of antiproliferative activities of the two substances was performed using four different cell-lines (WISH, A_{549}, Hs294-T and Hs695-T). The results obtained lend some support to the claim of bioequivalence between Rebif and hIFN-β.

Short term in vivo studies in cynomolgus monkeys, submitted as a response to questions from the CPMP, have shown that Rebif not only increases serum levels of the dynamic markers, neopterin and 2´,5´-OAS, but that TNF synthesis may be suppressed under certain experimental conditions.

A formal study of the general pharmacodynamics of Rebif was initially carried out in the rat which is not a species responsive to Rebif. Investigations of the general pharmaco-dynamics of Rebif, including studies of CNS-effects, were subsequently carried out in the Cynomolgus monkeys. At a dose of 20 MIU/kg SC, a slight increase in body temperature was noted in all animals from 2 to 5 hours after administration. Otherwise, the examined parameters were not markedly affected by up to 20 MIU/kg of Rebif. ECG-parameters have been recorded in toxicity studies in Cynomolgus monkey without any indication of cardiac toxicity.

Pharmacokinetics

Single dose studies in Cynomolgus monkeys have shown elimination half-lives of 2-6 and 5-8 hrs after IV and SC dosing, respectively. The estimated bioavailability after SC administration, the route used in the longest toxicity study, varied between 0.12 and 0.26.

In a repeated dose study with SC administration in the same species, an accumulation index (over 7 days of daily dosing) of 2.7 was estimated. This increase in exposure with time was shown to result in a corresponding increase in the pharmacodynamic markers neopterin and 2´,5´-OAS.

Toxicity studies

Studies of single-dose toxicity in the rat and Cynomolgus monkey did not reveal important toxic effects. Thirteen-weeks IV and IM repeated dose toxicity studies were conducted in rats and Cynomolgus monkeys with doses up to 1.0 MIU/kg/d. Antibodies to HSA and rhIFN-β occurred in both species but antibody formation tended to be greater after IM than IV administration. Only monkeys exhibited significant elevation of rectal temperature.

ECG revealed some alterations of ventricular conductance and repolarisation that is considered to reflect spontaneous pathology in monkeys.

In a 26-week repeated dose study in Cynomolgus monkeys with SC doses of 1, 3 or 10 MIU/kg/d, no dose related general clinical signs were noted. However, a moderately (not significantly) reduced body weight was noted in high-dose females. Local reactions at injection sites were seen at the two higher dose-levels. Rectal temperature rose moderately but apparently dose-related after the first administration. Neutralising antibodies were observed at the 5th and 12th week of the treatment period. At 12 weeks of dosing, analysed samples were moderately to markedly positive. No gross pathology was observed apart from at the injection sites, where dose-related changes were seen. Parallel inflammatory changes were noted in the histo-pathological examinations. Interstitial inflammatory changes in the testes occurred in some high-dose animals.

Reproduction toxicity

One reproduction study was performed in Cynomolgus monkeys to assess both abortifacient and teratogenic activities of Rebif. There was a high prenatal loss in animals treated with 0.2 MIU/kg/d during days 90-150 but not in the higher dose groups when compared with pregnancy loss in controls.

Further studies to investigate other effects on reproduction have not been conducted. Since according to the proposed SPC, Rebif should not be administered in cases of pregnancy or lactation, further reproduction studies are not considered necessary.

Genotoxicity and carcinogenicity

A battery of tests for genotoxicity has given negative results, indicating that Rebif lacks a genotoxic potential. Carcinogenicity studies have not been conducted. Although a limited antibody formation to Rebif might not preclude a meaningful carcinogenicity bioassay, a suitable responsive model is lacking.

It is concluded that the preclinical documentation submitted with the initial application and in response to the CPMP questions is of sufficient quality and quantity to support the clinical efficacy and safety documentation. No special concerns have been identified that is not adequately covered in the SPC.

4. Clinical aspects

One trial, recruiting a total of 72 patients, thereof 68 treated with Rebif, was initially submitted to support the indication. The MRI results were interpreted as indicative of activity, the magnitude of which, however, was impossible to estimate in both absolute and relative terms. In addition, the safety database was very limited. A benefit risk assessment was therefore impossible to conduct. These major objections, together with the list of questions to be addressed were forwarded to the applicant in the CPMP Consolidated list of questions.

In addressing the major objection and questions of the CPMP the applicant submitted the results of a formal phase III trial, comparing placebo, 6 MIU and 12 MIU three times a week. From the data provided, the proposed dose to be used in MS was determined to be 6MIU (22μg) three times weekly.

Clinical pharmacology

Pharmacokinetics

Single dose study

Data from one single dose study with the administration of 6 MIU Rebif was initially provided, thus there was no information as to dose proportionality or possible time dependency. One multiple dose study was submitted in protocol form and the final report from this study was later submitted in response to the CPMP list of questions.

The absolute bioavailability, based on the results from the initially submitted, single dose study of SC Rebif was found to be low, of the order of 15%. This was initially thought to be due to sequestration or catabolism at the site of administration. The low sensitivity of immunoassay for the determination of interferon plasma levels and the similarity of the 2', 5'-OAS levels after IV and SC administration of the same dose, provide alternative explanations. The seemingly low bioavailability after SC and IM administration may also be partly due to lymphatic uptake and subsequent slow release into the plasma.

In common with other protein drugs, no recovery study has been performed and there is no information as to the route(s) of excretion of Rebif in man. This has been handled in the SPC section 4.4 by recommending that caution should be used and close monitoring considered when administering Interferon beta-1a to patients with severe renal and hepatic failure. However, the influence of less than severe liver or renal disease cannot be assessed without more precise knowledge of the excretion route(s).

In response to the CPMP list of questions, the company submitted a multiple dose, open-label, three Panel study in 28 healthy male and female volunteers. Each volunteer participated in one Panel of the study.

- Panel 1. Eight volunteers (4 male, 4 female) received three single increasing IV doses of IFN-β1a (6 MIU/22 μg, 12 MIU/44 μg and 18 MIU/66 μg) one week apart.

- Panel 2. Twelve volunteers (6 male and 6 female) received three 18 MIU/66 μg doses of IFN-β1a (IV, IM and SC) one week apart in a crossover latin square design.
- Panel 3. Eight volunteers (4 male, 4 female) received four SC injections of 18 MIU/66 μg doses IFN-β1a at 48 hours intervals. These volunteers also took a drug cocktail consisting of mephenytoin 100 mg, dextromethorphan 25 mg, midazolam 7.5 mg, and, soluble coffee 2 g, in order to assess drug interactions. The drug cocktail was taken the night before on the pre-study visit, and on the third day after the last drug injection.

Multiple blood samples were taken for the measurement of serum IFN-β1a after each dose. Serum β2-microglobulin, 2-5 synthetase activity, and neopterin concentrations were measured after the last dose in Panels 1 and 2, and after every dose in Panel 3.

Pharmacokinetic data analysis

Both a non-compartmental approach and a population approach have been used to analyse the IFN-β1a data. Due to the observation of sustained plasma levels after the last dose in Panel 3, blood samples taken for the analysis of pharmacodynamic markers were also analysed for IFN-β1a. These data were used only in the population analysis.

A non-compartmental approach was used to analyse the markers of pharmacodynamic activity.

Bioavailability of IFN-β1a was found to be about 0.28 (range 0.06 to 0.62) and 0.37 (range 0.08 to 0.8) after SC and IM administration, respectively. Absorption appears to be the dominant factor that influences disposition.

The half-lives were inestimable in many cases, as the data were not collected over a sufficiently long period. The model dependent analysis of all data combined estimated the terminal half-life-to is 21 hours. A log-linear regression of the extra data obtained after the last dose in panel 3 gave rise to mean half-life of 85 hours after SC administration, which was very variable (51 %CV).

Dose proportionality: The results from Panel 1 indicated that the area under the curve (AUC) (normalised for dose) was significantly smaller after the 6 MIU/22μ g administrations. These results, seemingly indicative of dose dis-proportionality, are most likely the consequence of too low sensitivity of the analytical method.

Time dependency: The accumulation factor calculated from AUC was 2.4±0.3. There is some evidence of prolonged half-life after the multiple dose SC injections. Whether this is a time dependent phenomenon, a "flip-flop" phenomenon or is due to methodological difficulties is impossible to assess.

As regards pharmacodynamic markers, no period effect (time effect) was found in Panel 3 for 2', 5' -OAS activity whether measured in serum or in PBMCs. Period effects were, however, observed for neopterin (p=0.0013) and beta$_2$-microglobulin (p=0.0035).

Overall, these results are interpreted as indicative of accumulation after repeated dose.

The interaction part of the study did not reveal any relevant effects on cytochrome P450. However, a prolonged study period is considered essential to refute previously observed effects of type I interferons. Clinically, interferons have been shown to alter the pharmacokinetics and/or metabolism of other drugs (AZT, theophylline). This information has been presented in the SPC where it has been stated that interferons can decrease the metabolism of compounds metabolised by the cytochrome P450 system.

No pharmacokinetic information has been submitted in patients with antibodies, whether neutralising or not. However, in response to the first list of questions, dynamic data have been provided. In summary, it was demonstrated that in patients with in vitro neutralising antibodies, the dynamic response to Rebif in vivo, as measured by beta-2 microglobulin and neopterin, was attenuated.

Multiple Sclerosis

Exploratory trial

One exploratory trial, recruiting a total of 72 patients, thereof 68 treated with Rebif, has been submitted to support this indication. A 6-month observation run-in was followed by randomisation and open treatment with 3 or 9 MIU, s.c., three times weekly for 6 months. Compared with baseline, MS activity, as measured by relapse rates and MRI, decreased significantly during therapy (50-70%), but no statistically significant difference between dosage groups was seen.

Phase III formal study (Study Protocol 6789) (see also sections 6 and 7)

A study report from a conventional, pivotal phase III study conducted in patients with relapsing remitting MS has been submitted. In this dose-comparative, placebo controlled trial; clinical activity has been documented in endpoints considered to be clinically relevant. In response to the second list of questions, additional information and analyses have been provided.

Altogether 560 patients with relapsing-remitting MS (Clinically definite or laboratory-supported definite MS, EDSS: 0-5.0, at least 2 exacerbations in the 2 years prior to, but stable for at least 4 weeks before study entry) were included in this randomised, placebo controlled, dose-comparative, parallel-group study. There were 22 participating centres from Europe, Canada and Australia, enrolling between (inclusive) 19 and 40 patients each.

Most of the trial centres were audited by the sponsor for the verification of the compliance to Clinical Good Practice rules. The CPMP also required an independent verification of some trial centres that was co-ordinated by the EMEA: the assessment of the GCP verification is presented in the final part of the assessment of the clinical package.

Rebif was administered subcutaneously three times a week for 24 months at doses of 6MIU, 12MIU, or matching placebo. Initially dosages were gradually increased over 4 to 8 weeks. In patients consenting to participate, an extension phase followed, for further 24 months of treatment following the initial placebo controlled phase.

The designated primary efficacy endpoint was the effect on number of exacerbations. An exacerbation was defined as; the appearance of a new symptom or worsening of an old symptom, attributable to MS, accompanied by an appropriate new neurologic abnormality or focal neurological dysfunction lasting at least 24 hours in the absence of fever, and proceeded by stability or improvement for at least 30 days. Patients were instructed to inform the study centre within 48 hours of the onset of an exacerbation and a visit was to be arranged as quickly as possible.

Secondary, exacerbation related endpoints were: time to first/second exacerbation, proportion remaining exacerbation-free at 1 and 2 years, duration and severity of exacerbation.

For grading of severity, the Scripps NRS score was to be used (change in NRS score, mild = 0-7, moderate = 8-14, severe > 14). In case of missing NRS data from date of maximum disability, anamnestic ADL information was used for grading (mild = no effect on ADL, moderate = significant effect, severe = hospitalisation). The use of steroids and hospitalisation for MS were also presented in the study report.

Disability (secondary endpoint), as measured by EDSS, was determined by a treatment blinded, evaluating physician. Progression was defined as an increase in EDSS of 1.0 point or more for at least 3 months (or 0.5 point between EDSS 6 and 7).

All patients were to undergo baseline and biannual proton density (PD)/T2 weighted MRI scans. Patients from 7 centres (n = 205) underwent monthly PD/T2 and T1 weighted, Gadolinium enhanced scans until the end of month 9 of therapy. At one centre (n = 39) monthly scans (T2 and T1) were conducted until the end of 24 months of treatment. Techniques and MRI endpoints were meticulously standardised and scans were read, blinded for treatment group, centralised, in chronological order. The total area of abnormal plaques seen on T2 weighted scans, defined burden of disease (BOD). BOD was presented as change from baseline. In patients undergoing monthly scans, disease activity was defined as a new, enlarging or recurrent T2 lesion or a Gd enhancing lesion.

Results

Of the 560 patients randomised, 58 patients stopped treatment before 24 months, but 31 of these were followed according to the protocol. Thus, full 24 months data was available on 95% of the enrolled

patients. Twenty-seven patients did not agree on, or stopped, the planned follow-up before the end of 24 months ("lost to follow up"). The distribution of completers, etc. was similar amongst the 3 treatment groups. The most commonly cited reasons for discontinuation were "patient decision" (26), adverse events (17), pregnancy (6), and progressive disease (4). As regards adverse events (AE), there were 6 withdrawals due to AE in the low dose-group and 9 in the high-dose group.

All randomised patients were included in the efficacy analyses and those "lost to follow up" up to the last study visit (27/560 patients, median time on study 350 days). Protocol deviations are detailed in the study report, but are not presented here, as they are considered unlikely to influence study outcome.

The proportion of females was slightly higher in the placebo group, 3:1 vs. 2:1 in the IFN groups. Median time since onset of MS was about 5 years (slightly longer in the 12 MIU group) and median number of exacerbations within 2 years of entry was 3 in all treatment groups. Also as regards the pattern of areas of CNS involvement at baseline, patient groups were similar, e.g. spinal cord signs (80%), brain stem (45%), optic nerve (53%), etc. Median (and mean) EDSS at baseline was 2.5, corresponding to "minimal disability in two functional systems" and similar in all groups of patients.

Efficacy

Exacerbation related endpoints

The reduction in relapse between placebo and IFN 6 MIU (- 29%) and 12 MIU (- 32%) was highly significant over 2 years of treatment ($p = 0.0002$ and < 0.0001, log linear model adjusted for centre and time on study). Similarly, a highly significant difference was also seen at 1 year ($p < 0.0001$).

The proportion of exacerbation free patients after 1 year increased from 24% (placebo) to 38% (6 MIU) and 45% (12 MIU) (6 MIU vs. placebo: $p = 0.0022$, 12 MIU vs. placebo: $p < 0.0001$, 6 MIU vs. 12 MIU: $p = 0.15$, logistic regression taking centre into account).

After 2 years corresponding figures were 15%, 26%, and 32%, still significant compared with placebo (6MIU vs. placebo p-value 0.0140; 12MIU vs placebo p-value <0.0001) and borderline in the comparison 6MIU vs. 12 MIU, $p = 0.08$.

Time to first exacerbation was also prolonged in the active treatment groups from median 4.5 months to median 7.6 and 9.6 months, 6 MIU and 12 MIU, respectively (highly significant vs. placebo in the Cox proportional hazard model taking centre into account, 6 MIU vs. 12 MIU $p = 0.16$). Time to second exacerbation was similarly prolonged.

Severity of exacerbations. There was a significant reduction in the mean number of mild, moderate, and severe exacerbations for both treatment doses.

No difference in the duration of exacerbations was seen (mean 47 days in all treatment groups).

Given the definition of exacerbation (see above) interferon-induced fever has been considered as a possible confounding factor in the assessment of relapse rate. However, out of the total number of exacerbations observed, a very small number coincided with fever and the investigators as "pseudo-exacerbations" classified a small number. Hence, IFN induced fever does not appear to be a confounding factor of importance in the assessment of exacerbation rate.

Disability related endpoints

Using the protocol definition of deterioration in disability, a significant prolongation of time to confirmed progression is observed (6 MIU vs. Placebo: $p = 0.04$, 12 MIU vs. Placebo: $p = 0.01$, Cox model, median not reached, but first quartile 358 vs. 554 vs. 638 days for placebo, 6 MIU and 12 MIU; respectively), however the clinical relevance of these findings warranted further evidence. The company submitted more data in the frame of the application for the line extension for Rebif 44 mcg, which are discussed in the sections 6 and 7 of this document. The results were considered by the CPMP as of clinical relevance.

MRI analyses

The mean number of active lesions at baseline was rather similar in the three treatment groups (mean 2.0-2.5). The mean number of active lesions per patient per scan differed between treatment groups

over the 9-month period of monthly scans**;** there were a total of 198 patients who qualified for the analyses, 66 in the placebo group, 64 in the 6 MIU Rebif group and 68 in the 12 MIU Rebif group.

Mean, active lesions: 1.6, 0.8, and 0.4, placebo, 6 MIU and 12 MIU groups, respectively.

Rebif 6 MIU or 12 MIU vs. placebo, $p < 0.0001$,

Rebif 12 MIU vs. Rebif 6 MIU $p = 0.16$,

ANOVA on the ranks, adjusted for centre and baseline number of active lesions.

As regards burden of disease, the percent change from baseline to 12 months differed between treatment groups: The means were: + 11.6% (placebo), - 1.2% (6 MIU), and - 6.7% (12 MIU). :

6 or 12 MIU vs. placebo, <0.0001,

12 MIU vs. 6 MIU $p = 0.1$,

ANOVA on the ranks, adjusted for centre and baseline disease burden.

Subgroup analyses

EDSS ≥ 4 and spinal cord involvement were found to be predictive for poor outcome (details not given in the study report). EDSS progression was therefore analysed using these factors as covariates.

In patients treated with 12 MIU, the proportion of progressed patients was the same in patients entering with EDSS < or ≥ 4. In the placebo group and 6 MIU groups, however, more patients progressed if baseline EDSS was ≥ 4. These data on proportion of progressed patients are essentially consistent with the "time to confirmed progression analyses", i.e. time to progression was not affected by baseline EDSS status in the 12 MIU group, while EDSS ≥ 4 adversely affected outcome in the placebo and 6 MIU groups.

There are safety data available from 373 patients treated with IFN for approximately 2 years. This overview is focused on adverse event areas reasonably related to IFN therapy based on previous experience from type I interferons, or events occurring with an increased incidence compared with placebo.

Serious adverse events were reported in 34, 32 and 27 patients, in the groups treated with placebo, 6, and 12 MIU, respectively. Events classified as "probably related" occurred in 1, 2 and 4 patients respectively (groups as previously) while there were 2, 6 and 7 events reported as possibly related (groups as previously). As expected AEs known to, or supposed to be related to the use of IFN, dominated these categories (probable, possible related), e.g. depression, lymphopenia, and injection site reactions.

In one patient (12 MIU), pregnancy was diagnosed at week 3 and therapy was withdrawn. At 12 weeks, no foetal heart sounds were heard and abortion was induced. In addition, one case of cataract, one case of acute bronchitis in a smoker, and one case of "pneumonia subsequent to influenza" (in the narrative "post haemophilus influenzae") were reported as possibly related (all in IFN groups).

Depression

One placebo patient committed suicide, and suicidal tendencies were reported in 3 patients in each patient group. Overall, depression was reported in more than 20% of the patients, mostly mild, and similarly distributed in the treatment groups (slightly more often in the placebo group). Patients in English-speaking centres were followed with psychological questionnaires every 6 months (General Health Questionnaire, Centre for Epidemiologic Depression Mood Scale, Beck's Hopelessness Scale). All scales indicated borderline status between "normal" and "mild disorder", without differences between treatment groups.

Patients with anamnestic severe depressions were not, according to the protocol, excluded from the study. However, whether any patients with a psychiatric history were actually included is not clear from the study report.

Injection site reactions

Necrosis was reported in 2 patients treated with 6 MIU and 3 patients given 12 MIU. Similarly abscess formation was reported in 2 + 4 patients. One patient in each IFN group permanently stopped

treatment due to injection site reactions. In all other patients the reactions resolved and the patients completed 2 years of therapy.

Flu-like symptoms"

This syndrome is most commonly encountered early in therapy. However, in the study report, no analysis taking time into account is presented and it is therefore, due to the non-specific nature of the symptoms, hard to present a reasonable overview of incidence, duration and severity. However, overall fever was more commonly reported in the IFN groups, 25 and 28 % vs. 16% in the placebo group.

Laboratory abnormalities

As expected, peripheral haematology was affected by IFN treatment. Overall, lymphopenia was seen in 11, 20 and 29% of the patients, placebo, 6 MIU and 12 MIU, respectively. Of these 30% were severe in the 12 MIU group. A dose-related reduction in granulocyte count was also observed and 2 patients in the 12 MIU group reported severe granulocytopenia. Overall the incidence of granulocytopenia was 4, 12 and 15%. No case of severe thrombocytopenia was reported, but the overall incidence was highest in the 12 MIU group, 8%. Anaemia was seen in similar incidence in the placebo and the 6 MIU groups (3%), but slightly more often in the 12 MIU group (5%).

IFN increased the mean of ALAT, ASAT, and ALP, and elevation in ALAT/ASAT was seen on at least one occasion in the 23% of the 22-mcg patients and 54% of the 44-mcg patients. These elevations were severe in 6 subjects in both IFN groups.

Neutralising antibodies

The liquid formulation of Rebif was used in this study and the immunogenicity was assessed at baseline and every 6 months. Samples, collected at least 24 hours after administration of study medication, were first tested at a central laboratory for binding antibodies (ELISA) and if positive were then tested for neutralising activity utilising a standard cytopathic protection assay. Results were, in the study report, not presented as titres of binding and neutralising antibodies, only as "positive patients" as regards neutralising antibodies. In the protocol, a positive patient was defined as one who maintained "positivity" for at least two consecutive visits.

Given the protocol definition, 24 % of the patients in the 6 MIU group vs. 0 (placebo) and 15 % (12 MIU) tested positive. If three or more positive results were required 14 and 11% tested positive, if four or more 9 and 4% (observe that during the study period, testing were made at base line + every 6 months, i.e. altogether 5 times). At least one patient showed a positive test result for the first time at month 24 and a number of patients at month 18.

On the data provided by the applicant and on the evaluation of the impact of binding and neutralising antibodies, the CPMP required the company to submit validations for the methods of analyses for binding and neutralising antibodies. Additional data on the incidence and titres of binding and neutralising antibodies over time were also requested.

The Sponsor, in response, submitted validation reports for the assays and tables with individual patient data with titres for binding and neutralising antibodies (NAb).

The antibody assays were found to be reasonably documented and validated. The biological validity of the in vitro testing for NAb has also been corroborated in vivo by pharmacodynamic studies showing an attenuated dynamic response to IFN beta in NAb+ patients.

Overall, high levels of binding antibodies were found to be strongly associated with positivity for NAb. There also seem to be roughly two populations of NAb+ patients, "low NAb titre responders" with a low highest titre (below, e.g. 20 NU/ml) and in most cases transient NAb positivity and "high NAb titre responders" where the titre tends to increase with time on therapy.

Thus, in patients with a highest titre below 20 NU/ml, 13/13 in the 12 MIU group and 8/10 in the 6 MIU group lost antibody positivity while on therapy. Conversely, in patients with at least one titre equal to or above 20 NU/ml, 4/49 in the 6 MIU group and 9/32 in the 12 MIU group lost antibody positivity. At 24 months, altogether 45/189 (thereof two with a highest titre <20) were NAb+ in the 6 MIU group and 23/184 in the 12 MIU group (thereof none with a highest titre <20).

These “low NAb titre” and “high NAb titre responder” categories, albeit somewhat arbitrarily dichotomised, are recognised from other therapeutic areas, e.g. from the treatment of haemophilia patients with factor concentrates.

At baseline, one patient was NAb+, and, interestingly, with a high titre (>5000) reverting to low titres while on therapy, e.g. a titre of 6 at month 24. One patient in the placebo group sero-converted at month 24 to high titres of binding and neutralising antibodies (>1000). In no other placebo patient were neutralising antibodies detected. Overall, the incidence of binding antibodies was low in the placebo group.

The tentative influence of NAb on the clinical activity of IFN beta in the treatment of MS is a rather complex issue. It is reasonable to postulate that this influence may depend on at least antibody titre, duration of antibody positivity, and the “phase” during which positivity occurs. The latter is due to the observed decrease in activity over time of IFN beta therapy compared with placebo (measured as relapse rate, both in absolute and relative terms). If there were no (“withdrawal”) rebound phenomenon, the effects of NAb would thus be difficult to detect after prolonged therapy due to the decreased efficacy of IFN therapy per se. Based on the Betaferon experience, there also seems to be a hysteresis between the development of NAb and the likely reduced activity of IFN. Whether the hysteresis is due to prolonged, disease-modulating effects, or, e.g. due to slowly increasing antibody titres is not clear.

In the small group of patients with NAb+ for more than three consecutive visits, most patients had high titres, at least during the last observation periods (months 12 or 18 to 24) and were overall positive for ¾ of the observation period. Nevertheless, there was no trend towards reduced overall activity. Thus, it was concluded that a major influence of NAb on the efficacy of Rebif was unlikely during the first two years of therapy that prolonged follow-up was needed and that no further analysis was warranted on the data available.

No ideal way has been presented on how to analyse the relationship between NAb and MS activity. However, it seems reasonable to concentrate on the “high NAb titre responder” group of patients, to test for different cut-off titres defining periods regarded as positive (titre min, e.g. >20, or >100). It is also important to consider duration of therapy in the analyses, to conduct within-patient, as well as between-group comparisons in an exploratory way and to use relapse rate, MRI changes and disability as activity measures.

There is an ongoing extension study. This study is planned to continue for at least 2 years after the completion of the 24 months, placebo comparative trial. For the extension study, patients on placebo in the “base line study” were randomised between 6 and 12 MIU and antibodies will be analysed on a 6 monthly basis. According to the Sponsor, effects of NAb on relapse rate, MRI changes and disability will be studied at the scheduled 4-year analysis and the report will be submitted in the second half of 1999.

Good Clinical Practice (GCP) compliance of the formal Phase III clinical study

At the request of the CPMP (September 1997), a GCP Inspection was conducted with a favourable outcome.

5. Overall conclusions

The efficacy and safety of Rebif in relapsing remitting multiple sclerosis have been documented in a 24 months, conventional, placebo and dose comparative, parallel-group study. Efficacy, as measured by the primary endpoint, i.e. reduced exacerbation rate compared with placebo (about 30% reduction) was highly statistically significant compared with placebo. Similarly, proportion of exacerbation-free patients was increased, time to relapse was prolonged and severity of exacerbations was reduced. No changes were, however, observed in the duration of the exacerbations.

Progression in disability was a secondary clinical efficacy end-point. Using the protocol definition of deterioration of disability, a significant prolongation of time to confirmed progression is observed, however the clinical relevance of these findings warranted further evidence. The company submitted more data in the frame of the application for the line extension for Rebif 44 mcg, which are discussed

in the sections 6 and 7 of this document. Later in the procedure, the results were considered by the CPMP as of clinical relevance.

Clinical efficacy data are also supported by consistent MRI data, here exemplified with effects on "burden of disease", i.e. the total area of abnormal plaques seen on T2 weighted scans. The percent change from baseline to 12 months differed between treatment groups, (mean) + 11.6%, - 1.2%, - 6.7% placebo, 6 MIU and 12 MIU, respectively.

No information on the influence of antibodies on the kinetics of Rebif has been provided. It has, however, been demonstrated that in patients with in vitro neutralising antibodies the dynamic response to Rebif in vivo is attenuated. With respect to the tentative influence of antibodies on the efficacy of Rebif, conclusive data are presently non-available. However, it may be concluded that a major influence on the efficacy of Rebif is unlikely during the first two years of therapy, and that prolonged follow-up is needed to resolve this issue. This information will be provided to the CPMP by the Marketing Authorisation Holder as indicated in the Specific Obligations set out for this Opinion adopted under exceptional circumstances.

Additional questions of clinical importance remain to be answered. Similar to the situation for the marketed beta interferons, it is unknown for how long therapy should be continued, i.e. benefit/risk put in relation to duration of therapy. On the basis of the current status of the scientific knowledge, despite the conduct of 4 placebo controlled, beta IFN phase III studies, the benefit/risk balance in subgroups of patients defined by different baseline characteristics remains to be defined. Any further progress in this area would most likely require the co-operation of the MAHs in a joint effort. The dose efficacy relationship is also insufficiently explored. The dose-comparative, extension study, which was ongoing for at least two years following the authorisation of the product, was expected to add valuable information as regards some of these issues.

Overall, the CPMP considering the data submitted to support the efficacy and safety of Rebif found that the absence of studies directly comparing Rebif with licensed interferons on this indication did not preclude conclusions as regards the clinical expediency of the product. Based on these considerations, the CPMP adopted a positive opinion for granting a marketing authorisation under exceptional circumstances.

The Marketing Authorisation Holder agreed to comply with the Specific Obligations to submit the additional information as set out here below:

Clinical aspects

- The Marketing Authorisation Holder should present exploratory analyses as regards the tentative influence of neutralising antibodies on the efficacy of Rebif on MS activity as measured by MRI.
- The Marketing Authorisation Holder should submit the full study report from the extension study based on 2 year data.
- The Marketing Authorisation Holder should in advance of the analyses of data from the dose comparative extension study:
- present and justify analyses to be conducted with respect to dose effect relationship in subgroups of patients,
- present and justify a plan on how to handle the situation if a "high Nab titre responder" group as regards neutralising antibodies can be identified where MS activity is relatively increased, pharmacodynamic markers of IFN activity are low, and systemic IFN side effects are absent (Withdrawal from IFN therapy and intensified MRI follow-up? Switch to alternative therapy? Dose escalation and/or attempts to induce tolerance?).
- The Marketing Authorisation holder should submit the study report from the ongoing phase III study in patients with secondary progressive disease.

6. Line extension for Rebif 44 mcg

The initial application for Rebif 22 mcg was based on the results of a large, dose-comparative, placebo-controlled study designed as a three-armed, dose-comparative trial with a pre-specified analysis plan with respect to the 44-mcg dose (12 MIU). The Marketing Authorisation Holder (MAH) applied for an extension for the strength of 44 mcg on the basis of the original dossier submitted, updated in the light of new data and analyses. This strength was approved by Commission Decision of 29 March 1999.
This application consisted of full part IIB, IIC, IIE. In order to support the clinical package of this extension application for the additional strength of 44 mcg, and for the additional therapeutic claim of effects on disability, new data and analyses have been submitted:

- MRI data after two years of therapy showing a dose related difference in drug activity
- Exploratory analyses to illustrate the clinical relevance of disability related results
- Subgroup analyses to indicate the proper clinical use of the two doses investigated in the trial.

Quality aspects

Rebif 44 mcg, is an additional strength to Rebif 22 mcg. It is a liquid formulation supplied in pre-filled syringes and appears as clear solution having pH ranging between 3.4 and 4.4. The active substance for both strengths Rebif 22 mcg and Rebif 44 mcg is identical in terms of manufacturing process, Quality Control tests, release specifications and manufacturing sites, and thus, documentation on the production and control of the bulk substance reference has not been included in the dossier.

Rebif 22 mcg and Rebif 44 mcg were developed in parallel, and the same manufacturing process is utilised for preparation of the finished product.

The master formula for Rebif 44 mcg is proportional to that approved for Rebif 22 mcg in terms of active substance and human serum albumin content and identical in terms of mannitol content. The mannitol, HSA, Sodium acetate, Sodium hydroxide, Acetic acid and Water for injection used for preparation comply with Ph. Eur. requirements. Moreover, the HSA is sourced from the same supplier meeting the specifications already approved for Rebif 22 mcg.

The control tests performed on the Rebif 44 mcg finished product are identical to those for Rebif 22 mcg, and both the release and shelf life specifications are qualitatively identical.

Toxico-pharmacological aspects

No new data were submitted, as the pre-clinical package submitted for the Marketing Authorisation of Rebif is considered relevant to Rebif 44 mcg.

Clinical aspects

The Marketing Authorisation for Rebif was based on the results of a large, dose-comparative, placebo-controlled study as discussed in the initial assessment. The primary objective of this study was to investigate "the effects of Rebif at 6 and 12 MIU (namely 22 and 44 mcg) compared with placebo on the number of exacerbations". The primary statistical efficacy analysis, was Rebif 44 mcg vs. placebo.

Summarised Clinical Efficacy Data, Rebif 44 mcg

Parameter	Placebo % progressed	Rebif 44 mcg % progressed
EDSS increase of 1 point, 3 months confirmation	39	27 (p=0.01)
Relapses per patients, % reduction vs. placebo		32 (p<0.005)
Percent relapse-free patients	15	32 (p<0.005)

Exploratory analyses to illustrate the clinical relevance of disability related results

The results of the Rebif study with respect to changes in EDSS-related endpoints comparing 44 mcg with placebo are summarised in the following table.

Efficacy Data Expressed in EDSS Related Endpoints

Parameter	Placebo% progressed	Rebif 44 mcg % progressed
EDSS increase of 1 point, 3 months confirmation	39	27 (p=0.01)
EDSS increase of 1 point, 6 months confirmation	25	19 (p=0.04)
EDSS increase of 2 points, 3 months confirmation	16	9 (p=0.03*)
EDSS increase of 2 points, 6 months confirmation	12	6 (p=0.01*)
Patients progressed to EDSS 6, 3 months confirmation	6	2 (p=0.04*)
Patients progressed to EDSS 6, 6 months confirmation	5	2 (p=0.03*)

* Exploratory analyses

Similar results in terms of relative decrease in the rate of disease progression or absolute decrease have also been shown in published literature and have been accepted by the CPMP as of a clinical relevance.

Risk/benefit comparison between Rebif 22 and Rebif 44 mcg.

The main clinical study was designed as a three-armed, dose-comparative trial with a prespecified analysis plan with respect to the 44-mcg dose. A reasonable way to handle the situation appears to be to give some priority to analyses related to the higher dose in the overall benefit risk assessment, but to accept results derived from the low-dose arm as valid for this comparative analysis.

Clinical safety comparison between Rebif 22 and Rebif 44 mcg.

Serious adverse events were reported in 34, 34 and 27 patients, placebo, 6, and 12 MIU, respectively. Events classified as "probably related" were, respectively, 1, 2 and 4 (groups as previously). As possibly related were 2, 6 and 6 events reported (groups as previously). As expected AEs known to, or

supposed to be related to the use of IFN, dominated these categories (probable, possible related), e.g. depression, lymphopenia, injection site reactions, etc.
One observed problem with long-term subcutaneous injection therapy with Rebif was the occurrence of injection site reactions. Slightly more patients reported severe injection site reactions in the Rebif 44 group. However, the difference (2.1% vs. 3.8%) was not statistically significant and Rebif 44 was not associated with more treatment discontinuation.

Injection site reaction, by severity, percentage of patients

		Mild	*Moderate*	*Severe*
Injection site inflammation	Placebo	14	1	0
	6 MIU	61	7	0.5
	12 MIU	61	11	2
Injection site "other"	Placebo	13	2	0
	6 MIU	24	8	0.5
	12 MIU	28	8	1

Laboratory abnormalities

As expected, peripheral haematology was affected by IFN treatment. Overall, lymphopenia was reported as an adverse event in 11, 20 and 29% of the placebo, 6 MIU and 12 MIU, patients respectively. Of these, 30% were considered severe in 12 the MIU group.
A dose-related reduction in granulocyte count was also observed and 2 patients in the 12 MIU group reported severe granulocytopenia. Overall the incidence of granulocytopenia was 4, 12 and 15%. No case of severe thrombocytopenia was reported, but the overall incidence was highest in the 12 MIU group, 8%. Anaemia was seen in similar incidence in the placebo and the 6 MIU groups (3%), but slightly more often in the 12 MIU group (5%).
IFN increased the mean of ALAT, ASAT, and ALP, and elevation in ALAT/ASAT was seen at least once in 23% of the 6 MIU and 54% of the 12 MIU patients. Six cases in each group were considered severe.
In conclusion, as regards safety, differences between dose groups were overall small. Treatment discontinuations for adverse events occurred in six patients on 22 mcg tiw and nine on 44 mcg tiw over 2 years.

Clinical efficacy comparison between Rebif 22 and Rebif 44 mcg.

With respect to conducted efficacy analyses in the whole study population, pre-planned or exploratory, there are trends in favour of 44 mcg tiw, but these trends do not achieve statistical significance.

In the two-year MRI analyses, T2 lesion count and proportion of T2 active scans was significantly reduced in the 44-mcg groups compared with the 22-mcg group ($p<0.001$). As regards burden of disease, however, in terms of difference between the active treatment groups there was a trend towards significance ($p=0.055$).
In summary, based on efficacy analyses related to the whole study population the efficacy compared with placebo has been demonstrated for both dosages of Rebif.
Given the small dose-related difference in safety, it is concluded that the benefit risk relationship is acceptable for both dosages. Trends to better outcome on 44-mcg tiw compared to 22 mcg tiw for clinical measures and significant differences on MRI measures with limited differences on safety, suggest high dose is preferable.

Overall Risk / Benefit analysis

Based on efficacy analyses related to the whole study population, it appears reasonable to conclude that efficacy compared with placebo has been demonstrated for both dosages of Rebif.
The adverse effects profile however tends to be worse with the use of Rebif 44, even though in absolute terms the difference is small.

The analysis of the efficacy data did not show any statistically significant difference in performance between the two dose groups. In patients with an EDSS>3.5 the use of the higher strength should be considered, given the small dose-related difference in safety. Given that the data in addition were derived from a limited experience with low numbers of patients, the need of firm evidence provided by prospective confirmative studies was discussed and considered necessary by some Members.

Taking into account the above-mentioned considerations the MAH was requested during an Oral Explanation to justify the marketing of the 44mcg strength from a risk/benefit balance point of view. For every single efficacy outcome parameter, results with Rebif 44 mcg are better than Rebif 22 mcg in the retrospectively defined subgroup of patients with EDSS>3.5. This difference across all parameters, assessed statistically using a Rank-Sum analysis ("Global Score"), indicates Rebif 44 mcg superior to Rebif 22 mcg. The results of this analysis demonstrate that Rebif 44 mcg is significantly better than Rebif 22 mcg ($p = 0.0036$ for Rebif 44 mcg vs. Rebif 22 mcg) using the protocol prespecified endpoints. Additionally, the difference between the two doses is statistically significant for 2 year prospectively defined MRI endpoints. Only Rebif 44 mcg significantly decreased the worsening in the ambulation index and decreased hospitalisations compared to placebo.

Conclusions

The CPMP found that the benefit/risk relationship was favourable for both dosages of Rebif, but questioned the robustness of the subgroup analysis. The clinical relevance of a specific dose recommendation targeting patients with EDSS score at base line was also questioned, given that beta-interferons have been available for treatment of MS for several years. Nevertheless taking into consideration the evidence supporting a dose-effect relationship, the heterogeneity of the disease, and the inter-individual variability in the pharmacokinetics of Rebif it was found that there is need of flexibility in the dose adjustments for individual patients.
On this risk/benefit ratio evaluation, the CPMP recommended the granting of the Marketing Authorisation for Rebif 44mcg.

7. Update of the SPC following the results of Extension study 6789

The MAH submitted the final study report of the Study 6789 as per the specific obligations (see section 5) and a type II variation to amend the Summary of Product Characteristics. Study 6789 was a randomised, double blind, placebo-controlled 2-year study to examine the effect of Rebif in relapsing-remitting MS (RRMS). A benefit for both doses of Rebif was shown relative to placebo. This study was extended for a further 2 years. The relevant decision by the European Commission was issued on 22 January 2001.

The data available from the two years extension of study GF 6789 demonstrate that over 4 years, the reduction in the mean exacerbation rate was 22 % in patients treated with Rebif 22 micrograms, and 29 % in patients treated with Rebif 44 micrograms compared with a group of patients treated with placebo for 2 years and then either Rebif 22 mcg or Rebif 44 mcg for 2 years. Although discontinuation for adverse events was greater in high vs. low dose treated patients, the results of study GF 6789 support the use of Rebif 44 mcg (instead of 22 mcg) as the recommended dose for patients with RRMS. The majority of dropouts due to adverse events in the extension phase were patients receiving 44 mcg, particularly those newly exposed to interferon. In order to improve tolerability, it is suggested that the patients when first starting treatment with Rebif should be maintained on the 22 mcg dose for a longer period of time (3 months) before increasing the dose to 44 mcg. With regard to the effect of neutralising antibodies, the data obtained in the extension study indicate an almost complete loss of MRI effect and a clear reduction in clinical effect once neutralising antibodies develop. A statement clarifying this issue was included in section 4.4 of the SPC.

Overall, it can be concluded that the results for several efficacy measures related to relapse rate, disability and MRI measures demonstrate a better efficacy for the 44 mcg dose, which is accompanied by a small increase in side effects. The submitted data are considered to support the use of the 44-mcg dose as the recommended normal dose. The analysis presented by the applicant has not shown that any

single factor is clearly predictive of a clinical dose response. The occurrence of adverse events and study withdrawal in relation to time on therapy does not indicate that patients would benefit from an extended time on the 22-mcg dose before increasing the dose to 44 mcg.
Based on the submitted data the CPMP approved on 22 January 2001 the recommended dose of Rebif as 44 micrograms given three times per week by subcutaneous injection. Rebif 22 micrograms, also given three times per week by subcutaneous injection, is recommended for patients who cannot tolerate the higher dose in view of the treating specialist.

8. Revision of the indication following the results of the study SPECTRIMS

One of the specified obligations of the MAH following the Commission decision was to provide the study report from the phase III study (Study GF 6954, SPECTRIMS) in patients with secondary progressive multiple sclerosis (SPMS). The MAH submitted the final study report for GF 6954. Based on the results of this study, the MAH submitted a type II variation with an application for revision of the currently approved Rebif 22 mcg and 44 mcg SmPC. The MAH proposed to extend the indication to *"patients with secondary progressive MS who have experienced relapses in the prior 2 years, Rebif XX micrograms has demonstrated efficacy in decreasing the frequency and severity of relapses as well as in slowing the progression of disability. Rebif therapy should not be initiated in secondary progressive MS patients who no longer experience relapses."*

The primary efficacy variable for study GF 6954 was time to confirmed progression in disability. No significant benefit for either dose of Rebif was shown in the primary analysis. With regard to the secondary clinical outcome measure, relapse rate per year, both doses of Rebif showed a significant benefit with a reduction of the relapse rate by approximately 30% ($p<0.001$). A *post-hoc* subgroup analysis indicated that patients with relapses in the two years before the study were more likely to respond to Rebif in terms of time to progression. The trend towards benefit observed within each of the two treatment groups in relapsing patients did not reach statistical significance, but when treatment groups were combined and compared with placebo, the odds ratio for progression among relapsing patients was 0.52 ($p= 0.027$) [non-relapsing patients odds ratio 1.07 ($p=0.802$)].

The overall interpretation of available data is that Rebif undoubtedly reduces relapse activity in patients with MS. In contrast, there is no data indicating that the course of SPMS, if not associated with relapsing/remitting activity, is modified by Rebif therapy. In patients with relapsing/remitting MS and at least 2 recurrent attacks of neurological dysfunction over the preceding 2-year period, reduced relapse activity is associated with a delay in time to progression in disability. These findings are reproduced, though statistically less convincing, in the subgroup of patients with SPMS associated with relapsing/remitting activity within two years prior to therapy. As these findings have a high degree of biological plausibility, it seems reasonable to reword the indication focusing on relapsing/remitting activity and to provide data from the SPECTRIMS study in 5.1.

The ad-hoc experts group on clinical efficacy of beta interferons in MS at the meeting on 28 May 2001 agreed that the effect of Rebif is on the delay of relapses and the indication should be focusing on the activity on relapses. A group convened at the margins of the Efficacy Working Party on 18 June 2001 confirmed this view and agreed on the revision of the indication as "*treatment of patients with multiple sclerosis and with 2 or more relapses within the last two years. Efficacy has not been demonstrated in patients with secondary progressive multiple sclerosis without ongoing relapsing activity."*
The European Commission issued a Decision amending the Summary of Product Characteristics on 20 November 2001.

9. Line extension for the replacement of the authorised producer clone with a new clone

The extension application related to the introduction of a new clone in the manufacturing process. The Marketing Authorisation Holder submitted an application for an Annex II application to the European Agency for the Evaluation of Medicinal Products (EMEA) for Rebif. During their October 2002

meeting, in the light of the overall data submitted and the scientific discussion within the Committee, the CPMP issued a positive opinion for granting an extension of the Marketing Authorisation to Rebif. The CPMP recommended the extension of the Marketing Authorisation for Rebif 22 µg and 44 µg to reflect the introduction of a new high producer clone in the manufacturing process. This line extension was approved by the Commission Decision of 16 January 2003.

Quality aspects

The new clone was established from the same CHO host cell line as the original clone but using a different expression vector construct. Comparative data were submitted showing genotypic and phenotypic characterisation and stability of the producing cell line for a time that exceeds production. Studies on the viral safety of the cell banks and on the viral clearance/inactivation of the production process have been designed to conform to the recommendations in relevant EU and ICH guidelines.
Basically the same production process is used for the new clone material as for the originally approved material. Extensive biochemical, physico-chemical and in-vitro biological characterisation studies were reported. The characterisation studies included analyses of the amino acids sequence, S-S bridging, carbohydrate chain structure. The same in process control tests and the same methods for specifications using the same acceptance criteria are applied.
The stability of the drug substance was tested under the following conditions: stress testing, accelerated stability and long term testing.

The drug product manufactured using r-hIFN-ß-1a bulk from the new clone has been shown to comply with all specifications approved for currently marketed drug product. It was therefore proposed to apply the same shelf-life as already applied for the currently approved presentations and that is 24 months when stored at 2-8°C and protected from freezing and 1 month at RT.

Toxico-pharmacological aspects

No new pre-clinical data have been submitted.

Clinical aspects

Previously conducted major long-term clinical studies, comparing the efficacy and safety of the 22 mg and 44 mg presentation, formed part of the basis for the discussion of this line extension application.

Overall Risk / Benefit analysis

From a biotechnology point of view the product was considered well characterised. Based on this characterisation and taking into account the clinical experience, there are no major clinical concerns. Nevertheless, it is recognised that the experience derived from “high-resolution” comparability exercises is still limited. In order to investigate further the antigenicity profile for the product from the new clone, the company committed to conduct a post-marketing trial on the immunogenicity and safety of the product in patients. The design of the study was agreed with the Rapporteur and the CPMP.

The CPMP expressed concern that the ‘possible’ different safety/antigenicity profiles of the products derived from the two clones could confound any analysis of spontaneous adverse event reporting. Therefore, the company committed to phase out product derived from the original clone.

Conclusions

Based on the CPMP review of data on quality, safety and efficacy, the CPMP considered by consensus that the benefit/risk profile of Rebif 22 µg and 44 µg produced by the new clone was favourable.

10. Update of Clinical Safety from post-marketing experience

All periodic safety updates reports (PSURs) since product authorisation have been submitted and assessed. In order to reflect the knowledge of the safety profile of Rebif progressively gained during the post authorisation phase, several revisions of the SPC (through Type II variations) and related revisions of the patient information leaflet have been submitted by the MAH.

The changes implemented in the SPC following the assessment of the **5th PSUR** were the following:
Under Section *4.4- Special warnings and special precautions for use:*

- Addition of a paragraph about hepatic function disorders:

"In clinical trials with Rebif, asymptomatic elevations of hepatic transaminases (particularly ALT) were common and 1-3 % of patients developed elevations of hepatic transaminases above 5 times the upper limit of normal (ULN). Dose reduction of Rebif should be considered if ALT rises above 5 times the ULN, and gradually re-escalated when enzyme levels have normalized. Rebif should be initiated with caution in patients with a history of significant liver disease, clinical evidence of active liver disease, alcohol abuse or increased serum ALT (> 2.5 times ULN). Serum ALT levels should be monitored prior to start of therapy, at months 1, 3 and 6 on therapy and periodically thereafter in the absence of clinical symptoms. Treatment with Rebif should be stopped if icterus or other clinical symptoms of liver dysfunction appear (see 4.8 undesirable effects)."
Rewording of the paragraph related to the monitoring of laboratory abnormalities:
"Laboratory abnormalities are associated with the use of interferons. Therefore, in addition to those laboratory tests, normally required for monitoring patients with multiple sclerosis, and in addition to liver enzyme monitoring, complete and differential blood cell counts and platelet counts are also recommended during Interferon beta-1a therapy".

- Addition of a paragraph on thyroid abnormalities:

"Patients being treated with Rebif may occasionally develop new or worsening thyroid abnormalities. Thyroid function testing is recommended at baseline and if abnormal, every 6-12 months following initiation of therapy. If tests are normal at baseline, routine testing is not needed but should be performed if clinical findings of thyroid dysfunction appear (see also 4.8 Undesirable effects)."

The following has been added under *Section 4.8-Undesirable effects*

- "Adverse hepatic reactions such as hepatitis, with or without icterus, have been rarely reported (cross-reference to 4.4)."
- "Angioedema and urticaria" as examples of hypersensitivity reactions that may occur.
- "Hair loss".
- "Occasional thyroid dysfunction, generally transient and mild, may occur during the first year of treatment, particularly in patients with pre-existing thyroiditis" with cross-reference to 4.4.
- "An increased formation of autoantibodies may occur during treatment with interferon beta (cross-reference to 4.4)".

These changes were reflected in the Package leaflet accordingly.

The changes implemented in the SPC following the assessment of the **6th PSUR** were the following:
Under *Section 4.4-Special warnings and special precautions for use:*

- The warning related to hepatic reactions has been strengthened with the addition of:

"Rebif, like other interferons beta, has a potential for causing severe liver injury (see Section 4.8) including acute hepatic failure. The mechanism for the rare symptomatic hepatic dysfunction is not known. No specific risk factors have been identified."

Under Section *4.8 Undesirable effects:*

- The section has been re-organised according to the EU guideline of SPC with the adverse reactions being classified according to frequency of occurrence.
- "Erythema multiforme" and "erythema multiforme-like skin reactions" have been added as very rare adverse reactions, and "injection site abscess" and "injection site mass" have been added as uncommon adverse reactions.

Under Section *4.6 -Pregnancy and lactation:*

- The first paragraph related to pregnancy has been modified as follows:

Because of the potential hazards to the foetus, Rebif is contraindicated in pregnancy. There are no studies of interferon beta-1a in pregnant women. At high doses, in monkeys, abortifacient effects were observed with other interferons (see 5.3 Preclinical safety data). It cannot be excluded that such effects will be observed in humans."

The Package leaflet has been amended accordingly.

The changes implemented in the SPC following the assessment of the **7th PSUR** were the following:

Under *Section 4.8 Undesirable effects*

- "Very rare anaphylactic reactions" have been added
- "Menorrhagia and metrorrhagia" have been added as pharmalogical class effect

The Package leaflet has been amended accordingly.