SCIENTIFIC DISCUSSION

This module reflects the initial scientific discussion for the approval of Avonex. This scientific discussion has been updated until 1 June 2002. For information on changes 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 etiology of the disorder is unknown, immunologic 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 patients) with attacks of neurologic dysfunction attributable to central nervous system plaques. Dysfunction resolves within weeks or 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 category during the course of their disease.

Therapy for MS can be symptomatic, for treatment of acute relapses, reducing relapse rate and progression towards disability or handicap. Acute relapses are often treated with corticosteroids.

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

β-Interferons have recently been recognised as potentially beneficial in the treatment of MS. Interferons are cytokines that mediate antiviral, antiproliferative and immunomodulatory activities. Whether the mechanism of action of the β-interferons in multiple sclerosis is mediated by the same pathway as the biological effects described above is not known because the pathophysiology of multiple sclerosis is not well-known.

AVONEX is a recombinant human beta-1a Interferon and is produced from Chinese Hamster Ovary (CHO) cells which contain the gene for human interferon beta. Interferon beta 1a (IFN-b-1a) is a glycosylated polypetide containing 166 amino acid residues. The amino acid sequence of AVONEX is reported to be identical to that of natural human interferon beta.

The indications of AVONEX are as follows:

"AVONEX (Interferon beta-1a) is indicated for the treatment of ambulatory patients with relapsing multiple sclerosis (MS) characterized by at least 2 recurrent attacks of neurologic dysfunction (relapses) over the preceding 3-year period without evidence of continuous progression between relapses. AVONEX slows the progression of disability and decreases the frequency of relapses.

Avonex is also indicated for the treatment of patients who have experienced a single demyelinating event with an active inflammatory process if it is severe enough to warrant treatment with intravenous corticosteroids, if alternative diagnoses have been excluded, and if they are determined to be at high risk of developing clinically definite multiple sclerosis *(approved post-authorisation, see section 6).*

AVONEX has not yet been investigated in patients with progressive multiple sclerosis, and should be discontinued in patients who develop progressive multiple sclerosis.

Not all patients respond to treatment with AVONEX. No clinical criteria that would predict the response to treatment have been identified.

2 Chemical, pharmaceutical, and biological aspects

AVONEX (Interferon beta-1a) is formulated as a white to off-white lyophilised powder, containing a 30 μg (6 million IU) dose of Interferon beta-1a per vial.

Using the World Health Organisation (WHO) natural interferon beta standard, Second International Standard for Interferon, Human Fibroblast (Gb-23-902-531), 30 μg of AVONEX contain 6 million IU of antiviral activity.

AVONEX (Interferon beta-1a) is available as a package of four individual doses of: AVONEX in a 3 ml clear glass vial with a 13 mm bromobutyl rubber stopper and aluminium seal. It is provided with a 1 ml pre-filled glass syringe of solvent for reconstitution and 2 needles, one to be used for the reconstitution of the solution, the other to be used for the injection. A new presentation consisting of a vial with Bioset device, which clips over the current rubber stopper of the vial has been recently approved. It facilitates the attachment of the prefilled syringe directly to the vial thereby removing the need for the reconstitution needle.

The stability of AVONEX is 24 months at up to 25°C and 6 hours at 2-8°C for the reconstituted product. A shelf life of 36 months for the active substance (IFN-beta-1a) is supported by the additional data submitted post-approval.

The active ingredient in AVONEX is Interferon beta-1a, the recombinant form of human interferon beta. It comprises 166 amino acids, is glycosylated at residue 80 and contains a single disulfide bond.

The interferon gene was obtained from a line of human leukocytes. The DNA was amplified by PCR and cloned into an expression vector. A CHO cell line was used as host.

The expression construct for IFN beta-1a is entirely sequenced by the company and the sequence of the selection plasmid has been verified.

Cells are grown in a bioreactor and Interferon beta-1a is purified from the conditioned medium by filtration and multiple chromatographic steps.

The purification process is designed to purify IFN beta-1a to an extent greater than 99% by eliminating these contaminants as well as clearing and inactivating inadventitious viruses.

Routine specifications for performance of each column have been defined and the manner of production collection has been clarified. The purified product is finally formulated with human serum albumin and lyophilised.

The full-scale production process was validated through a compilation of the process results of the manufacturing of five consecutive batches.

The results of batch analyses indicated that several specification limits could be tightened and the applicant agreed to them. The revised specification and analytical methods are considered adequate to ensure the quality and consistency of the active substance and the finished product. All questions raised regarding quality during the assessment of the application have been answered to the satisfaction of all member states.

The specifications for the active substance and finished product have been tightened post approval. In addition the methods for release testing of the IFN-beta-Ia bulk intermediate and finished product have also been reviewed and changed through relevant variations.

The major issue concerning the biopharmaceutical dossier of AVONEX was that in the development of AVONEX, the active substance used in the clinical trials (BG 9015) was not identical to the one contained in the medicinal product intended for marketing (BG 9418). Both molecules are secreted from the same Chinese Hamster Ovary (CHO) host cell line; however, the two molecules are derived from different plasmids and MCB. Furthermore, cell culture process and the purification scheme used in the preparation of BG 9418 and BG 9015 are not strictly identical.

This fact, in the initial assessment of the dossiers, caused the CPMP to raise questions about the overall compatibility of the results obtained in the various studies and trials.

In the absence of regulatory guidelines addressing the issue of the bioequivalence of medicinal products derived by r-DNA technology, and in the absence of a clear-cut knowledge of the mechanism of action of interferons in the treatment of multiple sclerosis, the Applicant carried out an in-depth structural and functional comparison of the two interferons beta-1a (BG 9015 vs BG 9418).

These biological, functional and physico-chemical tests have satisfactorily demonstrated that BG9015 and BG9418 are comparable.

On the basis of the data provided, the *in vitro* functional assays can be considered plausibly predictive of the clinical efficacy in MS, as the clinical efficacy of IFN beta-1a is understood to be the consequence of the intracellular events elicited by the binding of the interferon molecules to their receptor. On these grounds, the efficacy data obtained with BG9015 may be considered applicable for BG 9418, the product intended for marketing.

The antigenicity of AVONEX was directly measured in different clinical studies.

Data provided post-authorisation on chemical, pharmaceutical and biological aspects

The company continued to provide data on an ongoing basis in the form of the type type II variations, and precision, as well as I provided as part of the "Follow-up Biotechnology Measures. The resulting CPMP positive opinions dated 18 November 1997 and 6 November 1998 have led to:

- Improvement of the testing to be performed on both the active ingredient and finished product allowing a better definition of specifications. This has been achieved by:
- Improving peptide mapping method,
- Development of new methods for testing the active ingredient,
- Development in specific testing of the finished product,
- Suppression of DNA testing on the active ingredient and General Safety testing on the finished product as justified by experience gained.
- Approval of two alternate manufacturing sites (active ingredient manufacturing site in the US and formulation and lyophilisation of finished product in France).
- Extension of shelf life for both the active ingredient and finished product.

3 Toxico-pharmacological aspects

Pharmacodynamics

No acceptable animal model or *in vitro* model for MS exists as yet in a species that is pharmacodynamically responsive to recombinant human IFN beta-1a (rh IFN beta-1a).

The specific mechanism by which rh IFN beta-1a exerts its effect in MS is unknown.

Since the activities of rh IFN beta-1a are highly species-specific, the most relevant information is derived from *in vitro* studies in human cell cultures and *in vivo* studies in rhesus monkeys.

Pharmacokinetics

Serum concentrations of IFN beta-1a were measured as antiviral activity in the CPE bioassay.

Pharmacokinetics were studied after a single i.v., s.c., or i.m. administration. Following i.v. administration, the distribution volume was found to be within the range of the total body water volume and the clearance rate was found to exceed the approximate glomerular filtration rate for monkeys. It is therefore considered that rh IFN beta may be cleared by a combination of glomerular filtration and other mechanisms.

Upon i.m. administration, AUC and Cmax values were found to be in the same range as those found in human volunteers.

Limited pharmacokinetic data are available with respect to tissue distribution, plasma protein binding and metabolism due to the difficulties in measuring intact rh IFN beta-1a.

Toxicology

The pharmacokinetic studies showed that no acute toxicity was observed in rhesus monkey upon single i.v. and s.c. administration.

Several repeated s.c. dose studies were performed in rhesus monkeys; the duration of treatment ranged from 2 to 9 weeks (including recovery). In general body weights, clinical signs, physical examinations, heart rate, blood pressure, electrocardiograms, ophthalmic examinations, haematology, serum chemistry, urinalysis and organ weights were not affected by treatment with any of these preparations. A few clinical changes were evident, including elevated body temperature, decreased food consumption, decreased platelet counts and slightly decreased serum albumin concentrations.

All of these effects were negated by anti- rh IFN beta neutralising antibodies that became evident within 2 weeks after initiation of treatment.

Carcinogenicity studies were not performed because rh IFN beta-1a has no mutagenic or mitogenic potential. Its close similarity to the endogenous human protein that is not thought to be carcinogenic is also taken into account.

The Ames test showed that no mutagenic potential was evident at the concentrations tested.

Statistically reliable data in reproductive toxicity testing can only be obtained by using an excessive number of animals. In view of the data obtained, a warning is present in the SPC regarding the well-known abortifacient potential of IFN beta.

Local tolerance testing of AVONEX in rabbits following a single i.m. injection showed no signs of irritation. In general, the *in vivo* data show substantial equivalence of the Applicant's Interferon beta-1a preparations with regard to their pharmacological, pharmacokinetic, immunogenic and toxicological properties.

4 Clinical aspects

AVONEX is a recombinant Interferon beta-1a (IFN beta-1a) derived from Chinese Hamster Ovary cells containing the gene for human Interferon beta.

IFN beta-1a belongs to the interferon family. Interferons mediate antiviral, antiproliferative and immunomodulatory activities. The precise mechanism of action of IFN beta-1a, in multiple sclerosis, however, is not known.

The clinical data support the efficacy of AVONEX in slowing-down the progression of disability and decreasing the frequency of clinical exacerbations in patients suffering from relapsing multiple sclerosis, defined as multiple sclerosis with recurrent attacks of neurological dysfunction without evidence of continuous progression between relapses.

Reduction in the number and volume of active brain lesions in relapsing multiple sclerosis has been observed, but the relationship of this finding with the clinical manifestations of the diseases is not yet clearly established and therefore these data are not considered markers of efficacy in multiple sclerosis.

Different forms of recombinant human IFN beta-1a (r-HulFNß) were tested in the studies submitted. BG 9015 was the test drug used in the pivotal study submitted. The amino-acid sequence is reported to be identical to that of natural HuIFN-ß. The product selected for commercialisation is BG 9418. The amino-acid sequence is claimed to be identical to natural HuIFN-ß but the cell-line differs from that of BG 9015.

BG 9014 another r-HuIFNß, was used in the multiple sclerosis pilot study.

Content of the dossier:

Five volunteer studies, 2 studies in multiple sclerosis, of which one pivotal, and 7 clinical studies for other indications were submitted. Because the latter 7 studies do not concern the indication applied for they will not be discussed except for safety reasons when appropriate.

The clinical studies concerning the other indications were all uncontrolled and open-labelled. The indications were: basal cell carcinoma (n=17), recalcitrant warts (n=12), chronic hepatitis B (n=68), chronic hepatitis C (n=98), an extension study of the hepatitis B study (n=4) and an extension study of the hepatitis C study (n=11). INFß-1a was injected locally or subcutaneously. Different dosing schedules were used. Because these studies do not concern the indication applied for they will not be discussed except for safety reasons when appropriate.

Pharmacokinetics/pharmacodynamics

Overall, the information on human pharmacokinetics was limited.

Dose-proportionality was not demonstrated. It is suggested that high baseline variability in antiviral activity might mask the dose-response effect. Although there were no data, potential accumulation in serum or tissues following a once-weekly i.m. administration seems unlikely from the pharmacokinetic point of view.

Using the CPE assay to measure serum interferon levels, BG 9015 and BG 9418 are equivalent in terms of pharmacokinetic profiles (study C94-800). However, pharmacokinetics is highly variable: the large inter-subject variability and the poor CPE assay sensitivity makes more precise pharmacokinetic comparisons impossible.

It is not known whether the efficacy of IFN beta-1a in multiple sclerosis is mediated by the same pathway as the antiviral effect and induction of biomarkers by IFN beta-1a. For example, IFN-gamma, an interferon with antiviral effect, increases symptoms in multiple sclerosis. Consequently, markers of antiviral effect cannot necessarily be considered as surrogate parameters establishing therapeutic equivalence of IFN beta-1a in multiple sclerosis. These finding should be considered in the light of the overall information concerning the biopharmaceutical characterisation as previously discussed.

Clinical efficacy

Two pilot studies and one pivotal study with IFN beta-1a in multiple sclerosis patients were submitted. The study designs are summarised in the next table. The doses are expressed in millions of international units (MIU)/weekly injected intramuscular. The studies were performed in accordance with GCP.

REVIEW OF MULTIPLE SCLEROSIS STUDIES

Ref	Type of study/ Design	Treatment groups Doses	n	Duration of treatment
NS-2632-1-01A1 Pilot I, first part	Dose tolerance study. Randomised, placebo-controlled double-blind study	Placebo (partly) INFβ-1a — BG9014 Doses: 1.5, 3, 6, 9.5, 18 MIU/Week	5 Age: 25-43 yrs	91 weeks
Pilot I, second part	Crossover study Open study	INFβ-1a BG9014 vs BG9015 Doses : 3, 6, 9.5 MIU/Week	Same subjects	4 weeks

NS-263321 Pivotal	Efficacy study Randomised, placebo-controlled double-blind, multi-centre (4) parallel group study	Placebo INFβ-1a — BG9015 Doses: 6 MIU weekly i.m.	143 158 Age 16-55 yrs	Initially 2 years Later Variable per patient. See text.

Pilot studies

First pilot study

The ß$_2$-microglobulin levels measured at 48 hours after the dose injection, significantly increased compared to baseline, under IFN beta-1a 3 MIU, 6 MIU and 9.5 MIU given intramuscularly. Under 3 MIU IFN beta-1a the increased ß$_2$-microglobulin levels returned to baseline values within 24 hours. Under 6 MIU IFN beta-1a, the ß$_2$-microglobulin levels increased by about 0.5 mg/l and remained at these levels for 4 days and remained elevated to a lesser extent for the subsequent 3 days. The response was still present after one year in patients receiving 6 MIU IFN beta-1a weekly. So tolerance with respect to the ß$_2$-microglobulin levels seems not to occur.

2'5-oligoadenylate synthetase levels were measured 48 hours after each injection in the first pilot study. 2'5-oligoadenylate synthetase levels were significantly increased from baseline 48 hours after injection of both 3 MIU and 6 MIU IFN beta-1a.

Second pilot study

Only the ß2-microglobulin levels were measured. The magnitude and duration of ß2-microglobulin induction of BG 9015 and BG 9014 differed but the differences were inconsistent between the patients.

Pivotal study

One pivotal randomised, double blind, placebo-controlled, parallel group study was submitted. 301 patients entered the trial, 13 withdrew early.

Patients included had definite exacerbating-stable or exacerbating-progressive multiple sclerosis for at least one year, having had at least two well-documented exacerbations in the three years prior entry or at least one exacerbation per year prior entry when the duration of the disease was less than three years.

Also patients had to be exacerbation-free for at least two months prior to study entry and disability had to be between 1 and 3.5 points on the Kurtzke disability score (EDSS).

Patients with chronic progressive multiple sclerosis, patients with progression between relapses, patients on prior interferon treatment, on prior immunosuppressant drugs and on ACTH-corticosteroids within two months prior study entry were excluded.

ACTH and methylprednisolone were allowed on the occurrence of an exacerbation when symptoms warrant their use. Dosage was defined according to protocol. Symptomatic pharmacotherapy was permitted.

Patients were randomised to placebo or rIFN beta-1a $6X10^6$ IU (30 µg) intramuscular once weekly during two years. Simultaneously acetaminophen prophylaxis was given.

The primary efficacy parameter was the time to sustained progression in disability. This was defined as a sustained, that is at least six months persisting, one point increase (=worsening) in the Expanded Disability Status Score (EDSS)[1] as assessed by the blinded examining physician. The examining

[1] The EDSS is an ordinal scale taking values from 0.0, 1.0, 1.5 and thereafter increasing by 0.5 points up to a maximum of 10 points. An EDSS of 1.0 to 4.5 refers to patients fully ambulatory and grades 5.0 to 9.5 are defined by impairment of ambulation. An EDSS of 10 is defined as death due to multiple sclerosis.

physician was not involved in treatment. According to the study report a slightly modified EDSS was used.

Secondary efficacy parameters were EDSS-derived parameters, exacerbation-derived parameters, upper and lower extremity disability / visual function and MRI-identified plaque load. In addition 21 neuropsychological test performances, study blinding, IFNß-1a serum neutralising activity and $ß_2$-microglobulin levels were evaluated. $ß_2$-microglobulin sampling was discontinued because this marker was not of value to track compliance in individual patients.

There were no statistically significant differences between the two treatment groups in any baseline demographic or disease characteristic. Adjustment for prognostic factors identified did not invalidate the treatment effect. It was concluded that the treatment groups were homogeneous.

Time to sustained progression in disability

Time to sustained progression in disability was significantly longer in patients with interferon beta-1a than in placebo patients. The same tendency was observed in three of the four centres participating in the study but in the remaining Buffalo site, the interferon patients did worse than the placebo ones. The lower progression rate and lack of a positive effect at the Buffalo site is explained by inclusion of patients with less advanced disease relative to patients enrolled at the other three sites.

Although patient characteristics differed from site to site, at each site they were within the requirements of the inclusion and exclusion criteria specified in the protocol. A new analysis that excludes the patients at the Buffalo site yields a significant treatment effect with a p-value of 0.002 for the primary endpoint.

In addition, the results on time to disability were robust for more conservative endpoint indicating that the duration of the trial was sufficient:

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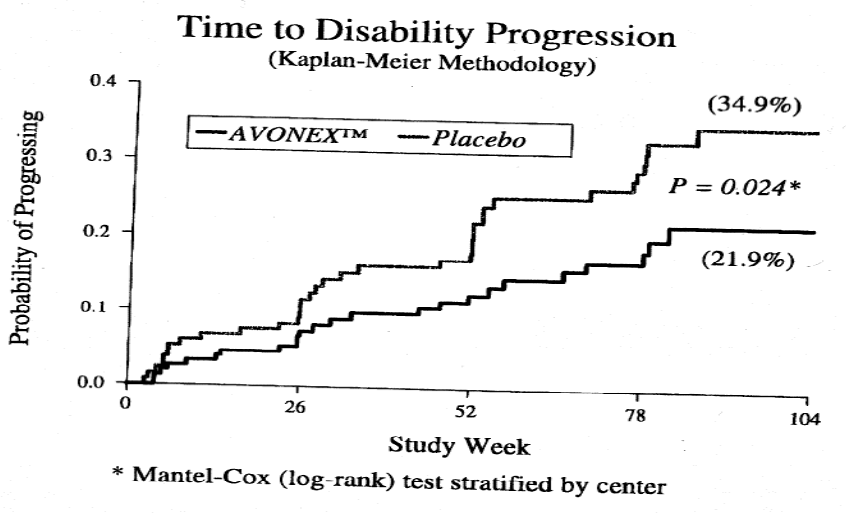
Number of progressors at endpoint

Progression level on EDSS	Placebo	INFβ-1a	Log-rank test	% reduction in proportion regression
			p value	
At least 1 point sustained 6 months	36 (25%)	24	0.024	40%
At least 1 point sustained 12 months	35 (24%)	(15%)	0.002	54%
At least 2 point sustained 6 months	17 (12%)	17 (11%)	0.028	58%
		8 (5%)		



Exacerbations

During the first year there was no statistically significant difference between the two groups in number of exacerbations. Over two years a statistically significant difference was seen between the two groups in exacerbation rate (p=0.002). During the second year the exacerbation rate difference between the two groups increased though there was no statistically significant difference in the proportion of patients who were exacerbation-free.

Magnetic Resonance

Results of the number of gadolinium-enhanced lesions are summarised in the next table. Gadolinium-enhanced lesions stand for active inflammatory lesions. Similar results were seen when the volume of Gadolinium-enhanced lesions was scored. With respect to the volume to T2 lesions, the actual and percentage change from baseline in volume of T2 lesions did not differ between the two treatment groups.

NMR-Gladolinium enhanced lesions

	PLACEBO	**INFβ-1A**	**COMMENTS**
Baseline	n=143	n=158	
0 lesions	46%	48%	p=0.821 Mann-Withney rank sum test
1 lesions	20%	14%	
2 lesions	8%	10%	In 11 and 14 cases respectively , NMR not available
3 lesions	8%	9%	
≥4 lesions	18%	20%	
After one year	n=123	n=134	Overall, p=0.024 Mann-Withney rank sum test
0 lesions	58%	70%	In 9 and 16 cases respectively , NMR not available
1 lesions	14%	13%	
2 lesions	10%	7%	
3 lesions	7%	3%	
≥4 lesions	11%	7%	
After two years	n=82	n=83	Overall p=0.051 Mann-Withney rank sum test
0 lesions	57%	71%	In 5 and 2 cases respectively, NMR not available
1 lesions	15%	13%	
2 lesions	15%	7%	
3 lesions	2%	2%	
≥4 lesions	11%	6%	

There was a statistically significant difference between treatments in both number (p=0.024) and volume (p=0.020) of Gadolinium-enhanced lesions favourable to interferon beta-1a in the first year. The difference was found to be less consistent in the second year; p=0.051 and 0.032 respectively for number and volume.

Lower extremity function

This was measured by the Ambulation index, Timed Tandem gait and best 25-foot walk.

For the best 25-foot walk, 31 out of 143 patients in the placebo group had a sustained progression versus 14 out of 158 in the IFNß-1a group. This difference was statistically significant p<0.002. There were no differences in time to first worsening in the best 25-foot walk between the two groups. There

were no differences between the treatment groups in time to first worsening or time to sustained progression with respect to the Ambulation index and Timed Tandem Gait.

Neuropsychological tests

No significant treatment effect was found.

The incidence of depressive symptoms, scored on the Beck Depression Inventory, did not differ between the two groups.

Clinical Safety

In the integrated safety analysis, four patient populations were distinguished: 1) MS-patients population involving 301 subjects of which 143 were receiving placebo and 158 IFN beta-1a 6 MIU weekly for 2 years. 2) Short-term dosing studies population. The patients involved received IFN beta-1a for less than 6 weeks of treatment. This population incorporated 42 patients treated with IFN beta-1a for cervical dysplasia and 17 patients treated for basal cell carcinoma. 3) Long-term dosing studies population, incorporating 234 patients treated with INF beta-1a for hepatitis B or C and 12 patients treated with IFN beta-1a for warts. 4) Overall population incorporating all patients treated with INF beta-1a.

The overall safety analysis of IFN beta-1a was heavily based upon the safety in the multiple sclerosis study.

The most commonly observed treatment-related effects

Treatment related events	Placebo	INFβ-1a
n	**129**	**153**
Flu-like symptoms	33%	54%
Headache	40%	51%
Muscle ache	12%	32%
Nausea	17%	25%
Chills	6%	21%
Fever	9%	18%
Asthenia	8%	16%
Dyspepsia	3%	9%
Back pain	10%	5%
Rash	9%	3%
Edema	8%	3%

The incidence rates of flu-like symptoms diminished in time.

Risk of infection

Positive clues for a causal relationship between infection and IFN beta-1a were not found.

Depression/suicide

In the multiple sclerosis groups, the incidence rate of depressive symptoms was not different between the placebo and IFN beta-1a group. Suicidal tendency was more frequent in the IFN beta-1a group as compared to the placebo but the numbers of subjects is too small to conclude that IFN beta-1a is associated with a suicidal tendency.

Interactions

The company tried to analyse the occurrence of possible interactions of IFN beta-1a with ACTH, steroids and antidepressants. The data available did not allow the linkage of the onset of event to the initiation of the second drug (ACTH/steroids or antidepressants). Therefore the analysis was inconclusive.

Withdrawal effects

There is no indication that IFN beta-1a discontinuation led to a deterioration of multiple sclerosis but this was not studied systematically.

After two years in study, around 24% of the patients in the IFN beta-1a treatment group developed positive anti-IFN beta-1a serum-neutralising activity.

The development of neutralising activity was not associated (on the basis of the data commented upon so far) with an increased risk of disease progression. However, in the post-treatment period, a trend towards a higher exacerbation rate was seen among IFN beta-1a treated patients with positive on-treatment serum neutralising activity as compared to those without such activity. Also, compared to IFN beta-1a-treated patients without neutralising activity, patients with neutralising activity had significantly greater increases in T2 lesion volume and tended to have higher numbers of Gadolinium-enhancing lesions on the brain MRI. With respect to disability progression, exacerbation rate and MRI outcomes measures, the results among IFN beta-1a treated patients were at no point in time worse than those seen in placebo-treated patients. Whether disease progression and occurrence of serious adverse events differ between patients developing neutralising activity or not could not be assessed due to the lack of data.

Further data on safety

The company submitted a Safety Update in October 1996 in relation to the requests made to them after the hearing of May 1996. This Safety Update refers to the US post-marketing surveillance data (covering just the initial 3 months after marketing and safety data from the study used in order to generate the antigenicity data discussed above). On the whole, they give some assurance that, as expected, the safety profile of AVONEX does not differ from that of BG 9015 and what is known for interferons in general.

Antigenicity of AVONEX

The issue of antigenicity raised objections by the CPMP, in particular as most of the data initially available referred to BG 9015 and the antigenicity of BG 9015 and BG 9418 (the substance to be marketed as AVONEX) could not be considered equivalent. As a consequence, further data were asked from the company (hearing of May '96). Their answers included reanalyses of the phase III clinical trial (conducted with BG 9015) and new data from an on-going open-label study (C94-801) conducted with AVONEX:

- The relevance of the antibodies for the therapeutic response is re-addressed by the company. The data from the phase III trial with BG 9015 are reanalysed using a "new" assay in which a distinction is made between total (i.e. binding) antibodies and neutralising activity. There appears to be a trend towards similarity with placebo (lack of clinical efficacy) especially in those patients with high (=2 0) neutralising activity titres (around 22% after 2 years). This might not be the case for patients with binding antibodies of lower titres of neutralising activity but from the current data it is not possible to state a cut-off level. Although for the time being only a trend can be observed, the possibility that high titres of neutralising activity interfere with the therapeutic effects is logical enough and must be considered by the prescriber.
- Concerning AVONEX itself, the data submitted (up to 12 months) shows a lower incidence of neutralising activity than for BG 9015. At 12 months, about 1 in 3 patients with (binding) antibodies have titres = 20 of neutralising activity. It is not known how many more patients with antibodies will develop relevant levels of neutralising activity on continuation of treatment. If all patients with antibodies did eventually develop them, the percentage could in theory approach 15% (6-30%; 95% confidence interval); i.e the apparent percentage of patients with binding antibodies at plateau. The problem of long-term treatment of multiple sclerosis with beta interferons in the face of the development of neutralising activity in a subset of patients is at present a matter of debate and does not specifically apply to AVONEX.

5 Overall Conclusion and Benefit Risk assessment

One of the major issues concerning the initial assessment of the dossier of AVONEX was that in the development of the medicinal product the active substance used in the clinical trials (BG 9015) was not identical to the one contained in the medicinal product intended for marketing (BG 9418). Both molecules are secreted from the same Chinese Hamster Ovary (CHO) host cell line; however, the cell culture process and the purification scheme used in the preparation of BG 9418 and BG 9015 are not strictly identical. This raised questions about the results obtained in the various studies and trials. In absence of regulatory guidelines addressing the issue of the bioequivalence of medicinal products derived by r-DNA technology and in absence of a clear-cut knowledge of the mechanism of action of interferons in the treatment of multiple sclerosis, the Applicant carried out an in-depth structural and functional comparison of the two interferons beta-1a (BG 9015 *vs* BG 9418). From the data submitted, the CPMP considered that the two molecules were comparable concerning both structure and function. On this basis the efficacy data obtained with BG 9015 were considered to be applicable to BG 9418.

The applicant provided additional data on the antigenicity of AVONEX. The data on the antigenicity of AVONEX covered at least 12 months exposure so that they could be referred to the "plateau" phase.

Reanalysis of the phase III trial samples was performed using two different tests, a classical ELISA test to detect the frequency and the titres of anti-interferon beta-1a binding antibodies, and an in-house developed combined test ELISA+ Cytopathic Effect assays to determine frequency and titres of neutralising antibodies.

The results showed that AVONEX is no more antigenic than BG 9015, the interferon beta-1a used in the phase III clinical trial.

Whether the one single pivotal study submitted provided enough evidence for the efficacy and safety of IFN beta-1a was discussed thoroughly, especially because concerns were raised on the early termination of the trial. It was considered that the early termination of the trial was correct in the light of the study design in which, *a priori,* the provision of a possible termination of the study was set up once the clinical endpoint was reached. The Applicant also satisfactorily resolved some apparent internal inconsistencies. The results provided were considered robust enough to support the efficacy of AVONEX in slowing the progression of disability and in decreasing the frequency of relapses over a 2-year period.

However, additional data were required by the CPMP as specific obligations to be fulfilled by the Marketing Authorisation Holder in order to obtain comprehensive information on the long-term use of the substance.

In the margins of the scientific discussions it was agreed that the tradename AVONEX is not an outstanding issue, provided that the pharmaceutical form of AVONEX (powder and solvent for solution for injection) and Daivonex (ointment) remain unchanged.

After detailed discussion on the text of the Summary of Product Characteristics and of the Package User Leaflet and label, the CPMP, on 20 November 1996, adopted unanimously a favourable opinion for granting AVONEX a marketing authorisation under exceptional circumstances. All new information that will be submitted will be carefully scrutinised and form the basis of the annual risk/benefit assessment of the medicinal product.

From the clinical information accrued post authorisation the CPMP concluded that the efficacy of the drug is unchanged.

The safety profile has been evaluated since commercialisation and new information has been provided on the occurrence of neutralizing antibodies and on the adverse reactions collected.

The CPMP after the annual re-assessments of AVONEX based on new information and results of the specific obligations and follow up measures concluded that the risk/benefit evaluation remains in favour of the drug. As some specific obligations/follow-up measures have still to be fulfilled, the product should continue to be authorised under exceptional circumstances and re-evaluated in a year's time.

6. Clinical efficacy and safety data submitted post-authorisation

At the request of the CPMP the applicant provided additional data on the antigenicity of AVONEX. Analysis was carried out by an in-house developed two-step assay system. An ELISA test is used to identify patients who have formed antibodies to IFN-beta. . Samples testing positive are tested in a Cytopathic Effect assay for activity that neutralises the *in vivo* biological activity of IFN-beta. In this way, the frequency and titers of neutralising antibodies is being determined.

6. 1. Study C94-801: An ongoing, open label study in patients with multiple sclerosis (MS).

Three hundred and eighty two (382) patients have been enrolled into this study. The dosing regimen is 30 µg, intramuscularly (per week) for up to 4 years. Patients are to be followed for safety and antibody formation. The safety and antibody data are monitored continuously, but are also formally analysed and discussed in interim safety reports on an annual basis. An analysis of the effects of neutralising antibodies on the pharmacodynamic response to AVONEX was therefore submitted with the safety report in September 1997.

After the discussion of the new data, the CPMP considered that an incidence of antibodies of 8% could be quoted in the Summary of Product Characteristics. This new information on antigenicity originated a type II variation to revise the SPC, section 4.4 Special Warnings and Special Precautions for Use accordingly. A CPMP positive opinion was adopted on 22 April 1998 and the Commission Decision amending the Marketing Authorisation was adopted on 17 August 1998.

6. 2 Study C94-805: double blind, randomised dose comparison (30 µg vs 60 µg).

Patients with relapsing remitting MS or relapsing progressive MS were randomised to receive 30 µg (n=402) or 60 µg (n=400) once a week during three years. The primary endpoint was the increase in the time to reach a sustained progression of disability (one point increase in EDSS maintained for 6 months) and secondary endpoints were measures of MRI at one, two and three years of follow up, nine hole peg test, QoL and IV steroid use as a surrogate for relapses. Relapses were not even considered as a secondary endpoint. To maintain the blinding in spite the adverse effects of Avonex, different physicians were responsible for evaluating the EDSS (examining physician) and for patient management including adverse reactions and relapses assessment and treatment (treating physician).

The included population had a mean duration of disease of 6.5 years and a mean EDSS score at baseline of 3.6 in both treatment groups, with a 42% of subjects with an EDSS score of 4.0 or above (42% vs 43%). 70% of included patients remained on study drug for at least 3 years and no differences are seen between both groups in relation to discontinuations. 85% of included patients were relapsing remitting and 15 % were relapsing progressive.

No differences in efficacy are seen between 30 µg or 60 µg of AVONEX given once a week intramuscularly. It is difficult to ensure the sensitivity of the performed trial to detect existing differences in efficacy due to the characteristics of the disease, the ranges where the magnitude of the efficacy lies and the lack of sensitivity of the EDSS scale.

No relevant differences in clinical safety are shown between both doses although a higher incidence of flu-like syndrome appears with the higher dose.

Thus the specific obligation related to the performance of the trial exploring a 60µg dose is considered to be fulfilled.

This new information obtained after the dose comparison Study C94-805 required a type II variation to revise the SPC, section 4.2 and 5.1. The proposal of the MAH to insert the sentence “and no additional benefit has been shown by administering a higher dose (60 µg) once a week and remove the sentence: “However, the optimal dose of interferon beta 1a in MS may not have been established.” in

4.2 was considered to be acceptable by the CPMP. A CPMP positive opinion was adopted on 26 July 2001.

6. 3 Extension of the indication on the basis of the clinical trial C95-812 (CHAMPS)

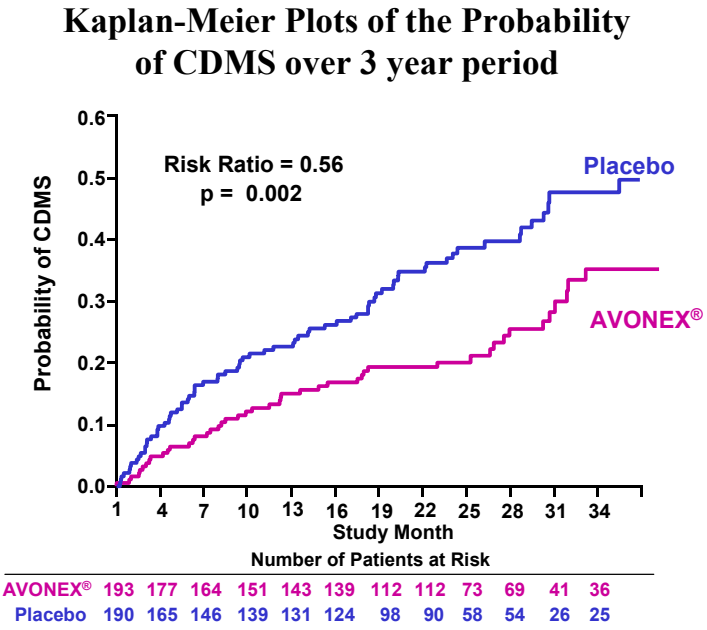
The MAH applied for a type II variation to extend the indication by proposing the following statement: *"In those patients characterised by one demyelinating event accompanied by MRI abnormalities, AVONEX reduces the risk of relapse".* This application for extension of the indication was based on the results of study C95-812 (CHAMPS) which was planned at the time of approval and was considered as a specific obligation of the MAH in order to confirm efficacy.

CHAMPS trial was a randomised double-blind placebo controlled clinical trial with 383 patients (AVONEX n= 193, placebo n=190) designed to determine whether a weekly *im* dose of 30 mcg of AVONEX reduces the risk of developing clinically definite multiple sclerosis (CDMS) in patients after a first demyelinating event (optic neuritis, brainstem/cerebellar syndrome or spinal cord syndrome) associated with at least two compatible brain MRI lesions.

The primary endpoint was the time to development of CDMS, defined by the occurrence of a second demyelinating event or progression of the initial disease or disability worsening of 1.5 points in the EDSS scale. Secondary endpoints were predefined MRI data at specified times.

An interim efficacy analysis was planned to occur 2 years after the enrollment of the last subject. Because of the number of patients having developed CDMS earlier than expected, the interim analysis was performed 6 months earlier than scheduled, with 18 months follow up of all subjects still on trial. After this interim analysis, the study was interrupted because of positive results according to the predefined stopping rule.

The diagnosis of CDMS was the result of a second demyelinating event in all but five patients. One patient in each group presented progressive neurologic worsening over the first two months and 3 patients (one AVONEX and two placebo) developed CDMS because of progressive neurologic disability without acute exacerbation. The magnitude of the reduction of the risk of developing CDMS was 44% which gives the estimate of 7 patients to be treated to avoid the occurrence (within the studied period of time) of a second event. AVONEX treated patients showed less disease activity (as measured by GD enhancement) and less lesion burden (as measured by T2) at all time points.



The estimated risk of a second event was 39% in 2 years and 50% in 3 years in the placebo group and 21% (2 years) 35% (3 years) in the Avonex group.

The incidence of neutralizing antibodies (NABs) over 3 years was low, with less than 2%. As NABs are known to reach a plateau at approximately 1 year after initiating therapy, it is likely that the long-term impact of NABs on Avonex efficacy will be very small.

CHAMPS were a well-designed, well-conducted, generally consistent study. It showed that AVONEX delayed the development to CDMS of patients at risk of developing the disease after having suffered a well-defined first clinical demyelinating event associated with at least two compatible brain MRI lesions although their long-term outcome is not studied. However, it was unclear whether the evidence provided by study was sufficient to grant the extension of the indication.

No new safety concern has been identified from this study. However, since the patients included in CHAMPS study were less severely ill than those currently treated with Avonex it does not necessarily follow that the same level of risk is acceptable in both groups.

Issues related to the clinical impact of the early treatment, long term benefit, treatment of patients vs. the safety profile of the product, validity of MRI parameters as surrogate and the identification of a population that would benefit of the early treatment, were discussed with the MAH during an oral presentation.

The MAH was requested by the CPMP to identify a subgroup of patients likely to have an unfavourable course of their disease as well as an acceptable response to the drug so as to avoid the early "blind" treatment of all patients with a single episode, which would appear unjustified. This was done by the MAH considering the 2-year risk rather than the 3-year risk due to the scarcity of patients beyond 2 years of follow-up. The subpopulation proposed included those patients having at least 1 Gd-enhancing lesion *and* 9 T2 lesions OR at least 2 Gd-enhancing lesions *and* 3 T2 lesions at baseline. In the corresponding cohort, which represents 65 of the 383 (17%) subjects enrolled in CHAMPS, the 2-year risk of developing CDMS is 66% and the treatment effect is 75% ($p = 0.00028$) i.e. the relative risk of Avonex vs placebo is 0.25.

These criteria identified patients with important predictors of high inflammatory activity that could benefit from Avonex treatment more than other patients within the whole CHAMPS cohort. This is consistent with the current belief that it is precisely the inflammatory component of MS the one that fundamentally responds to beta interferons. It can be very prominent in initial phases of the disease. The criteria used to define the high-risk high-benefit subgroup are plausible and consistent also with available data on the natural history of the disease. The identified cohort is in line with that of Barkhof et al[2]. in a study of 74 patients who were followed up for a median time of 39 months after a single demyelinating event. The authors concluded that the following MRI characteristics identified the patient with the highest risk of developing CDMS: 9 T2 lesions, 1 Gd-enhancing lesion, 3 periventricular lesions, 1 juxtacortical lesion. They also concluded that the number of Gd-enhancing lesions was the single best predictor of the risk of developing CDMS. Although the number of periventricular lesions and the number of juxtacortical lesions were not counted as part of the CHAMPS study, the inclusion criteria did require that at least 2 of the T2 lesions must be at least 3 mm in size and that one of the T2 lesion must be periventricular or ovoid.

The data from the CHAMPS study were presented at the *ad-hoc* experts group meeting on clinical efficacy of beta interferons in MS treatment and reanalysed in the light of recent publications.[3] [4]. These indicate that disease activity as measured by MRI (number of Gd enhancing and T2 lesions) is an important co-variate both for prognosis and treatment effect. The reliability of the diagnosis of MS,

[2] Comparison of MRI criteria at first presentation to predict conversion to clinically definite multiple sclerosis: F. Barkhof et al; Brain (1997) 120, 2059-2069.

[3] Guidelines from the International Panel on the Diagnosis of Multiple Sclerosis*"* Article from *Annals of Neurology*, *April 2001* McDonald et al

[4]Effect of early interferon treatment on conversion to definite multiple sclerosis: a randomised study"- G. Comi et al, -Lancet Vol 357, no 9268, 19 May 2001

was acknowledged as having improved with the new McDonald criteria (incorporating MRI criteria related to time and space dissemination) so that the possibility of misdiagnosis appears now low even at early stages of the disease. Based on clinical judgement patients could be considered at "high risk" of disease activity, e.g. if the first attack was associated with high MRI activity, confirmed at least 3 months later.

The clinical relevance of these data has been extensively discussed. There was agreement on the view that treatment should not be initiated as a rule after the first clinical attack of demyelinisation considering the unknown clinical evolution of the disease versus the adverse event profile of the drug. It was stated that inclusion of the predetermined "high risk" patients should not be accepted as even in case of a subsequent relapse, one might still consider treatment with interferon beta without loss of overall benefit.

A minority view was that, in clinical practice, one would probably treat a few patients early if, on a case by case basis clinical judgement, they could consider them to be at high risk of disease activity, e.g if the first attack was associated with high MRI activity, confirmed at least 3 months later. Based on study data, 2 or more Gd enhancing lesions at baseline were apparently predictive of a clinical relapse within 2-3 years in about 70% of the patients, i.e. 70 % of these patients will later qualify for treatment according to the present indication. If, in addition, a new MRI after three months or more shows ongoing activity, the new McDonald criteria for diagnosis of MS would be fulfilled. If furthermore only patients with at least 2 new Gd enhancing lesions were considered for therapy, the likelihood of treating patients with too low MS activity would be minimised. The CHAMPS study was not designed to support this post hoc interpretation but its results are compatible with it. A clinical rationale for early treatment would be that inactivity of the disease in terms of motor or sensory symptoms is compatible with disease activity in areas of the brain related to other functions, for example, cognitive deterioration, which may be a problem in patients with MS. MRI therefore provides valuable complementary information on disease activity.

Since an extension of the indication in an early stage of the disease was sought, the benefit – risk ratio was reconsidered. The CPMP concluded that the adverse events of the drug profile versus the limited predictive value of the data was not acceptable for the entire patient population as initially claimed in the proposed indication: "In those patients characterised by one demyelinating event accompanied by MRI abnormalities, AVONEX reduces the risk of relapse"was considered to be unfavourable. The CPMP at the meeting on 26 July 2001 recommended the refusal of the variation for the indication as applied on the following grounds:

- The clinical relevance of the findings of the study C95-812 (CHAMPS) is unclear.
  Even if the second episode is delayed, it cannot be theoretically excluded that there might be a catch up later during treatment and there is no real reduction in the long-term frequency of exacerbations as well in disability progression.
- The benefit risk balance was not found to be positive, considering both the direct side effects of interferon therapy and the consequences on quality of life of initiating long-term therapy in individuals with ill defined prognosis with respect to disease activity in an overall chronic and slowly progressive disease.

Definition of a high risk patients and restriction of the indication

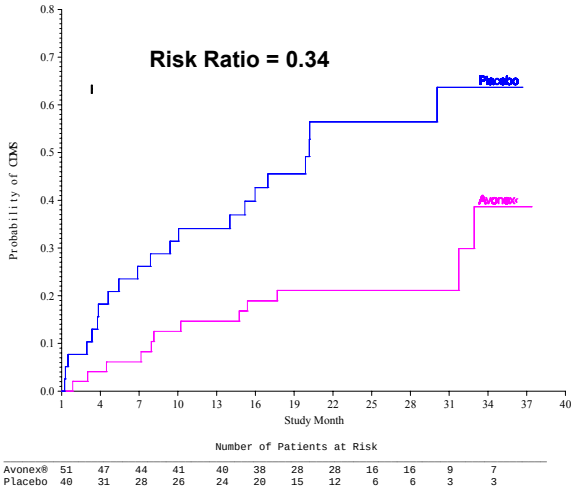
The MAH appealed to the CPMP opinion by providing responses to the CPMP objections and proposing a restricted indication. The definition of high risk of relapse patients following a first demyelinating event i.e. patients with high disease activity was based on both clinical and MRI criteria in the light of the recent publication by Brex et al [5] The final subset was identified as: Patients with at least 9 T2 hyperintense lesions AND at least one Gd-enhancing lesion. The prevalence in the placebo arm of the CHAMPS study was 21%. The 2-year risk of developing CDMS (Kaplan Meier estimate) is 0.56 with a sensitivity of 33% and a specificity of 83%.

[5] Brex & al. Assessing the risk of early multiple sclerosis in patients with clinically isolated syndromes: the role of a follow up MRI. J Neurol Neurosurg Psychiatry (2001) 70:390-393

Following a *post-hoc* analysis of the CHAMPS trial, those patients with a baseline MRI with at least 1 Gd-enhancing lesion and 9 T2 lesions had a 2-year risk of suffering a second event of 56% in the placebo group and 21% in the AVONEX treatment group.

Therefore, in this high-risk population, the CPMP agreed that there is enough evidence of efficacy derived from the CHAMPS study on the chosen endpoints. The full relevance of such endpoints remains debatable as any evidence of long-term effects on progression of disability is still lacking.

The treatment effect of Avonex in the subgroup of CHAMPS patients with ≥ 9 T2 lesions and ≥ 1 Gd-enhancing lesion at baseline



Discussion of the relevance of a restricted extension of indication was further debated at the CPMP level. For the time being there is no well-established definition of a high-risk patients. A more conservative approach is to accept at least 9 T2 hyperintense lesions on the initial scan and at least 1 new T2 or 1 new Gd-enhancing lesion on a follow-up scan taken at least 3 months after the initial scan. In any case treatment should only be considered for patients classified at high risk.
The long-term impact of early treatment with Avonex is unknown even in this high-risk subgroup as the study was mainly designed to assess the time to the second event rather than the long-term evolution of the disease. The MAH presented data to support the fact that patients at the initial clinical stage of the disease already exhibit evidence of irreversible CNS damage including axonal loss and brain atrophy that may impact the long term course of the disease and lead to irreversible disability if they are not prevented sufficiently early.

Furthermore, the applicant has committed to a long-term follow-up of the patients entered in the CHAMPS study. This add-on study is a follow-up study on the 383 eligible patients enrolled into CHAMPS at 50 sites. A 5-year MRI report should be submitted in September 2003 and the final study report should be submitted in December 2005.

Conclusion and benefit- risk assessment

Divergent opinions were expressed by some CPMP members were: treatment of patients with one demyelinating event should be considered versus the fact that the 50% of placebo treated patients in the CHAMPS study did not reach the MS diagnosis in 3 years of the first event; the subgroup was defined retrospectively; the duration of the trial and the trial design do not allow -at the time of the application- a conclusion on the long term outcome of early treatment.

However, the majority of the CPMP agreed that in this restricted, high-risk population, there was enough evidence of efficacy derived from the CHAMPS study on the chosen endpoints. In addition,

the safety profile of Avonex in the CHAMPS population has not been shown to be different compared to more advanced patients in the course of the disease. Therefore, the benefit/risk balance in the population of the indication: *"treatment of patients who have experienced a single demyelinating event with an active inflammatory process if it is severe enough to warrant treatment with intravenous corticosteroids, if alternative diagnoses have been excluded, and if they are determined to be at high risk of developing clinically definite multiple sclerosis"* was considered positive by majority decision. The results of the *post-hoc* analysis and subgroup definitions were described in the section 5. 1 of the SPC.

The CPMP also considered the commitment of the MAH to a long-term follow-up of the patients who entered CHAMPS study.

6. 4. Postmarketing Safety experience

According to Commission Regulation (EEC) 2309/93 the Marketing Authorisation Holder submitted during the concerned period the requested Periodic Safety Update Reports (PSURs) and Line Listings.

Based on the analysis of the additional data from ongoing studies, post-approval drug experience reports, Periodic Safety Update Reports (submitted at six month intervals for the first two years and annually thereafter, 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 following the evaluation of the PSURs. The following changes to the SPC and PL were proposed and were issued positive opinions by the CPMP:

- Addition of the undesirable effects alopecia, metrorrhagia and/or menorrhagia, syncope, transient hypertonia and/or severe muscular weakness that prevents voluntary movements in the SPC (section 4.8) and PL (section 9 'Description of undesirable effects under normal use) following the 1st PSUR.
- Two additional undesirable effects congestive heart failure and arthritis were included in the product literature following the 2nd and the 3rd PSURs.
- The 4th PSUR revealed some new adverse reactions, including the possible occurrence of cardiomyopathy and serious hypersensitivity reactions as well as serious cases of thrombocytopenia.
- Further amendments to the SPC and PL were agreed by the CPMP following the 5th PSUR. These included the adverse reactions: migraine, episodes of MS exacerbation's linked to injections, vesiculobullous rash, weight loss, LE syndrome and injection site pain.
- "Anaphylactic shock", "anaphylactic reactions" and "weight gain" were added in the section 4.8 of the SPC (adverse reactions) following the assessment of the seventh PSUR.

6. 5. Renewal of marketing authorisation

Based on the review of the available information, the CPMP considered on 17/01/2002 that the benefit/risk profile of AVONEX continued to be favourable in patients with relapsing multiple sclerosis (MS) in the approved indications. Consequently, the CPMP considered that the Marketing Authorisation could be renewed. It was considered that the Marketing Authorisation should remain.under exceptional circumstances as all clinical specific obligations had not been completely fulfilled: an interim report on safety from study C94-801 and the final study report providing safety and antigenicity data were still due. At the request of the CPMP, new adverse drug reactions were added in section 4.8 of the SPC following the assessment of the seventh PSUR (see above) and some minor changes proposed by the MAH to bring the product information in line with the latest QRD Product Information template (Version 5.2-04/2001) were accepted.