20 January 2010
EMA/374288/2011
Committee for Medicinal Products for Human Use (CHMP)

Avonex

(interferon beta-1a)

Procedure No. EMEA/H/C/000102/II/0108

CHMP assessment report for paediatric use studies submitted according to Article 45 of the Regulation (EC) No 1901/2006

Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted

Disclaimer: The assessment report was drafted before the launch of the European Medicines Agency's new corporate identity in December 2009. This report therefore has a different appearance to documents currently produced by the Agency.

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CHMP VARIATION ASSESSMENT REPORT

Invented name/Name: Avonex
International non-proprietary name/Common name: interferon beta-1a

TYPE II VARIATION: EMEA/H/C/000102/II/0108

Indication summary (as last approved):	treatment of multiple sclerosis
Marketing Authorisation Holder:	Biogen Idec Ltd.

I. SCOPE OF THE VARIATION AND CHANGES TO THE DOSSIER

Scope of the variation:	**Update of Summary of Product Characteristics** Update of sections 4.2, 4.8 and 5.1 of the Summary of Product Characteristics (SPC) to reflect paediatric information according to the SPC guideline and following CHMP assessment of the data submitted in the context of the article 45 of the Paediatric Regulation 1901/2006, as amended (FUM 76).
Rapporteur:	Dr. Concepcion Prieto Yerro
Product presentations affected:	See Annex A to the Opinion
Dossier modules/sections affected:	Modules 1, 2 and 5
Product Information affected:	SPC

II. STEPS TAKEN FOR THE ASSESSMENT

Submission date:	1 October 2009
Start of procedure:	18 October 2009
Rapporteur's preliminary assessment report circulated on:	26 November 2009
Rapporteur's updated assessment report circulated on:	14 December 2009
Request for supplementary information and extension of timetable adopted by the CHMP on :	17 December 2009
MAH's responses submitted to the CHMP on:	18 December 2009
Rapporteur's preliminary assessment report on the MAH's responses circulated on:	11 January 2010
Rapporteur's preliminary assessment report on the MAH's responses circulated on:	15 January 2010
CHMP opinion:	20 January 2010

III. SCIENTIFIC DISCUSSION

3.1. Introduction

Multiple sclerosis (MS) is a chronic disease characterized by an immune cell mediated inflammation and progressive degeneration of neurons and their axonal pathways. The use of interferon-beta therapies to treat adult patients with multiple sclerosis has demonstrated the ability to impact measures of disease activity as well as potentially slow disease progression.

Avonex (interferon beta-1a) is indicated for the treatment of patients diagnosed with relapsing multiple sclerosis (MS) and in the treatment of some patients with a single demyelinating event with an active inflammatory process. The recommended dosage for the treatment of relapsing MS is 30 micrograms (1 ml solution), administered by intramuscular (IM) injection once a week. No additional benefit has been shown by administering a higher dose (60 micrograms) once a week.

The course of MS in patients under 16 years of age (early-onset MS) appears similar to that in adults. No formal clinical trials in paediatric patients have been conducted by Biogen Idec Limited. However, limited published data, the majority of which is in patients 12 years and above treated with the adult approved dose (30 micrograms IM once per week), is available. An assessment of these data showed that efficacy has not been demonstrated clearly in this population although there appears to be an observed reduction in relapse rate. In addition, no specific safety signals have been identified in the published data with paediatric patients in comparison to those in adults. Consequently, a type II variation was approved to reflect this information (EMEA/H/C/102/II/82).

This variation application is submitted further to the request of the CHMP following assessment of the FUM 76 (submission of the article 45 of the Paediatric Regulation 1901/2006, as amended).

It refers to an update of sections 4.2 , 4.8 and 5.1 of the Summary of Product Characteristics (SPC) to reflect paediatric information according to the SPC guideline.

3.2. Clinical aspects

Clinical Aspects

Clinical efficacy

The MAH submitted a paper of one completed paediatric study for Avonex (Pakdaman et al 2006[1]), that was a prospective, randomized, single-centre trial treating 16 MS patients under the age of 16, with 15 micrograms IM Avonex once per week, aimed to determine the efficacy and safety of the half adult dose in this population. After the review of these data, the CHMP concluded the following: *"the results suggest that the use of interferon beta 1a at one half the standard dose use in adults, and currently recommended for children between 12-16 years (i.e. 30mcg once a week), is well tolerated and might be effective in reducing the rate of relapses (nearly twice in the non-treated group) and the degree of disease progression as assessed by changes in EDSS. Data provided are too limited to draw any dose-recommendation. However, the information may be included in the SPC Section 5.1 as it might be helpful for physicians. Based on data submitted, the MAH should briefly include this information in Section 5.1 of the SPC."*

As highlighted by the CHMP during their assessment, this study had a number of short-comings including low patient numbers and a lack of comparison with the approved 30 microgram IM once per week dose.

[1] Treatment of Early Onset Multiple Sclerosis with Suboptimal Dose of Interferon Beta-1a; Pakdaman H., Fallah A., Sahraian M.A., Pakdaman R., Meysamie A.Neuropaediatrics 2006; 37: 257-260.

The majority of data in paediatric patients were in patients 12 years of age and older treated with the approved adult dose (30 micrograms IM once per week).

As part of this type II variation application submitted to fulfil the CHMP request, the MAH presented data of a recent publication (Ghezzi et al 2009[2]), which describes a long-term follow-up of paediatric patients initiated on treatment with immunomodulators before the age of 16: 77 patients treated with 30 micrograms IM Avonex once per week, 36 with another interferon beta-1a, 3 with interferon beta-1b and 14 with glatiramer (total 130 patients). This paper was also submitted as part of the 22nd PSUR Bridging Report, currently under assessment by the CHMP.

In general, treatment with all interferons was initiated at a quarter or half dose before increasing to the full dose within 1 to 2 months.

Of the Avonex-treated patients, 34 (44%) continued treatment for the full period of the study (4.7 +or- 2 years, median 4.5), 20 subjects (26%) were lost to follow-up or stopped treatment after a mean follow-up of 3.9 ± 2.4 years (median 3.7), and 23 subjects (30%) transferred to other products after a mean interval of 2.5 ± 1.4 years (median 2.3).

Relapse rate decreased in all Avonex treated subgroups and the final Expanded Disability Status Scale (EDSS) score did not change significantly compared to the initial. The main efficacy outcomes of the study are summarized in Table 1.

Table 1: Demographic and clinical data of Patients treated with Avonex

Avonex	**Treatment duration (yrs)**	**Annualized pre-treatment relapse rate**	**Final relapse rate**	**Pre-treament EDSS**	**Final EDSS**
All Avonex patients (77)	4.46 ± 2.25	2.5 ± 1.9	0.4 ± 0.6	1.3 ± 1.0	1.5 ± 1.2
	Follow-up (yrs)				
Continued Avonex treatment (34)	4.7 ± 2.0	2.9 ± 2.2*	0.3 ± 0.4	1.3 ± 0.	91.2 ± 0.8
Lost to follow-up/stopped treatment (20)	3.9 ± 2.4	2.3 ± 1.9*	0.5 ± 0.7	1.5 ± 1.1	1.6 ± 1.5
Changed treatment (23)	5.3 ± 2.3	2.0 ± 1.4*	0.6 ± 0.7	1.3 ± 1.1	1.7 ± 1.3

* $p<0.0001$ significant difference between pre-treatment and final relapse rate (adapted from Ghezzi et al 2009

Clinical safety/ Pharmacovigilance Aspects

As of 30 April 2009, an estimated 375,000 patients have been exposed to Avonex worldwide (22nd PSUR July 2009), with over 1,200,000 person-years of exposure. Avonex exposure in the paediatric population is not known but certainly comprises only a very small percentage of the total exposure. As the incidence of MS presenting before the age of 12 years old is very low the majority of any paediatric exposure is predominantly in the adolescent population.

[2] Ghezzi A, Amato MP, Annovazzi P, et al. Long-term results of immunomodulatory treatmentin children and adolescents with multiple sclerosis: the Italian experience. Neurol Sci 2009;30(3):193-9

A small number of ADRs reported in paediatric/adolescent patients have been reported in postmarketing experience with Avonex. The data received to date suggests the safety profile of Avonex as judged by spontaneous suspected ADRs in this patient population is consistent with that of adults.

To date, there have been no findings suggestive of a signal specific to paediatric patients treated with Avonex.

Pakdaman reports the safety outcomes of treating 8 paediatric patients with 15 micrograms IM Avonex once per week, observing no drop-outs during the study with no patients discontinuing the drug or developing serious side-effects.

Ghezzi (et al 2009) reported clinical side-effects in 30 / 77 (39%) of Avonex treated subjects. As with the Pakdaman study the authors from the Ghezzi study concluded that the safety profile of Avonex treated paediatric patients was consistent to that observed in adult patients.

Discussion

After the review of the Pakdaman et al study results, the CHMP accepted the inclusion of a statement summing up the results in Section 5.1 of the SPC under the consideration of its relevance for prescribers. An additional change not requested by the CHMP was also presented: the MAH proposed to include the results of the above mentioned study in section 5.1 but also in section 4.2, which was not considered justified. Furthermore, the results of an additional recently published observational study in which 77 patients were exposed to Avonex for up to 4 years at the dose regimen currently recommended in adults were also presented. These results are consistent to the already known efficacy/safety profile of Avonex in adults and thus, reassuring. Nevertheless, the CHMP considered the data insufficient to justify the inclusion of any new statement in the SPC since it would not add relevant information to that currently included.

The CHMP therefore recommended changes in sections 4.2, 4.8 and 5.1 to reflect the Pakdaman results in section 5.1 and to reflect already approved paediatric information, in accordance with the SPC guideline.

3.3. Changes to the Product Information

The MAH proposed the following SPC changes (strikethrough= deleted text, underlined= new text):

- **Section 4.2**

Paediatric population

Children and adolescents: No formal clinical trials or pharmacokinetic studies have been conducted in children or adolescents. However, limited published data suggest that the safety profile in adolescents from 12 to 16 years of age receiving AVONEX 30 micrograms IM once per week is similar to that seen in adults. Use of doses of AVONEX 15 micrograms IM once per week have also been reported in the literature. There is ~~no~~limited information on the use of AVONEX in children under 12 years of age and therefore AVONEX should not be used in this population (see section 5.1).

- **Section 5.1**

Paediatric population
There are limited safety and efficacy data available on the use of AVONEX in paediatric patients. A cohort of 77 patients treated before 16 years of age, received AVONEX 30 micrograms IM once per week. After treatment duration of 53.6±27 months, relapse rates (RR) decreased significantly (pre-treatment RR 2.5± 1.9 vs. final RR 0.4 ± 0.6) and EDSS score remained unchanged with respect to the initial score (pre--treatment 1.3 ± 1.0 vs. final 1.5 ± 1.2). The frequency of adverse events was similar to that observed in adult patients. A study of 16 patients, aged 11 to 14 years, compared AVONEX 15 micrograms IM once

per week (n=8) to no treatment (n=8) with follow-up for 4 years. EDSS progression was 2.4 for the treated group compared with 3.3 in the untreated group; the relapse rate was lower and there were fewer new T2 lesions in the treated group. None of the patients discontinued AVONEX treatment and there were no significant side effects reported

Further to the assessment of the proposal of the MAH to amend the Product Information and in the light of the assessment of the submitted data (see section 3.2) and responses to the Request for Supplementary Information, the following SPC wording was recommended by the CHMP (strikethrough= deleted text, underlined= new text):

- **Section 4.2**

~~*Children and adolescents:* No formal clinical trials or pharmacokinetic studies have been conducted in children or adolescents. However, limited published data suggest that the safety profile in adolescents from 12 to 16 years of age receiving AVONEX 30 micrograms IM once per week is similar to that seen in adults. There is no information on the use of AVONEX in children under 12 years of age and therefore AVONEX should not be used in this population.~~

Paediatric population: The safety and efficacy of Avonex in adolescents aged 12 to 16 years have not yet been established.
Currently available data are described in section 4.8 and 5.1 but no recommendation on a posology can be made.
The safety and efficacy of Avonex in children below 12 years of age have not yet been established. No data are available.

- **Section 4.8**

Paediatric population: Limited published data suggest that the safety profile in adolescents from 12 to 16 years of age receiving AVONEX 30 micrograms IM once per week is similar to that seen in adults.

- **Section 5.1**

Paediatric population: Limited data of the efficacy/safety of AVONEX 15micrograms IM once per week (n=8) as compared to no treatment (n=8) with follow up for 4 years showed results in line to those seen in adults,although the EDSS scores increased in the treated group over the 4 year follow-up thus indicating disease progression. No direct comparison with the dose currently recommended in adults is available.

The MAH agreed with the above-mentioned recommendation and provided the Product Information amended accordingly.

IV. CONCLUSION

On 20 January 2010, the CHMP considered this Type II variation to be acceptable and agreed on the amendments to be introduced in the Summary of Product Characteristics.