15 December 2022
EMA/23616/2023
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Avonex

International non-proprietary name: interferon beta-1A

Procedure No. EMEA/H/C/000102/II/0193

Note

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

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1. Background information on the procedure

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Biogen Netherlands B.V. submitted to the European Medicines Agency on 25 March 2022 an application for a variation.

The following changes were proposed:

Variation requested		**Type**	**Annexes affected**
C.I.4	Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I and IIIB

Update of sections 4.2 and 4.8 of the SmPC in order to update safety information for the paediatric population based on the final results of the Tecfidera Paediatric study (109MS306) (CONNECT - part 1) that uses Avonex as an active comparator arm, availability of data from published literature and postmarketing data form Biogen global safety database; the Package Leaflet is updated accordingly.

Study 109MS306 was conducted to meet Paediatric Investigation Plan (PIP) requirements for Tecfidera (Dimethyl fumarate). Study 109MS306 was already submitted for Tecfidera and has been evaluated for inclusion of relevant data into the Tecfidera product information. The submission of the CSR for Avonex in accordance with the requirements of Article 46 of the Paediatric Regulation was inadvertently overlooked. Following identification of the issue the marketing authorisation holder (MAH) sought advice from the EMA Product Lead and it was agreed to submit the CSR for Avonex on the next available submission date of 08 March 2022.

Thus, this submission covers both procedures:
a) A type II variation for Avonex to update the Product Information (PI) with 109MS306 study data

b) P46-089 - Article 46 submission for CSR of a completed Paediatric study 109MS306 (part 1)

The requested variation proposed amendments to the Summary of Product Characteristics (SmPC) and Package Leaflet (PL).

2. Overall conclusion and impact on the benefit/risk balance

The MAH has requested a type II variation to update sections 4.2 and 4.8 of the SmPC to amend existing safety information of Avonex in paediatric population, following completion of Tecfidera Paediatric Study 109MS306 (CONNECT- part 1), that uses Avonex as an active comparator arm, available of data from published literature and postmarketing data from Biogen global safety database. Consequential changes to the PL are also proposed.

There is no specific discussion on the efficacy of Avonex in this population. The MAH states in the Clinical Overview addendum that the benefit of Avonex in the paediatric population remains undefined and therefore, Avonex should not be used in children without careful evaluation of the benefit-risk ratio.

No information on clinical pharmacology of Avonex in this population has been provided by the MAH.

As for safety, the overall safety evaluation plan of Avonex for paediatric patients is summarized from 2 interventional randomized, controlled trials that use intramuscular Avonex as an active comparator arm (Study 109MS306 [CONNECT] and PARADIGMS); 4 published literature observational trials in paediatric MS participants using Avonex and postmarketing data from the Biogen Global Safety Data.

Regarding CONNECT study, the most frequently reported treatment-emergent adverse events (TEAEs) (≥ 10% of participants) in the Avonex group that the Investigator considered related to study treatment were influenza like illness (50%), headache (25%), and pyrexia (17%). There were 25 treatment-

emergent serious adverse events (SAEs) in the Avonex group, including multiple sclerosis (MS) relapse (25%); and anemia, groin pain, hepatocellular injury, hypertension, influenza like illness, paraesthesia, and relapsing MS (1% each). Only SAE of influenza like illness was considered related to study treatment by the Investigator. The MAH was requested to provide more information about the cases of anaemia and hepatocellular injury and satisfactory responses were received. The case of anaemia is confounded by plasmapheresis and therefore it is difficult to establish a causal relationship with Avonex. The case of hepatocellular injury seems to be an autoimmune hepatitis that is already listed in the SmPC of Avonex. A total of 13 participants (9%) had a TEAE leading to discontinuation of study treatment (Avonex, 8 participants [11%]; Tecfidera, 5 participants [6%]). There were 10 TEAEs in the Avonex group that led to study treatment discontinuation, including MS relapse and altered mood, asthenia, headache, hepatocellular injury, influenza like illness, tremor, and vomiting. Overall, there were no trends in mean change from baseline clinical laboratory values and vital sign values with the exception of high pulse rate (Avonex, 24%; Tecfidera, 31%).

PARADIGMS was a 2-year, double-blind, randomized, active-control study to evaluate the safety and efficacy of fingolimod administered once daily as compared with Avonex (active comparator) once weekly. The trial period lasted up to 24 months. A total of 215 participants were included in the study (Avonex, 108 participants; fingolimod, 107 participants). In the Avonex group, the most frequently reported AEs (≥ 20.0%) were influenza like illness (37.4%), headache (29.9%), viral upper respiratory tract infection (24.3%), and pyrexia (20.6%). A total of 7 participants (6.5%) in the Avonex group had at least 1 SAE. A discrepancy regarding the case of supraventricular tachycardia was requested to the MAH that was clarified by the MAH.

Regarding the observational studies, as the company stated that there are methodological differences in the study designs of these interventional and observational studies, no formal statistical comparison of results in paediatric subjects was performed across the studies and therefore had a limited value.

In the observational short-term safety trial [Basiri K 2012], a total of 13 participants younger than 16 years of age who were recently diagnosed with RRMS were enrolled in the study. Six participants were treated with Avonex 30 µg IM once weekly, and 7 participants were treated with Betaferon 250 µg SC every other day.

The long-term results trial of immunomodulatory treatment of children and adolescents in Italy [Ghezzi 2009] comprised 130 participants (Avonex, 77; Rebif 22 µg/Betaferon, 39; Copaxone, 14).

The population of the long-term safety trial with Avonex 30 mg IM [Ghezzi 2007] comprised 52 participants with symptom onset at an average age of 11.7 ± 2.7 years. In 6 participants, treatment was interrupted (2 participants for lack of compliance, 1 participant for persistent leukopenia, 1 participant for ineffectiveness, 2 participants for other reasons).

Finally, the case series of IFN-β treatment [Mikaeloff 2001] included a total of 16 participants (14 females and 2 males) with a median age of 15.5 years. Two females had an autoimmune disorder of either type 1 diabetes or thyroiditis before starting treatment.

Clinical laboratory abnormalities observed in ≥ 2 studies were abnormal thyroid function and elevated liver enzymes. Most of these events were transient. No deaths or SAEs were reported across these studies.

When considering the post-marketing information, the estimated exposure in adults is based on Avonex market data available through 30 Mar 2021. Cumulative global patient exposure to Avonex is approximately 600,985 patients, representing approximately 2,752,261 patient-years. The most frequently reported SAEs (> 4) in paediatric patients from the same GSD search were MS relapse (n = 216), MS (n = 27), seizure (n = 14), pyrexia (n = 11), optic neuritis (n = 11), depression (n = 9),

hypoaesthesia (n = 9), paraesthesia (n = 6), encephalomyelitis (n = 5), generalised tonic-clonic seizure (n = 5), pain (n = 5), and vision blurred (n = 5).The proportion of reports of SAEs of optic neuritis and vision blurred was higher for paediatric MS patients than for adult MS patients, but this statement was based on absolute numbers and not in frequencies.

Considering the above mentioned information that was provided by the MAH, the CHMP considered that there was not enough data to ensure that safety data for the paediatric population is consistent to what seen in adults, especially considering that one of the main supporting data is based on the information of Tecfidera, which has recently updated the SmPC with a list of AEs that seem to be more common in the paediatric population (headache, gastrointestinal disorders, respiratory, thoracic and mediastinal disorders; and dysmenorrhea). In response to the first request for supplementary information, the MAH provided a discussion of the adverse events (AEs) reported in >10% of patients in the Avonex arm in the CONNECT and PARADIGM studies, as well as a comparison with the frequency of this AE in the information already included in the SmPC of Avonex. Although most of the AE from these studies have the same frequency category as described in the SmPC for adults, there were some AEs such as myalgia, pain in extremity, fatigue and arthralgia the have a higher frequency in paediatric population. Finally and according to the EMA Guideline on SmPC, this information has been included in the paediatric sub-section of section 4.8 and section 4 of the PL, subsection children (10 years and above) and adolescents.

Avonex is not approved for the treatment of paediatric patients with MS. There have been no formal clinical studies to assess the efficacy of interferon beta-1a in this population and the majority of data come from open-label observational or retrospective studies. Despite limited published data, Avonex (and other IFN β agents and glatiramer acetate) is used in paediatric patients with MS according to the dosage and administration instructions recommended for adults in the SmPC.

Three medicinal products have been recently approved for the treatment of RRMS in this population:

- Gilenya (fingolimod) is indicated as single disease modifying therapy in highly active relapsing remitting multiple sclerosis for the following groups of adult patients and paediatric patients aged 10 years and older:
    - patients with highly active disease despite a full and adequate course of treatment with at least one disease modifying therapy (for exceptions and information about washout periods see Sections 4.4 and 5.1)

    or

    - patients with rapidly evolving severe relapsing remitting multiple sclerosis defined by 2 or more disabling relapses in one year, and with 1 or more Gadolinium enhancing lesions on brain MRI or a significant increase in T2 lesion load as compared with a previous recent MRI.
- Aubagio (teriflunomide) is indicated for the treatment of adult patients and paediatric patients aged 10 years and older with relapsing remitting multiple sclerosis
- Tecfidera (dimethyl fumarate, DMF) is indicated for the treatment of adult and paediatric patients aged 13 years and older with relapsing remitting multiple sclerosis.

Of note, the main clinical trials conducted with fingolimod (study PARADIGMS) and DMF (study CONNECT) included Interferon beta-1a IM (Avonex 30 µg once weekly) as active comparator. Teriflunomide was compared to placebo in the study TERIKIDS. These clinical developments were agreed with the PDCO. In the case of DMF, the inclusion of IFN β-1a as control arm was done at request of the PDCO based on its consideration as standard of care.

The currently marketed formulation of Avonex® (30 micrograms/0.5ml solution for injection in pre-filled pen) was used in these paediatric studies, with an acceptable safety profile. As no indication in children is foreseen, there is no need for a paediatric specific formulation.

The results of these studies provide new evidence in the field and may have consequences in the therapeutic recommendations and/or clinical trial designs. However, treatments such as interferon- β (including Avonex) and glatiramer acetate are still recommended as first-line therapies in the consensus/guidelines of reference in the field[1,2,3,4,5] and they may remain as suitable for some patients. This accepted use of Avonex appears not to be in line with the information currently reflected in the SmPC (Section 4.2), where it is stated that the safety and efficacy of Avonex in adolescents aged 12 to 16 years have not yet been established and no recommendation on a posology can be made. At request during the procedure the MAH provided a discussion on the most recent Avonex® efficacy data available from the CONNECT and PARADIGMS clinical trials. These data, although limited to do a firm recommendation on posology, are considered useful for prescribers. A proposal for the update of section 5.1 of the SmPc was requested to reflect a summary of these efficacy data and it was provided.

In light of the above, the MAH is also requested to provide a proposal for the wording in sections 4.8 and 5.1 reflecting the available information in patients 10 to 18 years of age. The MAH submitted an updated PI. Changes has been made to sections 4.1, 4.2, 4.8 and 5.1 of the SmPC and sections 2 and 4 of the PL. Comments by two member states were received in relation to the wording for sections 4.8 and 5.1. The SmPC has been adapted accordingly. After this revision, it is considered that the updated PI reflects well the available, most useful, safety and efficacy data from clinical trials. The changes are now endorsed and the variation is recommended for approval.

The benefit-risk balance of Avonex, remains unchanged in the currently authorised conditions of use.

3. Recommendations

Based on the review of the submitted data, this application regarding the following change:

Variation requested		**Type**	**Annexes affected**
C.I.4	Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I and IIIB

Update of sections 4,1 4.2, 4.8 and 5.1 of the SmPC in order to update safety information for the paediatric population based on the final results of the Tecfidera Paediatric study (109MS306) (CONNECT - part 1), submitted as part of the PAM procedure P46/089, availability of data from published literature and postmarketing data form Biogen global safety database; the Package Leaflet is updated accordingly.

☒ is recommended for approval.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es) I and IIIB are recommended.

[1] Chitnis T, Tenembaum S, Banwell B, et al. Consensus statement: evaluation of new and existing therapeutics for pediatric multiple sclerosis. Mult Scler 2012;18: 116–127.
[2] Waubant E et al. Neurology 2019;92:e1-e12. doi
[3] Ghezzi A, Amato MP, Makhani N, Shreiner T, Gärtner J, Tenenbaum TS. Pediatric multiple sclerosis: conventional firstline treatment and general management. Neurology 2016; 87: Suppl 2: S97-S102.
[4] Yamout B et al. Consensus recommendations for the diagnosis and treatment of multiple sclerosis: 2019 revisions to the MENACTRIMS guidelines. Multiple Sclerosis and Related Disorders 37 (2020) 101459
[5] Chitnis, T., et al., 2016. Pediatric multiple sclerosis: escalation and emerging treatments.Neurology 87 (9 Suppl 2), S103–S109.

4. EPAR changes

The table in Module 8b of the EPAR will be updated as follows:

Scope

Please refer to the Recommendations section above

Summary

Please refer to Scientific Discussion 'Product Name-H-C-Product Number-II-0193'

For more information, please refer to the Summary of Product Characteristics.

Annex: Rapporteur's assessment comments on the type II variation

5. Introduction

Background information as submitted by the Applicant

Multiple Sclerosis in Paediatric Patients

ms is the most common disabling neurological disease of young adults [Browne 2014], with onset between 20 and 40 years of age in approximately 70% of patients [Flachenecker and Stuke 2008; Weinshenker 1989]. The disease is more common in women than men [Harbo 2013], and its prevalence is highest among Caucasians, with higher rates reported in North America, Europe, Australia, New Zealand, and northern Asia [Noseworthy 2000; Rosati 2001]. MS is a major cause of the overall neurological disease burden [Group GNDC 2017], with approximately 2.2 million individuals affected worldwide, corresponding to a prevalence of 30.1 per 100,000 [GBD 2016 Multiple Sclerosis Collaborators 2019].

Approximately 2.2% to 4.4% of all MS cases are in paediatric-onset patients [Chitnis 2011]. The majority (98%) present with a relapsing-remitting course and usually have a higher annual relapse rate than the patients with adult-onset MS [Alroughani and Boyko 2018; Pena and Lotze 2013] but tend to recover better than adults do [Chitnis 2013]. Overall, MS disease progression, including physical disability, is slower in children, and progression to secondary progressive MS occurs 10 years later than it does in adult-onset MS [Alroughani and Boyko 2018; Renoux 2007; Wright 2017]. However, while there is less likelihood of secondary progression of MS in childhood, by age 35 years half of the paediatric-onset MS population shows secondary progression. Treatment in children should be started early in the disease course to reduce the relapse rate and disease progression and to improve the long-term outlook. Similar to adult-onset MS, the treatment goal is to prevent acute relapses and the formation of new brain lesions and to slow disease progression. Although there are currently several medications with various mechanisms of action and routes of administration approved for adult-onset MS, fingolimod has been approved for paediatric-onset MS and, as of Jun 2021, the European Commission approved the use of teriflunomide (Aubagio®) for the treatment of paediatric patients aged 10 through 17 years with RRMS. On 22 April 2022, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion on the extension of the indication of Tecfidera (dimethyl fumarare) to the treatment of paediatric patients aged 13 years and older with relapsing remitting multiple sclerosis (RRMS). rior to these medications, studies have been conducted using interferon preparations (2 IFN β-1a and 1 IFN β-1b) and GA in the paediatric population with MS.

Biogen Idec initially developed a recombinant human form of IFN β-1a (Avonex) over 25 years ago, for the treatment of MS in adults. IFNs are a family of proteins and glycoproteins that are produced by eukaryotic cells in response to viral infection and other biological inducers and that mediate antiviral, antiproliferative, and immunomodulatory activities. Human IFN-β, a type I IFN, is produced by various cell types, including fibroblasts and macrophages, and exerts its biological effects by binding to specific receptors on the surface of human cells. The binding of this cytokine to specific receptors initiates a complex cascade of intracellular events that lead to the expression of numerous IFN-induced gene products and markers affecting the immune system. The mechanism of action by which Avonex exerts its effects in patients with MS is unknown, although Avonex has been shown to slow the accumulation of physical disability and to decrease the frequency of clinical exacerbations of MS in randomized and placebo-controlled clinical study.

Avonex was approved in the US on 17 May 1996 and in the EU on 13 Mar 1997. As of Feb 2021, Avonex

is approved in 89 countries worldwide, including the US and Europe. Avonex is indicated for the treatment of patients with RRMS to slow the accumulation of physical disability and decrease the frequency of clinical exacerbations, for treatment of patients who have experienced a single demyelinating event, and for treatment of patients who are at risk of developing clinically definite MS. In Canada and Australia, Avonex is also approved for the treatment of patients with secondary progressive MS, where relapse is still a feature of the disease. In the US, Avonex is approved in adults for the treatment of relapsing forms of MS, including clinically isolated syndrome, RRMS, and active secondary progressive MS. No market or registration withdrawals are associated with this product.

The MAH has requested a type II variation to update sections 4.2 and 4.8 of the SmPC to add new information regarding safety in paediatric population.

6. Clinical aspects

6.1. Information on the pharmaceutical formulation used in the study 109MS306 Part 1

Avonex was supplied in the Study 109MS306 Part 1 as an autoinjector pen (Avonex Pen®) in countries in which the Avonex Pen was approved. In countries in which the Avonex Pen was not approved, it was supplied as a liquid prefilled (Luer lock) syringe (Avonex Prefilled Syringe). These syringes were intended for single use injection only. In addition, the titration kit (Avostartgrip™ or Avostartclip™) was provided for the first 4 weeks of the Study Treatment Period.

The Avonex Pen and Avonex Prefilled Syringe are formulated as a sterile clear liquid for IM injection. Each 0.5 mL of Avonex in a prefilled glass syringe contains 30 µg of IFN β-1a. Other ingredients include sodium acetate trihydrate, glacial acetic acid, arginine hydrochloride, and polysorbate 20 in water for injection at a pH of approximately 4.8. Using the World Health Organization's natural IFN β standards, 30 µg of IFN β-1a contains approximately 6 million IU of antiviral activity.

The MAH confirms in the responses provided at Day 60 that there is a high experience with the use of the currently marketed formulation of Avonex® (30 micrograms/0.5ml solution for injection in pre-filled pen) in paediatric patients, with an acceptable safety profile. As no indication in children is foreseen, there is no need for a paediatric specific formulation. None of the excipients is known to have safety concerns used as intended in paediatric patients.

6.2. Clinical Pharmacology

No information on clinical pharmacology of Avonex has been provided by the MAH.

6.3. Clinical Efficacy aspects

There is no specific discussion on the efficacy of Avonex in this population. The MAH states in the Clinical Overview addendum that the benefit of Avonex in the pediatric population remains undefinedand therefore, Avonex should not be used in children without careful evaluation of the benefit-risk ratio.

Avonex is not approved for the treatment of pediatric patients with MS. There have been no formal clinical studies to assess the efficacy of interferon beta-1a in this population and the majority of data come from open-label observational or retrospective studies. Despite limited published data, Avonex (and other IFN β agents and glatiramer acetate) is allowed to be used in paediatric patients with MS

according to the dosage and administration instructions recommended for adults in the summary of product characteristics (SmPC).

Three medicinal products have been recently approved for the treatment of RRMS in this population:

- Gilenya (fingolimod) is indicated as single disease modifying therapy in highly active relapsing remitting multiple sclerosis for the following groups of adult patients and paediatric patients aged 10 years and older:
    - patients with highly active disease despite a full and adequate course of treatment with at least one disease modifying therapy (for exceptions and information about washout periods see Sections 4.4 and 5.1)

    or

    - patients with rapidly evolving severe relapsing remitting multiple sclerosis defined by 2 or more disabling relapses in one year, and with 1 or more Gadolinium enhancing lesions on brain MRI or a significant increase in T2 lesion load as compared with a previous recent MRI.
- Aubagio (teriflunomide) is indicated for the treatment of adult patients and paediatric patients aged 10 years and older with relapsing remitting multiple sclerosis
- Tecfidera (dimethyl fumarate, DMF) is indicated for the treatment of adult and paediatric patients aged 13 years and older with relapsing remitting multiple sclerosis.

Of note, the main clinical trials conducted with fingolimod (study PARADIGMS) and DMF (study CONNECT) included Interferon beta-1a IM (Avonex 30 µg once weekly) as active comparator. Teriflunomide was compared to placebo in the study TERIKIDS. These clinical developments were agreed with the PDCO. In the case of DMF, the inclusion of IFN β-1a as control arm was done at request of the PDCO based on its consideration as standard of care.

The results of these studies provide new evidence in the field and may have consequences in the therapeutic recommendations and/or clinical trial designs. However, currently treatments such as interferon- β (including Avonex) and glatiramer acetate, are still recommended as first-line therapies in the consensus/guidelines of reference in the field [1,2,3,4,5] and their use may remain suitable for some patients.
During the procedure, the MAH provided a discussion on the most recent Avonex® efficacy data available from the CONNECT and PARADIGMS clinical trials. These data, although limited to do a firm recommendation on posology, are considered useful for prescribers. A proposal for the update of section 5.1 of the SmPc is requested to reflect a summary of these efficacy data.

6.4. Clinical Safety aspects

6.4.1. Methods – analysis of data submitted & results

For the purpose of this type II variation, the MAH has considered 2 interventional randomized, controlled studies that use IM Avonex as an active comparator arm (Study 109MS306 [CONNECT] and published literature study PARADIGMS), as well as 4 published literature observational studies in MS paediatric participants using Avonex, and postmarketing data from the Biogen Global Safety Database (GSD).

Avonex has not been evaluated as the investigational medicinal product compared with placebo in any randomized, controlled studies for paediatric-onset MS. A targeted literature search for these published

observational studies was conducted in Embase with data lock point of 12 February 2021 to identify articles reporting safety findings for Avonex in the paediatric population employing the following search strategy: (child:ab,ti OR pediatric:ab,ti OR paediatric:ti,ab OR adolescent:ab,ti) AND ('beta interferon':ab,ti OR 'interferon beta':ab,ti OR 'beta1a interferon':ab,ti OR 'avonex':ab,ti). Search results were screened based on title or abstract, and relevant articles were selected based on full texts. Case reports for Avonex identified from the literature are included in the GSD and are therefore included or considered within the information submitted by the company.

The overall safety evaluation plan for these paediatric participants with an age range of 10 to 17 years is summarized as follows:

Study 109MS306 (Part 1)

STUDY POPULATION

The Part 1 study period is an open-label, randomized, multicenter, multiple-dose, active-controlled, parallel-group, efficacy, and safety study of Tecfidera versus Avonex as the active comparator arm. The treatment period for Part 1 lasted for 96 weeks. Part 2 is the optional extension phase, in which all participants will receive Tecfidera for assessment of the long-term safety outcomes of Tecfidera treatment. The extension phase has not yet been completed.

The safety analyses from Part 1 were performed using the intent to treat (ITT) Population (all participants who were randomly assigned to a treatment group and received at least 1 dose of study treatment). A total of 150 participants from 10 to 17 years old were included in the ITT Population (Avonex 30 µg IM weekly: 72 participants; Tecfidera 240 mg orally twice daily: 78 participants), and more than two-thirds of the participants were female (101 participants [67%]). Racial group was not collected for 53 participants (35%) because of confidentiality regulations and was missing or unknown for an additional 67 participants (45%). The mean (SD) weight was 63.88 (14.576) kg, the mean (SD) height was 164.5 (8.68) cm, and the mean (SD) body mass index was 23.5 (4.42) kg/m2 . The mean (SD) age was 14.9 (1.62) years. Overall, the mean (SD) time since the participants first MS symptoms was 1.5 (1.63) years, and the mean (SD) time since the participant's MS diagnosis was 0.8 (1.22) years.

ADVERSE EVENTS

Overall, 143 of 150 participants (95%) experienced at least 1 TEAE during the study (Avonex: 69 participants [96%]; Tecfidera: 74 participants [95%]). The majority of participants experiencing TEAEs had events assessed as mild or moderate in severity. In the Avonex group, the most frequently reported TEAEs (≥ 10% of participants) were influenza like illness (n = 37 [51%]), MS relapse (n = 33 [46%]), headache (n = 26 [36%]), pyrexia (n = 17 [24%]), nasopharyngitis (n = 9 [13%]), myalgia (n = 9 [13%]), pain in extremity (n = 8 [11%]), fatigue (n = 7 [10%]), and arthralgia (n = 7 [10%]).

There were 10 participants (14%) in the Avonex group who experienced 12 severe TEAEs including MS relapse (n = 3), headache (n = 2), influenza like illness (n = 2) hepatocellular injury (n = 1), infusion related reaction (n = 1), paraesthesia (n = 1), relapsing MS (n = 1), and unevaluable event (n = 1).

A total of 126 participants (84%) had a TEAE considered related to study treatment by the Investigators. The percentage of participants with a study treatment-related TEAE was similar across both treatment groups (Avonex: n = 59 [82%]; Tecfidera: n = 67 [86%]). The most frequently reported TEAEs (≥ 10% of participants) in the Avonex group that the Investigator considered related to study treatment were influenza like illness (n = 36 [50%]), headache (n = 18 [25%]), and pyrexia (n = 12 [17%]).

Deaths

No participants died during this study

Other Serious Adverse Events

A total of 39 participants (26%) had a treatment-emergent SAE during the study (Avonex: n = 21 [29%]; Tecfidera: n = 18 [23%]). There were 25 treatment-emergent SAEs in the Avonex group including MS relapse (n = 18 [25%]), anemia (n = 1 [1%]), groin pain (n = 1 [1%]), hepatocellular injury (n = 1 [1%]), hypertension (n = 1 [1%]), influenza like illness (n = 1 [1%]), paraesthesia (n = 1 [1%]), and relapsing MS (n = 1[1%]), The SAE influenza like illness was considered related to study treatment by the Investigator.

Other Significant Adverse Events

A total of 13 participants (9%) had a TEAE leading to discontinuation of study treatment (Avonex: n = 8 [11%]; Tecfidera: n = 5 [6%]). There were 10 TEAEs in the Avonex group that led to study treatment discontinuation including MS relapse (n = 3 [4%]), headache (n = 1 [1%]), tremor (n = 1 [1%]), asthenia (n = 1 [1%]), influenza like illness (n = 1 [1%]), vomiting (n = 1 [1%]), hepatocellular injury (n = 1 [1%]), and altered mood (n = 1 [1%]).

CLINICAL LABORATORY EVALUATIONS

Hematology Results

There were no trends in mean change from baseline values in erythrocyte counts, hemoglobin, hematocrit, or platelet counts in either treatment group. There were no trends in mean change from baseline values in partial thromboplastin time, prothrombin time, or international normalized ratio in either treatment group at Week 24, 48, or 96. Overall, mean leukocyte counts were variable in both treatment groups, and mean leukocyte counts remained normal in both groups throughout the study. No participants experienced a TEAE of leukopenia. A total of 4 participants (Avonex n=1, Tecfidera n=3) experienced postbaseline lymphocyte counts < 0.5x109 /L during the study. The participant in the Avonex group had 6 lymphocyte values less than the lower limit of normal between weeks 24 and 72. Between the Week 48 and 72 visits the participant had 3 lymphocyte counts 3× ULN, and 2 participants had postbaseline alkaline phosphatase values > 1.5× ULN. There were no participants who had postbaseline ALT or AST values > 3× ULN and bilirubin > 2× ULN (criteria for Hy's Law). No participants were discontinued from the study due to abnormal laboratory values.

Blood Chemistry Results

There were no trends in changes from baseline for any chemistry parameters in the Avonex group with the exception of alkaline phosphatase, where there was a decrease from baseline in mean alkaline phosphatase levels, but the mean values did not go below the normal levels. The incidence of participants in the Avonex group with ALT values greater than ULN are as follows:

· Baseline: Avonex: 4 of 72 participants (6%)
· Week 48: Avonex: 3 of 58 participants (5%)
· Week 96: Avonex: 2 of 39 participants (5%)

The incidence of participants in the Avonex group with AST values greater than ULN are as follows:

· Baseline: Avonex: 5 of 72 participants (7%)
· Week 48: Avonex: 2 of 57 participants (4%)
· Week 96: Avonex: 1 of 39 participants (3%)

A total of 3 participants in the Avonex group experienced postbaseline ALT or AST values > 3× ULN, and 2 participants had postbaseline alkaline phosphatase values > 1.5× ULN. There were no participants

who had postbaseline ALT or AST values > 3× ULN and bilirubin > 2× ULN (criteria for Hy's Law). No participants were discontinued from the study due to abnormal laboratory values.

VITAL SIGNS, PHYSICAL FINDINGS, AND OTHER OBSERVATIONS RELATED TO SAFETY

Vital Signs

The most common clinically relevant vital sign abnormalities (reported in > 10% of evaluated participants overall) were high pulse rate classified as > 120 bpm or an increase from baseline of > 20 bpm (n = 41 [27.0%]), low pulse rate classified as < 50 bpm or a decrease from baseline of > 20 bpm (n = 26 [17.0%]), and low DBP classified as < 50 mmHg or a decrease from baseline of > 20 mmHg (n = 16 [11.0%]). With the exception of high pulse rate (Avonex: n = 17/72 [24%]; Tecfidera: n = 24/78 [31%]), the percentages of participants experiencing each type of clinically relevant abnormality were generally similar across both treatment groups.

ECGs

Most participants in the Avonex group had normal ECG results throughout the study (ranging from 92% to 100% of participants evaluated across study visits, including follow-up). No participants had an abnormal ECG result that was considered to be an AE. No participants experienced a shift from normal to abnormal ECG that was considered to be an AE. A total of 4 of 68 participants (6%) in the Avonex group experienced a shift from normal ECG to abnormal ECG that was not AE.

During the procedure, the MAH provides information about the two AEs that were underpinned by the assessor in the Preliminary AR (anaemia and hepatocellular injury). Although the case of anaemia is temporally related to Avonex, the information is not solid enough to draw further conclusions concerning the need to include the event of anaemia under Avonex´s SmPC. In addition, although it cannot be discarded that the case concerning an autoimmune hepatitis could be a reactivation related to Avonex, it is already enclosed within Avonex´s SmPC and thus, no further actions would be considered necessary.

PARADIGMS Study

STUDY POPULATION

The sponsor of Study PARADIGMS was Novartis Pharma. The relevant study information and data available to Biogen were from the published literature article [Chitnis 2018b].

PARADIGMS was a 2-year, double-blind, randomized, multicenter, active-controlled, parallel group study to evaluate the safety and efficacy of fingolimod administered once daily versus Avonex (active comparator) once weekly. The study period lasted up to 24 months.

A total of 215 participants were included in the study: 107 participants were randomly assigned to oral fingolimod 0.5 mg (0.25 mg; participants ≤ 40 kg), and 108 participants were randomly assigned to Avonex 30 µg IM weekly. The mean age was 15.3 years, 62.3% of the study population was female, and the majority (91.6%) were White [Chitnis 2018b]. The mean weight was 62.6 kg, and there was a mean of 2.4 relapses during the 2 years prior to Screening.

ADVERSE EVENTS

Overall, 197 of 214 participants in the Safety Set (Avonex: n = 102 [95.3%]; fingolimod: n = 95 [88.8%]) experienced any AE. In the Avonex group, the most frequently reported AEs (≥ 10.0%) are as follows: influenza like illness (n = 40 [37.4%]), headache (n = 32 [29.9%]), viral upper respiratory tract infection (n = 26 [24.3%]), pyrexia (n = 22 [20.6%]), cough (n = 12 [11.2%]), and chills (n = 11 [10.3%]).

Deaths: There were no deaths during the study period.

Other Serious Adverse Events: A total of 7 participants (6.5%) in the Avonex group had at least 1 SAE. There were 3 participants (2.8%) in the Avonex group with an SAE of MS relapse, and 1 (0.9%) of each of the following SAEs: dizziness, fatigue, gastroesophageal reflux disease, headache, increased body temperature, optic neuritis, paronychia, pyrexia, sensory loss, supraventricular tachycardia, uveitis, and viral gastritis.

Other Significant Adverse Events: Study treatment was discontinued if the investigator determined that continuing it would result in a significant risk for that participant. The following conditions automatically resulted in permanent study treatment discontinuation per the study protocol: elevated liver aminotransferase levels, macular edema, cardiac arrythmias, ECG abnormalities, and pregnancy [Chitnis 2018b]. There were other conditions that supported the decision to discontinue study treatment. A total of 3 participants (2.8%) experienced AEs that led to permanent discontinuation of study treatment in the Avonex group [Chitnis 2018a].

CLINICAL LABORATORY EVALUATIONS

Hematology Results

In the Avonex group, no relevant changes were observed in the mean absolute lymphocyte count during the study. Overall, 24.3% of participants had an absolute lymphocyte count below the normal range at least once in the study. The majority of participants (n = 27 [93.1%]) had a normal absolute lymphocyte count within 45 days after discontinuation of treatment [Chitnis 2021]. Three participants (2.8%) experienced leukopenia, and there were no reports of a decrease in white blood cell count.

Blood Chemistry Results

In the Avonex group, 5 participants (4.7%) experienced an increase in ALT levels, and 5 participants (4.7%) experienced increase in AST levels. There were no participants who had an increase in γ-glutamyltransferase.

VITAL SIGNS, PHYSICAL FINDINGS, AND OTHER OBSERVATIONS RELATED TO SAFETY

Vital Signs Vital signs were evaluated by the Investigators or a specialist physician in the relevant medical field. Data regarding vital signs were not reported in the published literature article.

ECGs

There was 1 participant (0.9%) who experienced supraventricular tachycardia in the IFNβ-1a group. There were no other ECG findings reported in the published literature article.

Since a discrepancy was observed regarding the EPAR of fingolimod the MAH clarifies in the RSI that no cases of "tachycardia" was reported in the Avonex IM group and no more information about the SAE of supraventricular tachycardia was included.

Safety Data from Observational Studies in Published Literature

Interferon-β treatment in patients with childhood-onset multiple sclerosis: Reported on the use of IFN-β (Avonex, Rebif, Betaferon) in patients with childhoodonset MS [Mikaeloff 2001].

STUDY POPULATION

The case series of IFNβ treatment [Mikaeloff 2001] included a total of 16 participants (14 females and 2 males) with a median age of 15.5 years. Two females had an autoimmune disorder of either type 1 diabetes or thyroiditis before starting treatment. The 3 different treatments were as follows: Avonex 30 µg IM given every week (n = 13 participants), Rebif 22 µg SC given 3 times per week (n = 2 participants), and Betaferon 8 × 106 IU SC given every 2 days (n = 1 participant). From the 16 patients, 7 patients were 16 y.o. or over, therefore only 9 were below 16.

ADVERSE EVENTS

The common AEs for each observational study are listed in Table 1.

Table 1: Summary of observational studies in the literature

Study Information	**[Basiri K 2012]** **Interferon-beta in Pediatric Multiple Sclerosis Patients: Safety in Short-Term Prescription**	**[Ghezzi 2009]** **Long-Term Results of Immunomodulatory Treatment in Children and Adolescents With Multiple Sclerosis: the Italian Experience**	**[Ghezzi 2007]** **Treatment of Early-Onset Multiple Sclerosis With Intramuscular Interferonβ-1a: Long-Term Results**	**[Mikaeloff 2001]** **Interferon-β Treatment in Patients With Childhood-Onset Multiple Sclerosis**
Study Design	Short-term safety study IFNβ (6 Avonex and 7 Betaferon)	Long-term safety study immunomodulatory treatment: Italy	Long-term safety study IFNβ-1a	Case series of IFNβ treatment (13 Avonex, 2 Rebif, and 1 Betaferon)
Adverse Events	Transient side effects: flu like syndrome, mild leucopenia	In 30/77 participants (39%) treated with Avonex Flu like syndrome (19 participants [24.7%]), headache (15 participants [19.5%]), myalgia (7 participants [9.1%]), persistent fatigue (5 participants [6.5%]), persistent skin injection reaction (5 participants [6.5%]), and persistent psychological disturbance (2 participants [2.6%])	In 35/52 participants (67%); most transient Flu like syndrome (33%), headache (29%), myalgia (21%), fever (11%), fatigue (6%), nausea and vomiting (6%), and skin reaction (4%)	For IFNβs: flu like syndrome (11 participants), isolated myalgia (3 participants), moderate injection site reactions (3 participants; 1 Betaferon and 2 Avonex)
Laboratory Abnormalities	Not reported in publication	Increased liver enzyme (4 participants [5.2%]; transient in 3), abnormal thyroid function (8 participants [10.4%]; transient in 4), and 1 case of persistent lymphopenia	In 11/52 participants (21%) Leukopenia (6 participants [55%]; transient in 4), transient reduction in free T3/free T4 (3 participants [27%]), transient increase in ALT/AST (2 participants [18%]), and transient increase in ANA titer (2 participants [18%])	1 participant with moderate but transient increase in transaminase levels and 1 participant with type 1 diabetes developed transient hypoglycemia

According to the data provided, 6 patients worsened. Within the Avonex group, 4 patients interrupted the treatment because of frequent relapse attacks. This study shows a 25% of treatment failure, explained by the authors because of severe forms of the disease with numerous polysymptomatic onset.

Flu-like syndrome was observed in 11 cases and isolated myalgia in 3 patients. Injection site reactions were moderate (3 patients had localized erythema). No hematologic or hepatic effects were observed, except in one patient who had a moderate but transient increase in transaminase levels at initiation of treatment with spontaneous normalization. One patient with type 1 diabetes developed hyperglycaemia after injection of IFN-beta (no details of which of the IFN products).

Treatment of early-onset multiple sclerosis with intramuscular interferon β-1a: long-term results: Evaluated the safety, tolerability, and effectiveness of Avonex in patients with onset of MS symptoms [Ghezzi 2007].

STUDY POPULATION

The population of the long-term safety study with Avonex 30 mg IM [Ghezzi 2007] was composed of 52 participants with symptom onset at a mean age of 11.7 ± 2.7 years. There were 33 female participants and 19 male participants.

ADVERSE EVENTS

In the [Ghezzi 2007] article, treatment was changed during the follow-up period in 19 participants (36.5%). After a mean ± SD interval of 33.7 ± 19.6 months, 11 participants had their treatment changed to 22 µg of Rebif (8 due to lack of efficacy and 3 due to AEs), 2 participants were switched to other treatments (1 shifted to mitoxantrone, followed by Copaxone and 1 shifted to intravenous immunoglobulin), and 6 participants experienced interruption in study treatment (2 for lack of compliance, 1 for persistent leukopenia, 1 for ineffectiveness, and 2 for other reasons). Of these medication shifts, 13 participants were females, and 6 participants were male. As mentioned before, the most common AEs for each observational study are listed in Table 1.

Long-term results of immunomodulatory treatment in children and adolescents with MS: the Italian experience: Evaluated the effects of immunomodulatory agents (Avonex, Rebif/Betaferon, Copaxone) in a large cohort of MS patients with disease onset in childhood or adolescence [Ghezzi 2009].

STUDY POPULATION

The study of long-term results of immunomodulatory treatment of children and adolescents in Italy [Ghezzi 2009] was composed of 130 participants (Avonex [dose not specified]: n = 77, Rebif 22 µg/Betaferon [dose not specified]: n = 39, and Copaxone [dose not specified]: n = 14). There were a total of 83 females, with the male-to-female ratio and average age of onset in each treatment group broken down as follows:

- Avonex: male/female, 30/47; mean age, 11.4 ± 3.1
- Rebif/Betaferon: male/female, 14/25; mean age, 12.6 ± 2.6
- Copaxone: male/female, 3/11; mean age, 13.1 ± 1.5

Both studies have been performed in the same Italian database. This is a multicentric study of 2003, that takes part with the participation of 18 different centres that was designed with the purpose of assessing the effectiveness, safety and tolerability of patients with an early diagnosis of MS (< 16 y.o.). As indicated on the 2009 publication, briefly, patients were included in the study if they were given a diagnosis of definite MS according to McDonald's criteria, followed a relapsing course according to Lublin's criteria, experienced onset of symptoms of MS before 16 years of age and began treatment with IMAs before 16 years of age. Patients with pretreatment or follow-up duration <6 months were excluded. In the publication of 2007, the objective was to evaluate the safety, tolerability and effectiveness of IM interferon beta-1a 30 mg once a week in patients with onset of symptoms of MS in childhood or adolescence. As for the study of 2009, the main objective is to evaluate the effect of immunomodulatory agents in a large cohort of MS patients with disease onset in childhood or adolescence, treated before 16 years of age, after a long-term follow-up.

ADVERSE EVENTS

The common AEs for each observational study are listed in Table 1.

In the study of 2007, a total of 67% of patients presented clinical AE, being again flu-like syndrome (33%), headache (29%) myalgia (21%), fever (11%), fatigue (6%) nausea and vomiting (6%) and skin reaction (4%), and most of them were transient. The study only focuses on long-term safety of the 52 patients that continued the study and no comparison has been provided in order to know if these frequencies are similar to those in adults (as mentioned in the CONNECT study, headache seems to be more common in children and this data mentions as well evidence with Avonex). Therefore, it is very difficult to conclude any details about the safety of Avonex in children.

In the study of 2009, it seems that more patients have been included, with a longer-term follow-up. As well, it provides an specific evaluation for children between 12 and 16 y.o. In this case, some differentiation has been provided between the different IFNs. In this case, 30 out of the 77 patients treated with Avonex experienced clinical side effects: flu-like syndrome (19 patients, 24,7%); headache (15 patients, 19.5%); myalgia (7 patients, 9.1%); persistent fatigue (5 patients, 6.5%); skin injection reaction (5 patients, 6.5%); persistent psychological disturbances (2 patients, 2.6%). These events are all included within the adults ADRs for Avonex.

In light of the above, the safety information that derived from these two non-interventional studies is limited to a very limited number of patients and only belong to one region (Italy). Therefore, this safety information cannot be extrapolated to the rest of the population.

IFN-beta in paediatric multiple sclerosis patients: safety in short-term prescription: Evaluated the safety of paediatric patients < 16 years old with RRMS taking Betaseron and Avonex [Basiri K 2012].

STUDY POPULATION

In the observational short-term safety study [Basiri K 2012], a total of 13 participants younger than 16 years who were recently diagnosed with RRMS were enrolled in the study. Six participants were in the Avonex arm 30 µg IM once weekly, and 7 participants were treated with Betaferon 250 µg SC every other day. Eleven participants were female, and 2 participants were male. This study describes the effectiveness and tolerability of intramuscular interferon beta1-a, Avonex, and subcutaneously injected interferon beta 1-b in children with definite relapsing-remitting MS. It only includes short-term use (9 months) and therefore it does not consider relevant aspects of the use in children that involve long-term use.

A 46.2% of the patients present MS with only optic nerve involvement. Thus, this should be carefully considered taking into account that optic neuritis and vision blurred seem to be the SAEs that appear in higher proportion in paediatric population than in adults. Therefore, the solidness of this study in order to be considered for the safety of the paediatric population being consistent to the adults is questionable, despite its apparent improvement in relapses (of the 13 patients totally included, 9 had no relapse and 4 had one relapse only, during the 9 months of follow-up).

ADVERSE EVENTS

The common AEs for each observational study are listed in Table 1.The AEs that were observed in ≥ 2 studies were flu like syndrome, headache, myalgia, fatigue, and injection site reactions. Most of these events were transient. The abnormalities observed in ≥ 2 studies were abnormal thyroid function and elevated liver enzymes. Most of these events were transient. Vital signs and ECG data were not reported across the 4 studies. There were no deaths reported across these studies.

In summary, due to the methodological differences in the study designs of these paediatric interventional and observational studies, no formal statistical comparison of results across the studies was performed for this submission, however the paucity of a comparison between these retrieved and its extrapolation in the adult population, hampers the assessment of the data being consistent across the two different populations (adults and children). Furthermore, no information concerning the effect on growth and puberty or the long-term adverse effects on the immature system have been answered across these studies. Therefore, the data from non-interventional studies are not enough to support the requested change to indicate that the safety profile in children from 10 to 18 y.o. is consistent to what seen in adults.

Postmarketing Data

The estimated postmarketing exposure in adults is based on Avonex market data available through 30 March 2021. Cumulative global patient exposure to Avonex is approximately 600,985 patients, representing approximately 2,752,261 patient-years. There is limited postmarketing experience with administration of Avonex 30 µg IM in the paediatric population. Therefore, as of 03 May 2021, there were no data available allowing further calculation of Avonex exposure in paediatric patients (Section 8, Periodic Safety Update Report 04 May 2018 to 03 May 2021). The list of adverse reactions reported in paediatric participants (aged 2 to < 18 years) from postmarketing and clinical studies in Biogen GSD was attached in the relevant section of the information provided by the MAH, but not attached to this report.

As of 03 May 2021, cumulatively, a total of 3117 cases in paediatric participants were reported in the GSD, including 6663 nonserious AEs and 669 SAEs.

The most frequently reported AEs in paediatric participants (i.e.,> 100) obtained from a search of the GSD were off label use (n = 726), product administered to patient of inappropriate age (n = 665), influenza like illness (n = 485), MS relapse (n = 439), headache (n = 322), pyrexia (n = 274), chills (n = 190), fatigue (n = 176), MS (n = 148), injection site pain (n = 145), pain (n = 137), and pain in extremity (n = 116). The most frequently reported SAEs (i.e.,> 4) in paediatric participants from the same GSD search were MS relapse (n = 216), MS (n = 27), seizure (n = 14), pyrexia (n = 11), optic neuritis (n = 11), depression (n = 9), hypoaesthesia (n = 9), paraesthesia (n = 6), encephalomyelitis (n = 5), generalized tonic-clonic seizure (n = 5), pain (n = 5), and vision blurred (n = 5). MS relapse seems to be one of the most common effects on the paediatric population. Apparently, this can be explained by the annualized relapse rate of paediatric-onset being higher than that of the adult-onset MS (mentioned in the second observational study, for instance).The proportion of reports of SAEs of optic neuritis and vision blurred was higher for paediatric participants than for adult participants. This can be attributed to the higher prevalence of optic neuritis in the paediatric MS population, based on epidemiological study results reported in the published literature [Hennes 2017; Nikolić 2020; Yılmaz 2017]. However, it is difficult to assess these data without an estimation of the exposure since it is not clear if this statement is based on the absolute numbers or not.

After reviewing all data, the MAH was requested to provide a more detailed comparison and discussion of the safety of Avonex in adults versus paediatric population.

6.5. Discussion

Avonex is not approved for the treatment of paediatric patients with MS. There have been no formal clinical studies to assess the efficacy of interferon beta-1a in this population and the majority of data come from open-label observational or retrospective studies. Despite limited published data, Avonex (and other IFN β agents and glatiramer acetate) is allowed to be used in paediatric patients with MS according to the dosage and administration instructions recommended for adults in the SmPC.

The MAH has requested a type II variation to update sections 4.2 and 4.8 of the SmPC to amend existing safety information of Avonex in paediatric population, following completion of Tecfidera Paediatric Study 109MS306 (CONNECT- part 1), that uses Avonex as an active comparator arm, available of data from published literature and post-marketing data from Biogen global safety database.

The assessor considers that the aim of the provided data is contradictory with the benefit-risk conclusions that the MAH has provided, not recommending the use of Avonex in children, specially mentioned that the use in this population remains undefined.

The results of the studies conducted with the medicinal products recently approved for pediatric MS patients (i.e. fingolimod, teriflunomide, dimethyl fumarate) provide new evidence in the field and may

have consequences in the therapeutic recommendations and/or clinical trial designs. In some of these studies Avonex was use as active comparator. In fact, treatments such as interferon- β (including Avonex) are still recommended as first-line therapies in the consensus/guidelines of reference in the field and they are expected to remain suitable for some patients. This accepted use of Avonex appears not to be in line with the information currently reflected in the SmPC (Section 4.2), where it is stated that the safety and efficacy of Avonex in adolescents aged 12 to 16 years have not yet been established and no recommendation on a posology can be made. The wording now proposed in Section 4.2 with this variation ("There are limited data available in children and adolescents aged 10 to less than 18 years old ") does not represent a relevant change in this respect. It seems therefore appropriate that the MAH provides a proper discussion on the available efficacy data as well as a proposal to update the SmPC with the information to be useful for prescribers.

At request the MAH provided a discussion on the most recent Avonex® efficacy data available from the CONNECT and PARADIGMS clinical trials. These data, although limited to do a firm recommendation on posology, are considered useful for prescribers. A proposal for the update of section 5.1 of the SmPc is requested to reflect a summary of these efficacy data.

In addition, regarding safety the MAH provided limited data and information from non-interventional studies and postmarketing experience did not support the MAH's proposal for the inclusion in 4.8 that the safety profile in children and adolescents aged 10 less than 18 years of age receiving Avonex is consistent with that seen in adults. After request and regarding clinical trials, the discussion between the AEs observed in the two paediatric trials in which Avonex was the active comparator arm (CONNECT and PARADIGM) showed that most of the AEs from these studies have the same frequency category as described in the SmPC for adults. However, there were some AEs such as myalgia, pain in extremity, fatigue and arthralgia that have a higher frequency in paediatric population. According to the EMA Guideline on SmPC (EMA/551202/2010 Rev 1; Frequently asked questions on SmPC paediatric information), the information about the AEs reported with a higher frequency than in adults should be included in the paediatric sub-section of section 4.8, whether or not the medicinal product has an approved indication in the paediatric population". Therefore, section 4.8 of the SmPC and section 4 of the PIL, subsection children (10 years and above) and adolescents is updated to include some AEs such as myalgia, pain in extremity, fatigue and arthralgia that have a higher frequency in paediatric population (very common) than in the adult population (common).

In light of the above, the MAH was also requested to provide a proposal for the wording in sections 4.8 and 5.1 reflecting the available information in MS patients 10 to 18 years of age.

7. PRAC advice

N/A

8. Changes to the Product Information

As a result of this variation, sections 4.1, 4.2, 4.8, 5.1of the SmPC are being updated. The Package Leaflet (PL) is updated accordingly.

Section 4.1

Therapeutic indications

AVONEX is indicated **in adults** for the treatment of

- Patients diagnosed with relapsing multiple sclerosis (MS). In clinical trials, this was characterised by two or more acute exacerbations (relapses) in the previous three-years without evidence of

continuous progression between relapses; AVONEX slows the progression of disability and decreases the frequency of relapses.

- Patients with a single demyelinating event with an active inflammatory process, if it is severe enough to warrant treatment with intravenous corticosteroids, if alternative diagnoses have been excluded, and if they are determined to be at high risk of developing clinically definite multiple sclerosis (see section 5.1).

AVONEX should be discontinued in patients who develop progressive MS.

Section 4.2 Posology and method of administration

Paediatric population:
The safety and efficacy of AVONEX in **children and** adolescents aged **10 to 18** years have not yet been **fully** 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 **10** years of age have not yet been established. No data are available.

Section 4.8
Undesirable Effects

Paediatric population

Limited data from **literature, clinical trials and postmarketing experience** suggest that the safety profile in **children and** adolescents from **10 to less than18** years of age receiving AVONEX 30 micrograms IM once per week is **consistent with** that seen in adults.

The safety information obtained from the use of AVONEX as an active comparator in a 96 week open label, randomised trial in paediatric patients with relapsing remitting multiple sclerosis aged 10 to less than 18 years (with only 10% of the overall study population < 13 years) shows that in the AVONEX group (n=72), the following adverse events which are common in adult population were reported as very common in paediatric population: myalgia, pain in extremity, fatigue, and arthralgia.

Section 5.1
Pharmacodynamic properties

Paediatric population

Limited data of the efficacy/safety of AVONEX 15 micrograms 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.

AVONEX 30 micrograms/0.5 ml solution for injection was studied as an active comparator in 2 controlled clinical trials in paediatric patients aged 10 to less than 18 years with relapsing remitting multiple sclerosis (see section 4.2).

In an open-label randomised active controlled trial, 150 participants were randomly assigned in a 1:1 ratio to treatment with dimethyl fumarate, administered orally at a dose of 240 mg twice a day, or AVONEX, administered at a dose of 30 µg once weekly by intramuscular (IM) injection, for 96 weeks.
In the ITT population, treatment with dimethyl fumarate resulted in a higher proportion of patients with no new or newly enlarging T2 hyperintense lesions at Week 96 relative to baseline as compared with AVONEX [12.8% versus 2.8% respectively].

In a double-blind, double-dummy, active-controlled study, 215 participants were randomly assigned to receive either oral fingolimod (0.5 mg once daily or 0.25 mg once daily for patients weighing ⩽40 kg) or AVONEX 30 µg IM once weekly for up to 24 months.

The primary endpoint, the adjusted annualized relapse rate (ARR) at week 96, was significantly lower in patients treated with fingolimod (0.122) compared to patients who received AVONEX (0.675), translating into an 81.9% relative reduction in ARR (p <0.001).

Overall, the safety profile in patients receiving AVONEX in the two clinical trials was qualitatively consistent with that previously observed in adult patients.

9. Attachments

1. Product Information (changes highlighted) as adopted by the CHMP on 15 December 2022.