EMA/CHMP/285188/2019
Committee for Medicinal Products for Human Use (CHMP)

# Assessment report

## TECFIDERA

International non-proprietary name: dimethyl fumarate

Procedure No. EMEA/H/C/002601/II/0059

## Note

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

**Official address** Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
**Address for visits and deliveries** Refer to www.ema.europa.eu/how-to-find-us
**Send us a question** Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

# Table of contents

**1. Background information on the procedure ..... 3**

**2. Overall conclusion and impact on the benefit/risk balance ..... 3**

**3. Recommendations ..... 5**

**4. Introduction ..... 7**

**5. Clinical Efficacy aspects ..... 7**

5.1. Methods – analysis of data submitted ..... 7

5.2. Results ..... 8

**6. Clinical Safety aspects ..... 8**

6.1. Methods – analysis of data submitted ..... 8

6.2. Results ..... 9

**7. Changes to the Product Information ..... 10**

# 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 10 May 2019 an application for a variation.

The following changes were proposed:

| Variation requested | | Type | Annexes affected |
|---|---|---|---|
| C.I.4 | 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 4.8 and 5.1 of the SmPC in order to add the efficacy and safety information based on final results from study 109MS311, a multicentre extension study to determine the long-term safety and efficacy in paediatric subjects with RRMS (final study report already submitted under P46-020). The Package Leaflet is updated accordingly.

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

The requested variation proposed the following amendments to the Summary of Product Characteristics and Package Leaflet (marked ***bold italic***)

SmPC

Section 4.8

Paediatric population

The safety of Tecfidera in paediatric patients with multiple sclerosis below the age of 18 has not yet been established. In a small 24-week open-label uncontrolled study in paediatric patients with RRMS aged 13 to 17 years (120 mg twice a day for 7 days followed by 240 mg twice a day for the remainder of treatment; safety population, n=22), ***followed by a 96 week extension study (240mg twice per day; safety population n=20)***, the safety profile appeared similar to that observed in adult patients.

Section 5.1

Paediatric population

Tecfidera was evaluated in a prospective open-label, uncontrolled study in 22 paediatric patients with RRMS aged 13 to 17 years (4 patients aged ⩽14 years). Subjects received Tecfidera 120 mg twice a day for 7 days followed by 240 mg twice a day for 24 weeks. The median number of new or newly enlarging T2 hyperintense lesions changed from 2 in the 8 week pre-treatment evaluation period to 0 in the final 8 weeks of the treatment period (median change -2, n=16). ***Patients subsequently entered an extension study for a further 96 weeks. Among the 10 patients with MRI data between weeks 64 and week 72 of the extension study, the median number of subjects with new or newly enlarging T2 hyperintense lesions was 0 (range 0,2). Over the full treatment period (120-week), ARR was 0.2 representing an 84.5% relative reduction in relapses (n=20; 95% CI [66.8, 92.8], p<0.0001), when compared to the year prior to treatment initiation.*** These

data should be considered cautiously regarding limitations of the study design (no control arm, pre-versus post-dose comparison) (see section 4.2).

Patient leaflet

Section 2

Children and adolescents

***Tecfidera is not recommended for use in children and adolescents because there is limited experience in the use of Tecfidera in this population.*** ~~Tecfidera should **not be used** in children and adolescents below 18 years old. The safety and effectiveness of Tecfidera in this age group are not known.~~

In the Clinical Overview addendum the results of Study 109MS311 were summarized, which evaluated Tecfidera® (also known as BG00012 and dimethyl fumarate) in pediatric participants with relapsing-remitting multiple sclerosis (RRMS).

Study 109MS311: A Multicenter Extension Study to Determine the Long-Term Safety and Efficacy of BG00012 in Pediatric Subjects with Relapsing-Remitting Multiple Sclerosis.

Study 109MS311 was designed to evaluate the long-term safety and efficacy of Tecfidera in pediatric participants with RRMS. Eligible participants from Study 109MS202 (Open-Label, Multicenter, Multiple-Dose Study of the Effect of BG00012 on Magnetic Resonance Imaging [MRI] Lesions and Pharmacokinetics in Pediatric Subjects With Relapsing-Remitting Multiple Sclerosis Aged 10 to 17 Years) were enrolled into Study 109MS311. The pediatric participants received Tecfidera 240 mg twice daily (2 capsules of 120 mg) orally for 96 weeks, the same dosing regimen as the approved Tecfidera dosing regimen in adults with RRMS. The clinical study report for Study 109MS202 has previously been submitted to the European Medicines Agency (EMEA/H/C/002601/II/0042, approved November 2017).

The proposed update to the Tecfidera Summary of Product Characteristics (SmPC) and Package Leaflet with information from Study 109MS311 was supported.

The submission of the clinical study report for Study 109MS311, the post hoc efficacy analysis of ARR (with combined Study 109MS202 and Study 109MS311 treatment durations), and the proposed modifications to the EU Product Information (SmPC sections 4.8 and 5.1 and Package Leaflet section 2) to reflect the data that is now available for pediatric patients with RRMS treated with Tecfidera is supported.

No new safety concerns were identified in this long-term extension study of pediatric participants with RRMS treated with Tecfidera, and the findings are consistent with the safety profile seen in the initial pediatric study, Study 109MS202 and in the adult population.

Study 109MS311 demonstrated a maintenance of effect in pediatric participants with RRMS over 96 weeks of treatment. The data did not demonstrate any difference from the known benefit:risk profile of Tecfidera in adults with RRMS.

As there are no changes to the safety profile as a result of this study and no changes to the risks identified in the EU Risk Management Plan (RMP), no updates to the EU RMP are proposed at this time.

The benefit-risk balance of TECFIDERA, remains positive.

# 3. Recommendations

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

| **Variation accepted** | | **Type** | **Annexes affected** |
|---|---|---|---|
| C.I.4 | 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 4.8 and 5.1 of the SmPC in order to add the efficacy and safety information based on final results from study 109MS311, a multicentre extension study to determine the long-term safety and efficacy in paediatric subjects with RRMS (final study report already submitted under P46- 020). The Package Leaflet is updated accordingly.

☒ is recommended for approval.

# Annex: Rapporteur’s assessment comments on the type II variation

# 4. Introduction

Tecfidera (dimethyl fumarate (DMF), BG00012) is indicated for the treatment of adult patients with relapsing remitting multiple sclerosis (MS) and distributed in 120 mg and 240 mg hard gelatine capsules. The starting dose is 120 mg two times a day orally. After 7 days, the Tecfidera dose is proposed to be 240 mg BID (480 mg DMF per day). Temporary dose reduction to 120 mg twice a day is foreseen and may reduce the occurrence of flushing and gastrointestinal (GI) side effects. Within 1 month, the recommended dose of 240 mg twice a day orally should be resumed. Tecfidera received centralized European Union (EU) Marketing Authorization on 30 January 2014 for the treatment of adult patients with relapsing remitting multiple sclerosis (RRMS).

The MAH stated that study "A Multicenter Extension Study to Determine the Long-Term Safety and Efficacy of BG00012 in Pediatric Subjects With Relapsing-Remitting Multiple Sclerosis" – **109MS311** is a stand-alone study. Study 109MS311 is the extension of study **109MS202** that has been submitted via Type II variation in 2017, leading to changes/update of the SmPC.

Study 109MS202 was a 24 week, open-label, multicentre, uncontrolled study to assess the effect of Tecfidera on brain magnetic resonance imaging (MRI) lesions (number of new or newly enlarging T2 hyperintense lesions), as well as to evaluate the pharmacokinetics, safety and tolerability in paediatric patients with relapsing-remitting multiple sclerosis from 10 to 17 years of age.

Study 109MS202 as concerned in that variation procedure as well as study 109MS311 are not part of the Tecfidera PIP. The study 109 MS311 has also been submitted in accordance with article 46 of regulation (EC) No 1901/2006, as amended. For further information, reference is made to Procedure no.: EMA/H/C/002601/P46/020 and to the final updated variation assessment report (EMEA/H/C/002601/II/0042) as well.

It should be noticed that there is an ongoing randomised, open-label, controlled pediatric study (study 109MS306) which is agreed in the PIP (P/0167/2017). Upon completion of this study, the SmPC should be further updated.

# 5. Clinical Efficacy aspects

## *5.1. Methods – analysis of data submitted*

Study 109MS311 was designed to evaluate the long-term safety and efficacy of Tecfidera (also known as BG00012 and dimethyl fumarate) in pediatric participants with RRMS. Eligible participants from Study 109MS202 (Open-Label, Multicenter, Multiple-Dose Study of the Effect of BG00012 on Magnetic Resonance Imaging [MRI] Lesions and Pharmacokinetics in Pediatric Subjects With Relapsing-Remitting Multiple Sclerosis Aged 10 to 17 Years) were enrolled into Study 109MS311. The pediatric participants received Tecfidera 240 mg twice daily (2 capsules of 120 mg) orally for 96 weeks, the same dosing regimen as the approved Tecfidera dosing regimen in adults with RRMS. The clinical study report for Study 109MS202 has previously been submitted to the European Medicines Agency (EMEA/H/C/002601/II/0042, approved November 2017).

### *5.2. Results*

BG00012 demonstrated maintenance of effect in pediatric participants with RRMS over 96 weeks of treatment. These results are consistent with the findings seen in Study 109MS202, which demonstrated effectiveness in reducing the incidence of brain MRI lesions and relapses.

- Of the 17 participants with an MRI evaluation at Week 16 and Week 24, 12 (71%) participants had no new or newly enlarged T2 lesions from Week 16 to Week 24. Of the 10 participants with MRI evaluation at Week 64 and Week 72, 8 (80%) participants had no new or newly enlarged T2 lesions from Week 64 to Week 72.
- The total number of relapses in the 20 participants who continued from Study109MS202 into Study109MS311 decreased from 29 relapses at 1 year prior to enrollment into Study 109MS202 to 6 relapses during the 24-week period evaluated during Study 109MS202, and decreased even further to 4 relapses during the 96 weeks evaluated in Study 109MS311, for a total of 10 relapses over 120 weeks on treatment. The number of participants with no relapses increased from 2 participants at 1 year prior to enrollment into Study 109MS202 to 13 participants over 120 weeks on treatment.
    - The unadjusted ARR for the 1-year period prior to Study 109MS202 study entry was 1.5 relapses and for the 24-week treatment period in Study 109MS202 was 0.6 relapses. The unadjusted ARR continued to decrease to 0.1 relapses over the 96 weeks analyzed in Study 109MS311.
    - Two (10%) participants experienced a protocol-defined relapse (new or recurrent neurological symptoms not associated with fever or infection, lasting at least 24 hours, and accompanied by new objective neurological findings upon examination).
    - Three participants met the protocol definition of disability progression during the study period, of which 2 participants had an associated event of MS relapse. The median EDSS score was 1.00 (range: 0.0 to between 2.5 and 3.5) at each timepoint evaluated, except at Week 72, when the median EDSS score was 1.25 (range: 0.0 to 3.5).

The long-term efficacy results of BG00012 in pediatric participants demonstrated continued improvement in the occurrence of brain MRI T2 lesions and a continued decrease in relapses and the ARR. However, due to the small study size and the single-arm study design, these results should be interpreted with caution. Pediatric patients tend to have a higher ARR and more T2 lesions shown on MRI with more pronounced inflammation than adults and therefore tend to respond very well to immunomodulatory treatments, including treatment with BG00012.

## 6. Clinical Safety aspects

### *6.1. Methods – analysis of data submitted*

In Study 109MS311, the safety profile was consistent with the safety profile seen in Study 109MS202 and no new safety concerns related to long-term treatment with Tecfidera were identified in this study of pediatric participants with RRMS.

- The most common adverse events (AEs) among participants were flushing (5 participants [25%]); MS relapse (4 participants [20%]); and headache, abdominal pain, upper respiratory tract infection, viral upper respiratory tract infection, cough, and dysmenorrhea (3 participants [15%] each).

- The majority of AEs reported in this study were mild or moderate in severity and were considered not related to study treatment.
- Three participants experienced 4 serious advserve events (SAEs) during the study, including 3 events of MS relapse and 1 event of abdominal pain that required hospitalization. (This includes 1 participant with an SAE of MS relapse that began in Study 109MS202 and was ongoing when the participant started Study 109MS311.)
- No participants died during the study, discontinued from study treatment due to an AE, or withdrew from the study due to an AE.
- No apparent treatment-related or dose-related trends were observed in clinical laboratory parameters, vital signs, or electrocardiograms (ECGs). Results of laboratory, vital sign, and ECG assessments did not reveal any new safety concerns.
- Lymphocyte counts generally remained stable throughout study treatment, and low lymphocyte counts were not associated with any related AEs such as infection or fever. Given that the participants were continuing treatment with Tecfidera from Study 109MS202, stable lymphocyte counts were expected in Study 109MS311.

## *6.2. Results*

Results from this study demonstrated an acceptable safety profile for pediatric patients with RRMS. The maintenance of effect established in Study 109MS202 was seen in this study for 96 weeks as measured by EDSS score and MRI.

- In this extension study of Study 109MS202, 20 pediatric participants with RRMS received open-label BG00012 over 96 weeks and BG00012 continued to display an acceptable safety profile. There were no unexpected observations regarding AEs, clinical laboratory parameters, vital signs, or ECGs.
- No participants died during the study, discontinued from study treatment due to an AE, or withdrew from the study due to an AE.
- The long-term efficacy results of BG00012 in pediatric participants demonstrated continued improvement in the occurrence of brain MRI T2 lesions and a continued decrease in relapses and the ARR. However, due to the small study size and the single-arm study design, these results should be interpreted with caution.
- Pediatric patients tend to have a higher ARR and more T2 lesions shown on MRI with more pronounced inflammation than adults and therefore tend to respond very well to immunomodulatory treatments, including treatment with BG00012.

No new safety concerns were identified in this long-term extension study of pediatric participants with RRMS treated with Tecfidera, and the findings are consistent with the safety profile seen in the initial pediatric study, Study 109MS202 and in the adult population.

Study 109MS311 demonstrated a maintenance of effect in pediatric participants with RRMS over 96 weeks of treatment. The data did not demonstrate any difference from the known benefit-risk profile of Tecfidera in adults with RRMS.

As there are no changes to the safety profile as a result of this study and no changes to the risks identified in the EU Risk Management Plan (RMP), no updates to the EU RMP are proposed at this time.

# 7. Changes to the Product Information

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

Section 4.8
Paediatric population

The safety of Tecfidera in paediatric patients with multiple sclerosis below the age of 18 has not yet been established. In a small 24-week open-label uncontrolled study in paediatric patients with RRMS aged 13 to 17 years (120 mg twice a day for 7 days followed by 240 mg twice a day for the remainder of treatment; safety population, n=22), ***followed by a 96 week extension study (240mg twice per day ; safety population n=20)***, the safety profile appeared similar to that observed in adult patients.

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Tecfidera was evaluated in a prospective open-label, uncontrolled study in 22 paediatric patients with RRMS aged 13 to 17 years (4 patients aged ⩽14 years). Subjects received Tecfidera 120 mg twice a day for 7 days followed by 240 mg twice a day for 24 weeks. The median number of new or newly enlarging T2 hyperintense lesions changed from 2 in the 8 week pre-treatment evaluation period to 0 in the final 8 weeks of the treatment period (median change -2, n=16). ***Patients subsequently entered an extension study for a further 96 weeks. Among the 10 patients with MRI data between weeks 64 and week 72 of the extension study, the median number of subjects with new or newly enlarging T2 hyperintense lesions was 0 (range 0,2). Over the full treatment period (120-week), ARR was 0.2 representing an 84.5% relative reduction in relapses (n=20; 95% CI [66.8, 92.8], p<0.0001), when compared to the year prior to treatment initiation.*** These data should be considered cautiously regarding limitations of the study design (no control arm, pre-versus post-dose comparison) (see section 4.2).

The PL section 2 has been updated accordingly.

Patient leaflet

Section 2

Children and adolescents

***Tecfidera is not recommended for use in children and adolescents because there is limited experience in the use of Tecfidera in this population.*** ~~Tecfidera should **not be used** in children and adolescents below 18 years old. The safety and effectiveness of Tecfidera in this age group are not known.~~