Amsterdam, 27 January 2022
EMEA/H/C/5955/0000
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Dimherity (WD)

International non-proprietary name: dimethyl fumarate

Procedure No. EMEA/H/C/006042/0000

Note

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

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List of abbreviations*

ANOVA	Analysis of variance
AAS	Atomic Absorption Spectrometry
AP	Applicant's Part (or Open Part) of a ASMF
API	Active Pharmaceutical Ingredient
AR	Assessment Report
ARR	Annualized Relapse Rate
ASM	Active Substance Manufacturer
ASMF	Active Substance Master File = Drug Master File
ATC	Anatomical Therapeutic Chemical
AUC	Area Under the Curve
AUCinf	Area under the plasma concentration-time curve from time zero to infinity
AUCt	Area under the plasma concentration-time curve from time zero to time t
BCS	Biopharmaceutics Classification System
BE	Bioequivalence
CEP	Certificate of Suitability of the EP
CFU	Colony Forming Units
Cmax	Maximum plasma concentration
CMS	Concerned Member State
CNS	Central Nervous System
CoA	Certificate of Analysis
CRS	Chemical Reference Substance (official standard)
CTD	Common Technical Document
CYP	Cytochrome P450
DMF	Dimethyl fumarate
DMT	Disease-Modifying Treatment
DP	Decentralised (Application) Procedure
DPM	Drug Product Manufacturer
DSC	Differential Scanning Calorimetry
EDQM	European Directorate for the Quality of Medicines
EDSS	Expanded Disability Status Scale
EMA	European Medicines Agency
EP	European Pharmacopoeia

FT-IR	Fourier Transform infrared spectroscopy
GC	Gas chromatography
Gd(+)	Gadolinium enhancing lesion
HDPE	High Density Polyethylene
HPLC	High performance liquid chromatography
ICP-OES	Inductively coupled plasma – optical emission spectroscopy
IMP	Investigational Medicinal Product
IPC	In-process control
IR	Infrared
ISR	Incurred Sample Reanalysis
IU	International Units
LC-MS/MS	Liquid Chromatography with tandem Mass Spectrophotometry
LDPE	Low Density Polyethylene
LLOQ	Lower Limit of Quantitation
LOA	Letter of Access
LOD	Limit of Detection
LOQ	Limit of Quantitation
LoQ	List of Questions
MA	Marketing Authorisation
MAH	Marketing Authorisation holder
MEB	Medicines Evaluation Board
MEK	Methyl ethyl ketone
MMF	Monomethyl fumarate
MRI	Magnetic Resonance Imaging
MS	Multiple Sclerosis
MS	Mass Spectrometry (Quality part)
MTBE	Methyl *tert*-Butyl Ether
ND	Not detected
NEDA	No Evidence of Disease Activity
NLT	Not less than
NMR	Nuclear Magnetic Resonance
NMT	Not more than
Nrf2	Nuclear factor-like-2

NtA	Notice to Applicants
OC	Oral Contraceptive
OOS	Out of Specifications
OTC	Over the Counter
PDE	Permitted Daily Exposure
PE	Polyethylene
Ph.Eur.	European Pharmacopoeia
PIL	Patient Information Leaflet
PK	Pharmacokinetics
PL	Package Leaflet
PP	Polypropylene
PPMS	Primary Progressive Multiple Sclerosis
PVC	Poly vinyl chloride
QC	Quality Control
QOS	Quality Overall Summary
RH	Relative Humidity
RMS	Reference Member State
RP	Restricted Part (or Closed Part) of a ASMF
RRMS	Relapsing-Remitting Multiple Sclerosis
RRT	Relative retention time
RSD	Relative standard deviation
SmPC	Summary of Product Characteristics
SPMS	Secondary Progressive Multiple Sclerosis
T1/2	Elimination half-life
TGA	Thermo-Gravimetric Analysis
TEA	Triethylamine
Th	T helper cell
Tlag	Lag time
Tmax	Time to reach maximum plasma concentration
Tmax	Time to reach maximum plasma concentration following drug administration
TTC	Threshold of Toxicological Concern
USP/NF	United States Pharmacopoeia/National Formulary
UV	Ultraviolet

XRD	X-Ray Diffraction

* This is a general list of abbreviations. Not all abbreviations will be used.

1. CHMP Recommendation

Based on the review of the data on quality and BE, the generic application for Dimherity (Dimethyl Fumarate) in the treatment of relapsing remitting multiple sclerosis in adult patients,

is not approvable since "major objection" has been identified, which preclude a recommendation for marketing authorisation at the present time.

In addition, satisfactory answers must be given to the "other concerns" as detailed in the List of Outstanding Issues.

The major objection precluding a recommendation of marketing authorisation, pertain to the following principal deficiencies :

- The Applicant applies for the 120 mg and 240 mg strength of the gastro-resistant capsule (multiple unit formulation). In support of the 120 mg strength, the Applicant performed a dissolution study to compare the 120 mg and 240 mg strengths. It was stated in the Quality AR that the dissolution profiles of the 120 mg and 240 mg strengths were considered similar (for the 240 mg strength, the biobatch was used). The approach is acceptable (see FIP guideline for dissolution testing of solid oral products). The dissolution testing should be repeated under acceptable conditions.

Deficiencies arising from concerns over the restricted part of the ASMF are mentioned in the appendix (this appendix is not supplied to the applicant). These concerns will be conveyed in confidence to the holder of the ASMF.

Update following the withdrawal of the application as requested by the Applicant on 22 February 2022

The CHMP noted the withdrawal request letter received on 22 February 2022. It was acknowledged that the Applicant responded to the List of Outstanding Issues adopted in January, including the alignement of the dossier to the iMAA dossier of H-005955. Following the responses, the concerns listed in the List of Outstanding Issues were considered resolved and the Dimherity iMAA could have been approvable before the iMAA was withdrawn.

1.1. Questions to be posed to additional experts

N/A

1.2. Proposal for inspection

1.2.1. GMP inspection(s)

N/A

1.2.2. GCP inspection(s)

N/A

1.3. Similarity with authorised orphan medicinal products

N/A

1.4. Derogation(s) from market exclusivity

N/A

2. Executive summary

2.1. Problem statement

Multiple sclerosis (MS) is the most common chronic inflammatory disease of the central nervous system (CNS). Although the exact cause and mechanisms of MS are unknown, MS is considered an immune-mediated disease. Indeed, inflammatory infiltrates are invariably present in CNS samples taken from patients with MS. The prevalence of MS is growing, with about 2.3 million people diagnosed with MS worldwide. Because inflammation in MS can affect any CNS site, patients with MS may have many different symptoms, such as loss of vision, limb weakness, sensory loss, ataxia, urinary urgency or urinary retention, and impaired gait. At the initial stage of the disease, about 85% of patients with MS have periodical exacerbations of neurological function (relapses), during which new neurological symptoms appear. These initial symptoms tend to improve or disappear completely, hence relapsing-remitting multiple sclerosis - RRMS. After many relapses, however, patients with MS may accumulate considerable disability. Moreover, after 10-20 years since the diagnosis, there is a constant progression of the disease, which leads to immobility, cognitive dysfunction, and loss of independence (secondary progressive MS, SPMS). Disease progression in MS is most commonly assessed on the Extended Disability Status Scale (EDSS), with scores from 0 (no symptoms) to 10 (death due to MS). About 15% of patients have disease progression since the onset of MS (primary progressive MS, PPMS) (Browne 2014, Kurtzke 1983, Thompson 2018).

Currently, the cause of MS is unknown, and the disease is incurable. However, there are several approved medicinal products for the treatment of RRMS. Because these products change the course of MS, they are referred to as disease-modifying treatments (DMTs) (Fogarty 2016).

All DMTs reduce the annualized relapse rate (ARR), which is the number of relapses over a period of one year. The effect of the currently available DMTs on disease progression in patients with RRMS is less clear. The approved DMTs in RRMS contain one of the following active ingredients: dimethyl fumarate, interferon beta, teriflunomide, glatiramer acetate, clardribine, fingolimod, and natalizumab. Based on their potency, these agents are classified as first-line treatments or second-line treatments. Newly diagnosed patients with RRMS typically receive one of the first-line agents, which include interferon beta, glatiramer acetate, teriflunomide, and dimethyl fumarate. Compared to placebo, the first-line DMTs reduce the ARR from about 30% (glatiramer acetate) to about 50% (dimethyl fumarate). When first-line DMTs are ineffective or when MS starts aggressively, patients receive second-line DMTs, which include clardribine, fingolimod, or natalizumab (Montalban 2018). The second-line DMTs reduce the ARR from about 50% (fingolimod) to about 70% (natalizuamb) (Rae-Grant 2018). Although the second-line DMTs are more effective than first-line DMTs, their safety profile is less favourable. In particular, there have been cases of progressive multifocal leukoencephalopathy (PML), which is a life-threatening opportunistic CNS infection, in patients with RRMS who received fingolimod, natalizumab, or dimethyl fumarate (Tecfidera SmPC 2018, Czlonkowska 2017, Mills 2018a).

Dimethyl fumarate is one of the fumaric acid esters that are the active ingredients of the medicinal product Fumaderm, which is used to treat patients with severe psoriasis (Salmen 2014). Similarly to psoriasis, MS is an inflammatory disease with an unknown cause; thus, Fumaderm was tested in an open pilot study in 10 patients with RRMS (Schimrigk 2006).

In that study, starting from the 18th week of treatment, Fumaderm significantly reduced both the number and volume of gadolinium-enhancing [Gd(+)] lesions on brain magnetic resonance imaging (MRI) [Gd(+) lesions indicate active disease]. Subsequently, in a randomized, doubleblind, placebo-

controlled phase IIb study among 257 patients with RRMS, Kappos et al. confirmed that treatment with dimethyl fumarate significantly reduced the number of Gd(+) lesions; it also reduced the ARR (non-significantly) (Kappos 2008). These findings encouraged phase III studies. Based on these pivotal phase III studies, in 2014, the European Commission granted dimethyl fumarate a marketing authorization for the treatment of patients with RRMS.
It is worth to mention that there are also studies showing that dimethyl fumarate may be effective in progressive forms of multiple sclerosis, however more clinical studies, controlled and randomised, are needed to fully evaluate this therapeutic potential (Strassburger-Krogias 2014).
Since then, dimethyl fumarate has been continuously used in clinical practice in this indication.
Currently, only one medicinal product containing dimethyl fumarate (the reference product Tecfidera) is available for the treatment of patients with RRMS.

2.2. About the product

The medicinal product Dimethyl fumarate is manufactured as gastro-resistant capsules, hard containing 120 or 240 mg of the active substance -.
Excipients used in the formulation are all conventional, present at typical levels. The majority of the excipients of Dimethyl fumarate, 120 mg, 240 mg, gastro-resistant capsule, hard have monographs in the European Pharmacopoeia (Ph. Eur.). Others are controlled as per in-house standards. All the excipients have a very low or even negligible risk to produce any toxic effects.
According to the proposed Summary of Product Characteristics (SmPC), the medicinal product Dimethyl fumarate, 120 mg, 240 mg, gastro-resistant capsules, hard is indicated for the treatment of adult patients with RRMS. Treatment should be initiated under supervision of a physician experienced in the treatment of the disease. The drug should be administered according to the following posology (Tecfidera SmPC 2018):
• **Adults:** The starting dose is 120 mg twice a day. After 7 days, the dose is increased to the recommended dose of 240 mg twice a day. Temporary dose reduction to 120 mg twice a day may reduce the occurrence of flushing and gastrointestinal adverse reactions. Within 1 month, the recommended dose of 240 mg twice a day should be resumed. The medicinal product Dimethyl fumarate should be taken with food. For those patients who may experience flushing or gastrointestinal adverse reactions, taking the product with food may improve tolerability.
• **Elderly:** Clinical studies of dimethyl fumarate had limited exposure to patients aged 55 years and above, and did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently than younger patients. Based on the mode of action of the active substance, there are no theoretical reasons for any requirement for dose adjustments in the elderly.
• **Renal and hepatic impairment:** Dimethyl fumarate has not been studied in patients with renal or hepatic impairment. Based on clinical pharmacology studies, no dose adjustments are needed. Caution should be used when treating patients with severe renal or severe hepatic impairment.
• **Paediatric population:** The safety and efficacy of dimethyl fumarate in children and adolescents aged 10 to 18 years have not yet been established. Currently available data do not allow making recommendations regarding posology. There is no relevant use of dimethyl fumarate in children aged less than 10 years for the indication of RRMS.
The product is intended for oral administration. The capsule or its contents should not be crushed, divided, dissolved, sucked or chewed.

2.3. The development programme/compliance with CHMP guidance/scientific advice

The applicant did not receive CHMP Scientific Advice pertinent to the clinical investigation.

Relevant for the assessment are the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98), Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms (EMA/CHMP/EWP/280/96 Rev1), Dimethyl fumarate gastro-resistant capsule 120 mg and 240 mg product-specific bioequivalence guidance (EMA/CHMP/421315/2017), Guideline on Bioanalytical method validation (EMEA/CHMP/EWP/192217/09).

2.4. General comments on compliance with GMP, GLP, GCP

GMP

Manufacturer's Authorisations and/or GMP certificates have been provided for all manufacturing sites or are available in EudraGMP database.

For API manufacturing site valid QP declaration has been presented (checked date: 27/12/2021). QP declaration has been issued.

GLP

N/A

GCP

By the sponsor's statement the BE studies carried out outside the European Union (Study 2149 and Study 2150) met the ethical requirements of the European Regulation EU 536/2014.

2.5. Type of application and other comments on the submitted dossier

2.5.1. Legal basis

Article 10(1) of Directive 2001/83/EC, as amended – relating to applications for generic medicinal product.

The chosen reference product is:

Medicinal product which is or has been authorised in accordance with Union provisions in force for not less than 10 years in the EEA:

- Product name, strength, pharmaceutical form: Tecfidera, 120 mg, 240 mg, gastro-resistant capsule, hard
- Marketing authorisation holder: Biogen Idec Ltd
- Date of authorisation: 30-01-2014
- Marketing authorisation granted by:
  - Union
- Marketing authorisation number: EU/1/13/837/001; EU/1/13/837/002-003

Medicinal product authorised in the Union /Members State where the application is made or European reference medicinal product:

- Product name, strength, pharmaceutical form: Tecfidera, 120 mg, 240 mg, gastro-resistant capsule, hard
- Marketing authorisation holder: Biogen Idec Ltd
- Date of authorisation: 30-01-2014
- Marketing authorisation granted by:
  - Union
- Marketing authorisation number: EU/1/13/837/001; EU/1/13/837/002-003

Medicinal product which is or has been authorised in accordance with Union provisions in force and to which bioequivalence has been demonstrated by appropriate bioavailability studies:

- Product name, strength, pharmaceutical form: Tecfidera, 240 mg, gastro-resistant capsule, hard
- Marketing authorisation holder: Biogen Idec Ltd
- Date of authorisation: 30-01-2014
- Marketing authorisation granted by:
  - Union
- Marketing authorisation number(s): EU/1/13/837/002-003
- Bioavailability study number(s): 2149, 2150

2.5.2. Orphan designation

Not Applicable.

2.5.3. Similarity with orphan medicinal products

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

2.5.4. Derogation(s) from orphan market exclusivity

N/A

2.5.5. Information on paediatric requirements

N/A

3. Scientific overview and discussion

3.1. Quality aspects

3.1.1. Introduction

The finished product is presented as gastro-resistant hard capsules, containing 120 mg and 240 mg of Dimethyl fumarate as active substance.

Other ingredients are:

Capsule content: Croscarmellose sodium, Silica, colloidal anhydrous, Sodium stearyl fumarate, Methacrylic acid-methyl methacrylate copolymer (1:1), Methacrylic acid-ethyl acrylate copolymer (1:1) dispersion 30%, Talc, Triethyl citrate, Polysorbate 80, Glyceryl monostearate

Capsule: Gelatin, Titanium dioxide (E171), Yellow iron oxide (E172), Brilliant blue FCF (E133)

Capsule ink: Shellac glaze, Black iron oxide (E172), Propylene glycol (E1520), Ammonium hydroxide 28%

The product is available in Aluminium/PVC/PVDC blisters.

3.1.2. Active Substance

3.1.2.1. General Information

Dimethyl fumarate (INN) is a white to off-white powder, sparingly soluble in methanol, acetone and dimethyl sulfoxide, soluble in DMF and highly soluble in buffer solutions of pH 1.2, 4.5 and 6.8. The drug substance is non-hygroscopic by nature and exists is one crystal form. Dimethyl fumarate is not described in Ph.Eur.

The chemical name of Dimethyl fumarate is Dimethyl (E)-but-2-enedioatecorresponding to the molecular formula $C_6H_8O_4$. It has a relative molecular mass of 144.13 g/mol and the following structure:

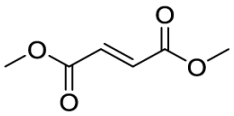

Figure 1: Active substance structure

The chemical structure of active substance was elucidated by a combination ofvarious characterization techniques, i.e.: UV, FT-IR, NMR [^{1}H-NMR and ^{13}C-NMR], Mass spectra, Elemental Analysis. The solid state properties of the active substance were measured by melting temp., XRD and DSC.

3.1.2.2. Manufacture, process controls and characterisation

The active substance Dimethyl fumarate is manufactured by one manufacturer.

Information on manufacture of Dimethyl fumarate is provided via the active substance master file procedureDetailed information on the manufacturing of the active substance has been provided in the restricted part of the ASMF.

The active substance Dimethyl fumarate is synthesized in one-step synthesis using commercially available, well defined starting material with acceptable specification.

In-process controls of the manufacturing process have been identified and adequate controls established. There are no intermediates in drug substance synthesis.

The chemical structure of Dimethyl fumarate has been adequately confirmed by the active substance manufacturer (ASM).

Potential and actual impurities have been discussed with regards to their origin. 3.1.2.3. Specification (s)

The active substance specification , includes tests for description (visual), solubility (Ph. Eur.), identification (IR, HPLC), water content (Ph. Eur.), sulphated ash (Ph. Eur.), related substance (HPLC), assay (HPLC), and residual solvents (GC). The active substance specification covers all required parameters and is acceptable. The impurity levels are within the qualification threshold according to ICH Q3A and this was considered satisfactory. The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for testing has been presented.

Batch analysis data on 3 commercial scale batches of non- micronized and micronized of the active substance are provided. The results are within the specifications and consistent from batch to batch.

3.1.2.3. Stability

Stability data for API has been included in ASMF. The Applicant has not performed his own stability studies.

ASMF holder has presented stability study for six batches, three of which were micronized and three unmicronized. All batches are described as process validation batches. Unmicronized batches were tested in long-term (25±5°C, 60±5%) and accelerated conditions (40±5°C, 75±5%).

The stability results indicate that the unmicronized and micronized active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 48 months stored at temperature 2-8 °C for the unmicronized active substance and 36 months for micronized material in the proposed container.

3.1.3. Finished Medicinal Product

3 . 1 . 3 . 1 . Description of the product and Pharmaceutical Development

The applied product is in form of gastro-resistant hard capsules of 120 mg and 240 mg strength for oral use.

3.1.3.2.

The finished product has been developed to be a generic equivalent to the reference medicinal product Tecfidera® 120 mg, 240 mg gastro-resistant hard capsules, marketed by Biogen. Consequently, the objective was to prepare a gastro-resistant hard capsules being essentially similar to the reference medicinal product.

The active substance Dimethyl fumarate is white to off-white powder with an affinity to sublimation.

All the excipients used in the formulation are well known and widely used in the pharmaceutical industry. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report. Functions of excipients, used in the drug product formulation have been briefly discussed in the documentation.

Formulation development studies have been started from extensive characterisation of reference products.

Comparison of impurity profile of the applied product and the reference one (for 240 mg strength) has been presented. These profiles are considered as similar.

Detailed description of manufacturing process development has been presented. Quality Risk Management approach was used to optimize Dimethyl Fumarate, 120 mg, 240 mg, gastro-resistant capsules, hard manufacturing process.

The primary packaging is Al/PVC/PVDC blister packs. Primary packaging materials comply with the requirement of Commission Regulation (EU) no. 10/2011 of 14 January 2011 as amended and with the Ph.Eur. (chapter 3.1.11. "Materials based on non-plasticized poly (vinyl chloride) for containers for dry dosage forms for oral administration"). The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product

3.1.3.3. Manufacture of the product and process controls

The manufacturing process consists of 16 main steps.

Holding time for the in-bulk product has been established by appropriate stability studies discussed below in this report.

Major steps of the manufacturing process have been validated by a number of studies in 3 commercial scale batches per strength. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing.

3.1.3.4. Product specification (s)

The finished product release and shelf life specifications include appropriate tests for this kind of dosage form.

Drug product specification covers adequate parameters for the proposed pharmaceutical form. The determination of appearance is performed by visual examination. Identification of colourants has been described in detail for each excipient. Identification of API is performed by HPLC and GC methods. Drug substance content and related substances content are tested by HPLC, while content of residual solvent is tested by GC.

Dissolution testing is set in line with pharmaceutical form.

The potential presence of elemental impurities in the finished product has been assessed by a risk-assessment in line with the ICH Q3D Guideline for Elemental Impurities. The Applicant has concluded that no further control of elemental impurities is required.

A risk evaluation concerning the presence of nitrosamine impurities in the finished product has been only declared as “no risk identified” by the Applicant. A summary of risk analysis has been requested to support that statement.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results are provided confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

3.1.3.5. Stability of the product

Stability data from finished product under long term conditions (25 ºC / 60% RH) and under accelerated conditions (RH , i.e. 40 ºC / 75% RH) according to the ICH guidelines were provided. The batches of medicinal product are representative to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Photostability studies were performed in accordance with: "Note for guidance on the photostability testing of new active substances and medicinal products", ICH Q1B (CPMP/ICH/279/95).

The Applicant declares that the shelf-life is calculated from the first day of combining active ingredient with other ingredients according to CPMP/QWP/072/96 "Annex to note for guidance on the manufacture of the finished dosage form".

Stability data provided by the Applicant covers testing in long-term, intermediate and accelerated conditions, as well as photostability and hold time study. Proposed shelf-life of 24 months with storage condition – do not store above 30°C – is considered acceptable at this point.

3.1.3.6. Post approval change management protocol(s)

N/A

3.1.3.7. Adventitious agents

Gelatine obtained from animal (bovine) origin is used in the manufacturing of the applied product. TSE safety has been confirmed by respective CEPs.

3.1.4. Discussion and conclusions on chemical, pharmaceutical and biological aspects

The chemical-pharmaceutical documentation in relation to Dimherity gastro-resistant capsule, hard 120 mg & 240 mg is not yet of sufficient quality in view of the present European regulatory requirements as there is a need for additional information to complete quality documentation. Some other concerns have been identified.

3.1.5. Conclusions on the chemical, pharmaceutical and biological aspects

The application cannot be recommended for approval from a chemical and pharmaceutical point of view until complementary information has been received and judged to be acceptable.

3.1.6. Recommendation(s) for future quality development

N/A

3.2. Non clinical aspects

Pharmacodynamic, pharmacokinetic and toxicological properties of Dimethyl fumarate are well known. As dimethyl fumarate is a widely used, well-known active substance, the applicant has not provided additional studies and further studies are not required. Overview based on literature review is, thus, appropriate.

3.2.1. Ecotoxicity/environmental risk assessment

No Environmental Risk Assessment was submitted. This was justified by the applicant as the introduction of Dimherity is considered unlikely to result in any significant increase in the combined sales volumes for all dimethyl fumarate containing products and the exposure of the environment to the active substance. Thus, the ERA is expected to be similar and not increased.

However, in line with Guideline on the environmental risk assessment of medicinal products for human use EMEA/CHMP/SWP/4447/00 Rev. 1: ”An ERA is required for all new marketing authorisation applications for a medicinal product through a centralised, mutual recognition, decentralised or national procedure. According to Directive 2001/83/EC, applicants are required to submit an ERA irrespective of the legal basis. Generic medicinal products are therefore not exempted from providing an ERA”.

Therefore, the Applicant should provide Environmental Risk Assessment or present data to substantiate the claim that an increase in environmental exposure of the active substance is not to be expected e.g. consumption data or PEC determination **(OC).**

3.2.2. Discussion on non-clinical aspects

No Environmental Risk Assessment was submitted. In line with Guideline on the environmental risk assessment of medicinal products for human use EMEA/CHMP/SWP/4447/00 Rev. 1, generic medicinal products are not exempted from providing an ERA.

Therefore, the Applicant should provide Environmental Risk Assessment or present data to substantiate the claim that an increase in environmental exposure of the active substance is not to be expected e.g. consumption data or PEC determination **(OC).**

NC sections of the SmPC are in line with the reference product SmPC.

3.2.3. Conclusion on non-clinical aspects

The application could be recommended for approval from a non-clinical point of view.

3.3. Clinical aspects

3.3.1. Exemption

The Applicant intends to register two strengths of Dimethyl fumarate: 120 mg and 240 mg.

Bioequivalence was demonstrated for the 240 mg strength and a biowaiver for the additional 120 mg strength was requested. In line with the Guideline, this exemption required that the composition is proportional, the formulations contain identical granules and are produced by the same manufacturing process, and the dissolution profiles are similar.

The 2 strengths of drug product are manufactured by the same process and the same manufacturer. The qualitative composition is the same and the composition is proportional.

The dissolution tests were conducted with Dimethyl fumarate 240 mg and 120 mg on 12 capsules each.

Assessor's comment

The Applicant applies for the 120 mg and 240 mg strength of the gastro-resistant capsule (multiple unit formulation). In support of the 120 mg strength, the Applicant performed a dissolution study to compare the 120 mg and 240 mg strengths. It was stated in the Quality AR that the dissolution and that the dissolution profiles of the 120 mg and 240 mg strengths were considered similar (for the 240 mg strength, the biobatch was used). The approach is acceptable (see FIP guideline for dissolution testing of solid oral products). However, dissolution testing should be repeated **(MO).**

As per Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms (EMA/CHMP/EWP/280/96 Rev1), *for multiple unit formulations of a medicinal product with several strengths, it is sufficient to conduct the studies listed in section 6.1.1 only at the highest/most sensitive strength if the compositions of the strengths are proportional, the formulations contain identical beads or pellets (and these are produced by the same manufacturing process) and the dissolution profiles are similar.* Therefore, BE studies for 120 mg strength are not required.

3.3.2. Clinical pharmacology

To support the application, the applicant has submitted 2 bioequivalence studies (in fasting and fed conditions). This is in line with the EMA guideline: "Dimethyl fumarate gastro-resistant capsules 120 mg and 240 mg product-specific bioequivalence guidance, EMA/CHMP/421315/2017".
No pharmacodynamic studies and therapeutic equivalence studies have been conducted by the Applicant to support the MAA. This is acceptable for a generic application.

3.3.2.1. Pharmacokinetics

Study Number 2149

Title: A Single-Dose, Randomized, Open-Label, Four-Way, Fully Replicate, Pivotal, Bioequivalence Study of Dimethyl Fumarate 240 mg Gastro-Resistant Hard Capsules and Tecfidera® (dimethyl fumarate) 240 mg Gastro-Resistant Hard Capsules (Biogen Idec Ltd.) in Healthy Male and Non-Pregnant Female Volunteers under Fasting Conditions.

- **Study design**

This was a pivotal, single-dose, randomized, open-label, four-period, two-sequence, two treatment, single-Centre, fully replicate study designed to evaluate the comparative bioavailability of monomethyl fumarate from Dimethyl Fumarate 240 mg gastro-resistant hard capsules and Tecfidera® 240 mg gastro-resistant hard capsules administered to healthy male and non-pregnant female subjects under fasting conditions. Subjects were randomly assigned to one of the two dosing sequences.

Duration of treatment:

The study consisted of four study periods. Each study period included a single-dose drug administration of either the Test product or the Reference product.

Drug Concentration Measurements
Blood samples were collected from 22 time points in each study period.

Treatments Administered
In each study period, subjects were dosed according to the randomization scheme with one of the following treatments:
Treatment A: 1 x 240 mg Dimethyl Fumarate gastro-resistant hard capsules

Treatment B: 1 x 240 mg Tecfidera® gastro-resistant hard capsules
(By: Biogen Manufacturing ApS., Denmark; MAH: Biogen Idec Ltd, Berkshire)

Each subject was scheduled to receive a total of two treatments (each treatment twice) by the end of the study.

	Period 1	Period 2	Period 3	Period 4
Sequence 1	A	B	A	B
Sequence 2	B	A	B	A

The washout interval between drug administrations was 3 days.

- **Population studied**

- Healthy volunteers were enrolled and dosed in Period 1 and completed the study in its entirety. The data were included in the pharmacokinetic and statistical analysis.

- **Analytical methods**

A validation procedure was performed for analysing monomethyl fumarate in human plasma using high-performance liquid chromatography with tandem mass spectrometry (LC-MS/MS).

- **Pharmacokinetic variables**

Pharmacokinetic parameters were to be calculated using non-compartmental analysis (NCA) method. The following PK parameters were to be estimated (where possible) for monomethyl fumarate and included in the PK and statistical analysis for the subjects in the final data set:

AUCinf: Area under the concentration-time curve from time zero to infinity

AUCt: Area under the concentration-time curve from time zero until the last measurable concentration or last sampling time t, whichever occurs first.

Cmax: The maximal observed plasma concentration. Residual Area or AUC(res%) Extrapolated area under the curve, (AUCinf - AUCt)/AUCinf.
T1/2: Terminal elimination half-life.

Tmax: Time when the maximal plasma concentration is observed.

λ: Terminal elimination rate constant.

- **Statistical methods**

- The 90% confidence intervals of the Test/Reference ratios for AUCt, AUCinf, and Cmax were calculated. Power for treatment comparisons for the pharmacokinetic parameters was calculated as the probability (type I error fixed at the 5% level) of detecting a difference at least equal to 20% of the reference treatment mean.
- The following standards were used to determine bioequivalence for monomethyl fumarate:
- 1. The Geometric Mean Ratio (GMR) of the test to reference product and associated 90% CI of the AUCt should be within 80% - 125% regardless of its variability.
- 2. The GMR of the test to reference product of the Cmax should be within 80% - 125%.
- 3. The 90% CI for the GMR of the test to reference product of the Cmax should be within the following limits, depending on the calculated SWR (within subject standard deviation of the reference product) of the ln-transformed Cmax. As per EMA guidance, the extent of the widening is defined based upon the within subject variability seen in the bioequivalence study using scaled-average bioequivalence according to [U, L] = exp (± k × SWR), where U is the upper limit of the acceptance range, L is the lower limit of the acceptance range, k is the regulatory constant set to 0.760.
- a) Lower limit of 80.00% to upper limit of 125.00%, if SWR ≤ 0.294 (i.e., CV ≤ 30%)
- b) Lower limit of exp (-0.760 × SWR) × 100.00% to upper limit of exp (0.76×SWR)×100.00%, if 0.294 <SWR<0.472 (30% < CV <50%).
- c) Lower limit of 69.84% to upper limit of 143.19%, if SWR ≥ 0.472 (CV≥50%)

- ***Results***
- **Table 3.3.2.1.** Bioequivalence results of plasma monomethyl fumarate

Bioequivalence Results of Plasma- Monomethyl Fumarate

TREATMENT A vs TREATMENT B

Parameter (N_A/N_B)#	Geometric Means Arithmetic Means (CV %) TRT A		TRT B		Ratio of Geometric Means	90% Confidence Interval	Intra-Subject CV (%)
AUCt (ng.h/mL)	3861.98 3968.09	(22.08)	3962.89 4076.01	(22.41)	97.45	95.40 - 99.55	
AUCinf (ng.h/mL)	3941.93 4048.34	(21.61)	4011.69 4148.69	(22.37)	98.26	96.16 - 100.41	
Cmax (ng/mL)	2184.28 2282.27	(28.92)	2159.25 2295.22	(36.63)	101.16	96.23 - 106.34	
Tmax* (h)	2.33 (1.33 - 7.00)		2.33 (1.00 - 7.00)				
Lambda** (1/h)	1.0854 (30.25)		1.1745 (24.95)				
T1/2** (h)	0.73 (48.96)		0.65 (47.88)				
AUCt/AUCinf**	0.9885 (1.18)		0.9886 (1.87)				
AUC(res%)**	0.0115 (101.23)		0.0114 (161.88)				

** Presented as arithmetic mean (CV%) only
* Presented as median and range
# N_A: Number of observations for Treatment A; N_B: Number of observations for Treatment B

- The final bioequivalence analysis results, based on the revised data to include the revised dilution factor (1:1), are included below:

Table 3.3.2.2. Bioequivalence results of plasma monomethyl fumarate (after inclusion of dilution factor 1:1)

Bioequivalence Results of Plasma- Monomethyl Fumarate (After Including Dilution Factor 1.1)

TREATMENT A vs TREATMENT B

Parameter (N_A/N_B)#	Geometric Means Arithmetic Means (CV %) TRT A		TRT B		Ratio of Geometric Means	90% Confidence Interval	Intra-Subject CV (%)
AUCt (ng.h/mL)	3862.53 3969.36	(22.11)	3963.80 4076.88	(22.39)	97.45	95.37 - 99.56	
AUCinf (ng.h/mL)	3944.25 4051.58	(21.63)	4015.78 4156.37	(22.33)	98.22	96.10 - 100.39	
Cmax (ng/mL)	2191.35 2290.56	(28.93)	2159.72 2295.84	(36.62)	101.46	96.48 - 106.70	
Tmax* (h)	2.33 (1.00 - 7.00)		2.33 (1.00 - 7.00)				
Tlag* (h)	0.67 (0.33 - 3.67)		0.67 (0.33 - 4.67)				
Lambda** (1/h)	1.1373 (27.85)		1.1822 (27.09)				
T1/2** (h)	0.67 (37.32)		0.66 (55.69)				
AUCt/AUCinf**	0.9879 (1.25)		0.9875 (1.95)				
AUC(res%)**	0.0121 (101.76)		0.0125 (153.83)				

** Presented as arithmetic mean (CV%) only
* Presented as median and range
# N_A: Number of observations for Treatment A; N_B: Number of observations for Treatment B

Assessor's comment
In study 2149 (fasted state study)it should be explained why the samples of this subject were not analysed and included in the pharmacokinetic and statistical analysis if data from 3 periods were available. The protocol indicates in section 10.1.1 *Samples to be Assayed* that the samples from subjects who were dismissed due to non-compliance will not be analyzed, but if the subject complied in periods 1 to 3, there was no reason for exclusion. The cause of non-compliance should be clarified as to affect also the validity of data from periods 1 to 3 **(OC).**

Study Number: 2150

Title: A Single-Dose, Randomized, Open-Label, Two-Way, Crossover, Pivotal, Bioequivalence Study of Dimethyl Fumarate 240 mg Gastro-Resistant Hard Capsulesand Tecfidera® (dimethyl fumarate) 240 mg Gastro-Resistant Hard Capsules (Biogen Manufacturing ApS) in Healthy Male and Non-Pregnant Female Volunteers under Fed Conditions

Objectives:
The objective of this pivotal study was to demonstrate the bioequivalence of monomethyl fumarate

from Dimethyl Fumarate 240 mg gastro-resistant hard capsules and Tecfidera® 240 mg gastro-resistant hard capsules in Healthy Male and Non-Pregnant Female Volunteers under fed conditions.

Methods

- **Study design**

This was a pivotal, single-dose, randomized, open-label, two-period, two-sequence, two-treatment, single-centre, crossover study designed to evaluate the bioequivalence of monomethyl fumarate from Dimethyl Fumarate 240 mg gastro-resistant hard capsules and Tecfidera® 240 mg gastro-resistant hard capsules administered to healthy non-smoking, male and non-pregnant female subjects under fed conditions. Subjects were randomly assigned to one of the two dosing sequences.

Duration of treatment
The study consisted of two study periods. Each study period included a single-dose drug administration of either the Test product or the Reference product.

Treatments Administered
The study drugs were dispensed into unit dose packages according to the randomization scheme prior to each study period.

In each study period, subjects were dosed according to the randomization scheme with one of the following treatments:
Treatment A: 1 × 240 mg Dimethyl Fumarate gastro-resistant hard capsules
()
Treatment B: 1 × 240 mg Tecfidera® gastro-resistant hard capsules
(Biogen Manufacturing ApS., Denmark)

Subjects were randomized equally into one of the following two sequence groups:

	Period 1	Period 2
Sequence 1	A	B
Sequence 2	B	A

Each subject was scheduled to receive a total of two treatments by the end of the study. The washout interval between drug administrations was 3 days.

Drug Concentration Measurements

Blood samples were collected from 24 time points in each study period.

- **Population(s) studied**

Healthy volunteers were enrolled and dosed in Period 1 and completed the study in its entirety. The data were included in the pharmacokinetic and statistical analysis.

- **Analytical methods**

Similar to the Study 2149 (see above).

- ***Results***

Table 3.3.2.3. Bioequivalence results of plasma MMF

Bioequivalence Results of Plasma Monomethyl Fumarate:

TREATMENT A vs TREATMENT B

Parameter (N_A /N_B)	Geometric Means Arithmetic Means (CV %) TRT A		TRT B		Ratio of Geometric Means	90% Confidence Interval	Intra-Subject CV (%)
AUCt (ng.h/mL) (38 /38)	3468.81 3545.86	(21.09)	3509.22 3601.21	(22.52)	98.85	95.62 - 102.19	8.59
AUCinf (ng.h/mL) (25 /20)	3703.23 3780.10	(20.45)	3745.12 3805.26	(19.16)	98.88	95.07 - 102.85	5.74
Cmax (ng/mL) (38 /38)	1372.61 1469.81	(37.04)	1528.82 1649.22	(36.72)	89.78	80.79 - 99.77	27.76
Tmax* (h) (38 /38)	7.50 (5.00 - 10.50)		7.26 (4.50 - 10.63)				
Lambda** (1/h) (25 /20)	0.9089 (37.82)		1.1126 (40.68)				
T1/2** (h) (25 /20)	0.92 (50.61)		0.83 (76.47)				
AUCt/AUCinf** (25 /20)	0.9840 (1.14)		0.9799 (3.05)				
AUC(res%)** (25 /20)	0.0160 (70.36)		0.0201 (148.44)				

Note: N_A /N_B are the number of observations for Treatment A and B , respectively
*: Presented as median and range
**: Presented as arithmetic mean (CV%) only

The final bioequivalence analysis results, based on the revised data to include the revised dilution factor (1:1), are included below:

Table3.3.2.5. Bioequivalence results of plasma monomethyl fumarate (including dilution factor 1:1)

Bioequivalence Results of Plasma- Monomethyl Fumarate (After Including Dilution Factor 1.1)

TREATMENT A vs TREATMENT B

Parameter (N_A /N_B)	Geometric Means Arithmetic Means (CV %) TRT A		TRT B		Ratio of Geometric Means	90% Confidence Interval	Intra-Subject CV (%)
AUCt (ng.h/mL)	3447.27 3527.44	(21.55)	3485.86 3575.36	(22.43)	98.89	95.81 - 102.07	
AUCinf (ng.h/mL)	3699.86 3779.87	(20.64)	3750.33 3811.29	(19.36)	98.65	94.83 - 102.63	
Cmax (ng/mL)	1372.61 1469.81	(37.04)	1534.91 1659.44	(37.44)	89.43	80.46 - 99.39	
Tmax* (h)	7.50 (5.00 - 10.50)		7.26 (4.50 - 10.63)				
Tlag* (h)	4.00 (1.00 - 7.52)		5.00 (1.00 - 7.52)				
Lambda** (1/h)	0.9080 (40.03)		1.1051 (41.11)				
T1/2** (h)	0.93 (51.17)		0.84 (75.87)				
AUCt/AUCinf**	0.9830 (1.09)		0.9790 (3.02)				
AUC(res%)**	0.0170 (62.88)		0.0210 (140.62)				

The Test/Reference ratio of geometric means and the corresponding 90% confidence intervals for the ln-transformed AUCt and Cmax parameters were entirely contained within the acceptance range of 80.00% to 125.00%.

- ***Safety data***

A total of 25 AEs was experienced by the subjects after treatment with the Test product. A total of 35 AEs was experienced by the subjects after treatment with the Reference product. The safety profiles of the Reference and the Test Product were comparable

3.3.2.2. Pharmacokinetic Conclusion

Based on the presented bioequivalence studies Dimherity (Dimethyl Fumarate) gastro – resistant hard capsules, 240 mg is considered bioequivalent with Tecfidera gastro – resistant hard capsules, 240 mg.

The results of studies 2149 and 2150 with 240 mg formulation can be extrapolated to the other strength 120 mg according to conditions in the Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev.1, section 4.1.6 and *Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms* (EMA/CHMP/EWP/280/96 Rev1), section 6.1.2.2.
A biowaiver for the 120 mg strength is therefore agreed.

3.3.2.3. Pharmacodynamics

No new pharmacodynamic studies were presented and no such studies are required for this application.

3.3.3. Discussion on clinical pharmacology

The Applicant conducted 2 separate bioequivalence studies under fasting and fed conditions to demonstrate that the Test Product – Dimethyl Fumarate gastro – resistant hard capsules, 240 mg is bioequivalent to the Reference Product – Tecfidera, gastro – resistant hard capsules, 240 mg.

The design of the performed BE studies is considered acceptable.

The choice of analyte (MMF) is in line with EMA/CHMP/421315/2017 recommendations and is endorsed.

The chosen study population- healthy volunteers is appropriate. The validation method was performed according to the procedure recommended with the guidelines.

The point estimates and 90% confidence intervals for the ln-transformed pharmacokinetic variables C_{max} and AUC were within the predefined bioequivalence range of 80.00% - 125.00% in both performed studies. Therefore the results indicate bioequivalence between the test and reference products.

However, in study 2149 (fasted state study), subject #40 samples were taken in period 1, 2 and 3. This subject was dismissed prior to period 4 check in due to non-compliance. It should be explained why the samples of this subject were not analysed and included in the pharmacokinetic and statistical analysis if data from 3 periods were available. The protocol indicates in section 10.1.1 *Samples to be Assayed* that the samples from subjects who were dismissed due to non-compliance will not be analyzed, but if the subject complied in periods 1 to 3, there was no reason for exclusion. The cause of non-compliance should be clarified as to affect also the validity of data from periods 1 to 3 **(OC).**

Furthermore, the Applicant should justify the validity of the studies taking into account that the extrapolation of AUC was not estimated in a large number of profiles in study 2150 **(OC).**

The safety profiles of the Reference and the Test Product were comparable in both studies. No serious adverse events were reported.

The results of studies 2149 and 2150 with 240 mg formulation can be extrapolated to the other strength 120 mg according to conditions in the *Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev.1*, section 4.1.6 and *Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms* (EMA/CHMP/EWP/280/96 Rev1), section 6.1.2.2.

The dissolution testing should be repeated under acceptable conditions (MO).

3.3.4. Clinical efficacy

N/A

3.3.5. Clinical safety

N/A

3.3.5.1. Immunological events

N/A

4.1.1.1. Safety related to drug-drug interactions and other interactions

4.1.1.2. Discontinuation due to adverse events

N/A

4.1.2. Post marketing experience

No post-marketing data are available. The medicinal product has not been marketed in any country.

4.1.3. Discussion on clinical safety

No dedicated studies intended to evaluate safety of the Test product was conducted. However, this is not required for a generic application. The safety of the Test Product was evaluated in the conducted BE studies. The safety profiles of the Reference and the Test Product were comparable in both studies. No serious adverse events were reported.

4.1.4. Conclusions on clinical aspects

Based on the presented bioequivalence studies Dimethyl Fumarate gastro – resistant hard capsules, 240 mg is considered bioequivalent with Tecfidera gastro – resistant hard capsules, 240 mg.

The results of studies 2149 and 2150 with 240 mg formulation can be extrapolated to the other strength 120 mg according to conditions in the Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev.1, section 4.1.6 and *Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms* (EMA/CHMP/EWP/280/96 Rev1), section 6.1.2.2.
A biowaiver for the 120 mg strength is therefore agreed.

The dissolution testing should be repeated under acceptable conditions (MO).

The safety profiles of the Reference and the Test Product were comparable in both studies.

4.2. Risk management plan

4.2.1. Safety Specification

4.2.1.1. Summary of safety concerns

The applicant proposed the following summary of safety concerns in the RMP:

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	Progressive Multifocal Leukoencephalopathy (PML) Decreases in leukocyte and lymphocyte counts Drug-induced liver injury
Important potential risks	Serious and opportunistic infections (other than PML) Malignancies Effects on pregnancy outcome Interaction with nephrotoxic medications leading to renal toxicity
Missing information	Long term efficacy and safety Safety profile in patients over the age of 55 years Safety profile in patients with renal impairment Safety profile in patients with hepatic impairment Safety profile in patients with severe active gastrointestinal (GI) disease Increased risk of infection in patients concomitantly taking anti-neoplastic or immunosuppressive therapies

4.2.2. Discussion on safety specification

Having considered the data in the safety specification, the Rapporteur agrees that the safety concerns listed by the Applicant are appropriate.

4.2.3. Conclusions on the safety specification

Having considered the data in the safety specification, the Rapporteur agrees that the safety concerns listed by the Applicant are appropriate.

4.2.4. Pharmacovigilance plan

The Applicant states that routine pharmacovigilance activities beyond adverse reactions reporting and signal detection are not applicable.

No on-going, planned or completed additional pharmacovigilance activities are included in the Pharmacovigilance Plan.

Assessor's comment:

No routine pharmacovigilance activities beyond adverse reactions reporting and signal detection were proposed by the applicant.

However, the MAH of the reference product Tecfidera performs the following routine pharmacovigilance activities in order to provide further characterisation data for specific safety concerns and increase data quality:

Specific adverse reaction follow-up questionnaires

Data collection forms at different time points post-event (up to 24 months) are used for case reports of PML, to aid further characterisation of the event and identification of potential risk factors. These data collection forms aim to collect detailed information relating to suspected PML events in a standardised fashion, to enable timely and robust collection of data, thereby optimising risk evaluation.

Data collection forms are also used to enable timely and robust collection of data for events of drug-induced liver injury, serious and opportunistic infections (other than PML and herpes zoster), malignancies, moderate lymphopenia, and severe lymphopenia, thereby optimising risk evaluation.

Generic marketing authorisation holders should implement specific adverse reaction follow-up questionnaires in line with the ones in use for the reference product, in order to collect data for events of PML, drug-induced liver injury, serious and opportunistic infections (other than PML and herpes zoster), malignancies, moderate lymphopenia, and severe lymphopenia and thereby optimising risk evaluation. **(OC)**

The specific adverse reaction follow-up questionnaires have to be provided in full in Annex 4 **(OC)**. As outlined in the "*Guideline on good pharmacovigilance practices (GVP) Module V – Risk management systems (Rev 2)*":

"*Without prejudice to the originality of the format of the questionnaire(s), it is in the interest of public health that questionnaire(s) used by different Applicants/marketing authorisation holders for the same adverse event should be kept as similar as possible, in order to deliver a consistent message and to provide useful data for the analysis of the reports, which are relevant for regulatory decisions, while decreasing the burden on healthcare professionals. Therefore, marketing authorisation holders are strongly encouraged to share the content of their questionnaire(s) upon request from other marketing authorisation holders.*"

No additional pharmacovigilance activities are currently considered required. Two category 3 post-authorisation safety studies (PASS) are ongoing for the innovator product Tecfidera, one observational

study to further characterise the long-term safety of DMF and one pregnancy registry study. It is noted that both studies are expected to be completed rather soon. Therefore, it is currently not expected that the conduct of such post-authorisation safety studies also by marketing authorisation holders of generic DMF products would provide additional knowledge about the safety profile. Therefore, these studies are not required for the product under review.

4.3. Overall conclusions on the PhV Plan

The PRAC Rapporteur, having considered the data submitted, is of the opinion that routine pharmacovigilance is sufficient to identify and characterise the risks of the product.

The PRAC Rapporteur also considered that routine PhV remains sufficient to monitor the effectiveness of the risk minimisation.

However, further routine risk minimisation measures are required in line with the reference product, as detailed above.

4.4. Risk minimisation measures

4.4.1.1. Routine Risk Minimisation Measures

The safety information in the proposed product information is aligned to the reference medicinal product.

4.4.1.2. Additional risk minimisation measures

The applicant states that routine risk minimisation activities are sufficient to manage the safety concerns of the medicinal product.

There are no ongoing additional risk minimisation measures in place for the reference product, either.

Assessor's comment:

No additional risk minimisation measures are considered warranted, in line with the reference product.

4.5. Overall conclusions on risk minimisation measures

The PRAC Rapporteur having considered the data submitted was of the opinion that:

In line with the reference product the proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication.

4.5.1. Conclusion on the RMP

The RMP could be acceptable provided an updated RMP and satisfactory responses to the list of questions below is submitted.

PRAC outcome

During the plenary meeting held on 10-13 January 2022, the PRAC fully supported the PRAC Rapporteur's assessment of the pharmacovigilance plan and risk minimisation measures as detailed in this assessment report. The PRAC agreed that no additional pharmacovigilance activities or risk

minimisation measures are required and that the RMP of Dimherity in the proposed indication could be acceptable provided that an update of version 1.1 and satisfactory responses to the questions as detailed below are submitted.

4.6. Pharmacovigilance

4.6.1. Pharmacovigilance system

Having considered the data submitted in the application, it is not appropriate to conclude on pharmacovigilance system at this time. The Applicant should provide Qualified Person Responsible for Pharmacovigilance CV **(OC).** See list of questions.

4.6.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

For dimethyl fumarate PSURs are currently not required for products referred to in Articles 10(1), 10a, 16a of Directive 2001/83/EC as amended.

5. Benefit/risk assessment

This application concerns a generic version of dimethyl fumarate gastro-resistant capsule 120 mg and 240 mg. The reference product Tecfidera is indicated for the treatment of adult patients with relapsing remitting multiple sclerosis. No nonclinical studies have been provided for this application but an adequate summary of the available non-clinical information for the active substance was presented and considered sufficient. However, the Applicant should provide Environmental Risk Assessment or present data to substantiate the claim that an increase in environmental exposure of the active substance is not to be expected e.g. consumption data or PEC determination **(OC).**

From a clinical perspective, this application does not contain new data on the pharmacokinetics and pharmacodynamics as well as the efficacy and safety of the active substance; the Applicant's clinical overview on these clinical aspects based on information from published literature is considered sufficient.

The Applicant conducted 2 separate bioequivalence studies under fasting and fed conditions to demonstrate that the Test Product – Dimethyl Fumarate gastro – resistant hard capsules, 240 mg is bioequivalent to the Reference Product – Tecfidera.

Two bioequivalence studies (under fasting and fed conditions) form the pivotal basis with a single dose, randomized, open-label, two period (Study 2150) or four period (Study 2149), two-sequence, two treatment, single centre, crossover study design. Both studies design is considered adequate to evaluate the bioequivalence of this formulation and both studies were conducted in line with the respective European requirements.

The choice of the dose, sampling points, overall sampling time as well as wash-out period were adequate. The analytical method was validated. Pharmacokinetic and statistical methods applied are adequate.

The test formulation of Dimethyl fumarate met the protocol-defined criteria for bioequivalence when compared with the reference product Tecfidera. The point estimates and their 90% confidence intervals for the parameters AUC0-t, AUC0-∞, and Cmax were all contained within the protocol-defined

acceptance range of [range, e.g. 80.00 to 125.00%]. Bioequivalence of the two formulations was demonstrated.

The results of studies 2149 and 2150 with 240 mg formulation can be extrapolated to the other strength 120 mg according to conditions in the Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev.1, section 4.1.6 and *Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms* (EMA/CHMP/EWP/280/96 Rev1), section 6.1.2.2.
A biowaiver for the 120 mg strength is therefore agreed.

The dissolution testing should be repeated under acceptable conditions (MO).

From the quality point of view some other concerns need to be solved before the dossier can be recommended for approval.

5.1. Conclusions

The overall benefit /risk balance of Dimherity is currently negative.

Update following the withdrawal of the application as requested by the Applicant on 22 February 2022

The CHMP noted the withdrawal request letter received on 22 February 2022. It was acknowledged that the Applicant responded to the List of Outstanding Issues adopted in January, including the alignement of the dossier to the iMAA dossier of H-005955. Following the responses, the concerns listed in the List of Outstanding Issues were considered resolved and the Dimherity iMAA could have been approvable before the iMAA was withdrawn.