21 March 2024
EMA/321710/2024
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Dimethyl fumarate Neuraxpharm

International non-proprietary name: dimethyl fumarate

Procedure No. EMEA/H/C/006500/0000

Note

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

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List of abbreviations

AE	Adverse Events
ANOVA	Analysis of variance
AP	Applicant's Part (or Open Part) of a ASMF
API	Active Pharmaceutical Ingredient
ASM	Active Substance Manufacturer
ASMF	Active Substance Master File = Drug Master File
ATC	Anatomical Therapeutic Chemical
AUC	Area Under the Curve
AUC0-t	Area under the plasma concentration versus time curve from time zero to the last measurable concentration
AUC_%Extrap_obs	Residual area in percentage
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
CI	Confidence Intervals
Cmax	Maximum plasma concentration
CNS	Central Nervous System
CRS	Chemical Reference Substance (official standard)
CV	Coefficient of Variation
DMF	Dimethyl fumarate
DSC	Differential Scanning Calorimetry
EMA	European Medicines Agency
EP	European Pharmacopoeia
ERA	Environmental Risk Assessment
FT-IR	Fourier Transform infrared spectroscopy
GC	Gas chromatography
GMR	Geometric least square mean ratio
HDPE	High Density Polyethylene
HPLC	High performance liquid chromatography
IPC	In-process control
IR	Infrared
LC-MS/MS	Liquid Chromatography with tandem Mass Spectrophotometry

LLOQ	Lower Limit of Quantitation
LOD	Limit of Detection
LOQ	Limit of Quantitation
MMF	Monomethyl fumarate
MS	Mass Spectrometry (Quality part)
ND	Not detected
NMR	Nuclear Magnetic Resonance
Nrf2	Nuclear factor-like-2
OOS	Out of Specifications
PD	Pharmacodynamic
PE	Polyethylene
Ph.Eur.	European Pharmacopoeia
PK	Pharmacokinetic
PL	Package Leaflet
PVC	Poly vinyl chloride
QC	Quality Control
QOS	Quality Overall Summary
RH	Relative Humidity
RMP	Risk Management Plan
RP	Restricted Part (or Closed Part) of a ASMF
RRMS	Relapsing-Remitting Multiple Sclerosis
SmPC	Summary of Product Characteristics
SWR	within subject standard deviation of reference product
T1/2	Elimination half-life
Tlag	Time prior to the first measurable (non-zero) concentration
Tmax	Time to reach maximum plasma concentration
UV	Ultraviolet
λz	First order rate constant associated with the terminal (log-linear) portion of the curve

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Neuraxpharm Pharmaceuticals S.L. submitted on 3 January 2024 an application for marketing authorisation to the European Medicines Agency (EMA) for Dimethyl fumarate Neuraxpharm, through the centralised procedure under Article 3 (3) of Regulation (EC) No. 726/2004– 'Generic of a Centrally authorised product'. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 14 October 2021.

The application concerns a generic medicinal product as defined in Article 10(2)(b) of Directive 2001/83/EC and refers to a reference product, as defined in Article 10 (2)(a) of Directive 2001/83/EC, for which a marketing authorisation is or has been granted in in the Union on the basis of a complete dossier in accordance with Article 8(3) of Directive 2001/83/EC.

The applicant applied for the following indication:

> Dimethyl fumarate Neuraxpharm is indicated for the treatment of adult and paediatric patients aged 13 years and older with relapsing remitting multiple sclerosis (RRMS).

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Generic application (Article 10(1) of Directive No 2001/83/EC).

The application submitted is composed of administrative information, complete quality data and a bioequivalence study with the reference medicinal product Tecfidera instead of non-clinical and clinical unless justified otherwise.

The chosen reference product is:

Medicinal product which is or has been authorised in accordance with Union provisions in force for not less than 8 years in the EEA:

- Product name, strength, pharmaceutical form: Tecfidera, 120 mg and 240 mg gastro-resistant hard capsules
- Marketing authorisation holder: Biogen Netherlands B.V.
- Date of authorisation: 30-01-2014
- Marketing authorisation granted by:
  - Union
- Marketing authorisation number: 120 mg: EU/1/13/837/001; 240 mg: 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 and 240 mg gastro-resistant hard capsules
- Marketing authorisation holder: Biogen Netherlands B.V.
- Date of authorisation: 30-01-2014
- Marketing authorisation granted by:
  - Union

- Marketing authorisation number: 120 mg: EU/1/13/837/001; 240 mg: 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, 120 mg and 240 mg gastro-resistant hard capsules
- Marketing authorisation holder: Biogen Netherlands B.V.
- 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

1.3. Information on paediatric requirements

Not applicable.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

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.

1.5. Scientific advice

The applicant did not seek Scientific advice from the CHMP.

1.6. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was:

Rapporteur: Ewa Balkowiec Iskra

The application was received by the EMA on	3 January 2024
The procedure started on	22 January 2024
The Rapporteurs first CHMP and PRAC Joint Assessment Report was circulated to all CHMP and PRAC members on	23 February 2024
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	7 March 2024
The CHMP members comments on	11 March 2024

The CHMP Rapporteur circulated the CHMP and PRAC Rapporteurs Joint updated Assessment Report to all CHMP members on	14 March 2024
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Dimethyl fumarate Neuraxpharm on	21 March 2024

2. Scientific discussion

2.1. Introduction

This application concerns a generic application according to article 10(1) of Directive 2001/83/EC for Dimethyl fumarate Neuraxpharm 120 and 240 mg hard capsules. The reference product is Tecfidera 120 mg and 240 mg hard capsules. Tecfidera was approved in Europe on 30 January 2014 (EU/1/13/837/001-003, Biogen Netherlands B.V.).

The proposed indication for Dimethyl fumarate Neuraxpharm is the same as for the reference product Tecfidera: Dimethyl fumarate Neuraxpharm *is indicated for the treatment of adult and paediatric patients aged 13 years and older with relapsing remitting multiple sclerosis (RRMS)*.

To support the application the applicant submitted two pivotal bioequivalence studies between Dimethyl fumarate Neuraxpharm 240 mg hard capsules and reference product Tecfidera 240 mg hard capsules in order to assess the bioequivalence between the products. A biowaiver for the additional 120 mg strength was requested.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as hard gastro-resistant 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 per cent, talc, triethyl citrate, polysorbate 80, and glycerol monostearate 40-55;

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 as described in section 6.5 of the SmPC.

2.2.2. Active substance

2.2.2.1. General Information

The chemical name of the active substance is dimethyl (E)-but-2-enedioate corresponding to the molecular formula $C_6H_8O_4$. It has a relative molecular weight of 144.13 and the following structure:

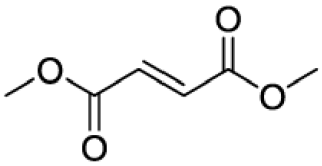

Figure 1: Active substance structure

The chemical structure elucidated by a combination of termal analysis by DSC, UV study, FT-IR study, NMR Study (^{1}HNMR and ^{13}CNMR), mass spectra, X-ray powder diffraction, and elemental analysis.

The active substance is a non-hygroscopic, white to off-white powder, highly soluble in buffer solutions of pH 1.2, 4.5 and 6.8 at room temperature (25 °C).

Two geometric isomers/stereoisomers *Cis* and *Trans* exist. *Trans* isomer is thermodynamically stable and is the desired isomer. Undesired isomer (cis-isomer) is not possible in the active substance.

Polymorphism has not been observed for active substance.

Manufacture, characterisation and process controls

The active substance is manufactured by one manufacturer.

Detailed information on the manufacturing of the active substance has been provided in the restricted part of the ASMF and it was considered satisfactory.

Dimethyl fumarate is synthesized in 1 main step using well-defined starting material with acceptable specifications.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for starting material and reagents have been presented.

A discussion concerning possible organic and inorganic impurities, potential genotoxic impurities, nitrosamine impurities, elemental impurities and residual solvents has been presented. Further details concerning potential impurities, control strategy, supporting analytical data and analytical methods validation reports were provided in the restricted part (RP) of the ASMF documentation. Impurities originating from starting material, or from solvents are provided in the RP ASMF.

The characterisations of the active substance and its impurities are in accordance with the EU guidelines.

Potential and actual impurities were well-discussed with regards to their origin and characterised.

Specification

The active substance specification includes tests for appearance (visual), 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 two commercial scale batches of the active substance are provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data from 7 commercial scale batches of the non-micronised active substance from the proposed manufacturer stored in the intended commercial package for up to 60 months under long term conditions (25 ºC / 60% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided.

Stability data from 3 commercial scale batches of the micronised active substance from the proposed manufacturer stored in the intended commercial package for up to 60 months under long term conditions (5 ºC) and for up to 6 months under accelerated conditions (25 ºC / 60% RH) according to the ICH guidelines were provided.

The following parameters were tested*:* description, identification, water*,* related substances and assay (on anhydrous basis)*.* The analytical methods used were the same as for release and were stability indicating.

The stability results indicate that the unmicronised and micronised 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 unmicronised active substance and 36 months for micronised material in the proposed container.

2.2.3. Finished medicinal product

Description of the product and Pharmaceutical development

The 120 mg strength finished product is presented as a hard gelatin capsules, length: 19 mm, with white body and light-green cap, with overprint on the body 120 mg.

The 240 mg strength finished product is presented as a hard gelatin capsules, length: 23 mm, light-green, with overprint on the body 240 mg.

The primary goal of the development was to formulate a finished product that could be easily manufactured, that would be stable in the proposed packaging and that would be essentially similar to the reference medicinal product Tecfidera. The reference product is a multiparticulate dosage form – hard gelatin capsule filled with enteric coated minitablets. It was decided that the developed product should have similar (multiparticulate) design, however the form of the capsule filling will be different

from the reference medicinal product. A product in form of hard gelatin capsules filled with granules coated with gastroresistant polymers has been developed.

Compatibility tests of the active substance with the prosed excipients were performed in order to detect potential incompatibilities, which could be observed in final formulation. No remarkable interactions between dimethyl fumarate and the excipients selected for the final formulation were found.

The selection of excipients was made mainly based on the composition of the reference medicinal product as well as based on the development experiments. All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC.

Two pivotal bioequivalence studies with the 240 mg strength under fast and fed conditions have been carried out between the generic and the reference medicinal product. The results of the studies confirmed bioequivalence of the developed generic product with the reference product.

A detailed description of the manufacturing process development has been provided.

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.

Manufacture of the product and process controls

The finished product is manufactured by two manufacturing sites.

The manufacturing process consists of 18 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.

Product specification

The finished product release and shelf-life specifications include appropriate tests for this kind of dosage form: appearance (visual), appearance of capsule content (visual), capsule average net weight (weight), uniformity of dosage units (Ph. Eur.), identification of titanium dioxide (chemical identification), identification of yellow iron oxide (E172) (chemical identification), identification of brilliant blue FCF –FD&C Blue 1 (E133) (UV/VIS), water content in filling of capsule (KF), identification of dimethyl fumarate (HPLC, GC), related substances (HPLC), assay of dimethyl fumarate (HPLC), content of 2-propanol (GC), dissolution test, microbiological tests (Ph. Eur.), total aerobic microbial count (TAMC) (Ph. Eur.), total yeast / moulds count (TYMC) (Ph. Eur.), and escherichia coli (Ph. Eur.).

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. Based on the risk assessment it can be concluded that it is not necessary to include any elemental impurity controls.

A risk evaluation concerning the presence of nitrosamine impurities in the finished has been performed considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the information provided it is accepted that no risk was identified on the possible presence of nitrosamine impurities in the active substance or the related finished product. Therefore, no additional control is needed.

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 for 17 commercial band pilot batches per strength manufactured by the two manufacturing sites confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data from 19 commercial pilot and commercial batches of finished product stored for up to 36 months under long term conditions (25 ºC / 60% RH), stored up to 12 months under intermediate conditions (30 ºC / 65% RH) for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The batches of medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for appearance, appearance of capsule content, capsules average net weight, water content in filling of capsules, related substances, assay, dissolution, total aerobic microbial count (TAMC), total yeasts/ moulds count (TYMC) and Escherichia coli. The analytical procedures used are stability indicating.

No significant changes have been observed under long term conditions.

In addition, one batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. The finished product is considered as photo-stable. The product does not require any special protection form light.

Holding time studies were performed for the finished product to establish the in-bulk storage period before packaging in the immediate package. The batches were packed in PET-Al-PE multilayer bag and in PE bag and stored for up to 6 months under long term conditions (25 ºC / 60% RH). Based on the available data the total holding time should not take more than 6 months and is calculated from the first day of combining active ingredient with other ingredients according to CPMP/QWP/072/96 Guideline.

Based on available stability data, the proposed shelf-life of 3 years and the storage conditions "Do not store above 30 °C" as stated in the SmPC (section 6.3 and 6.4) are acceptable.

Adventitious agents

The hard capsules used in the product manufacturing contain gelatine obtained from bovine sources. Valid TSE CEP from the suppliers of the gelatine used in the manufacture is provided.

2.2.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner.

The biowaiver for the 120 mg strength is in line with the Guideline on the Investigation of Bioequivalence and thus accepted. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

The applicant has applied QbD principles in the development of the active substance and/or finished product and their manufacturing process. However, no design spaces were claimed for the manufacturing process of the active substance, nor for the finished product.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.2.6. Recommendation(s) for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

The non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. 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. The non-clinical aspects of the SmPC are in line with the SmPC of the reference product. The impurity profile has been discussed and was considered acceptable.

Therefore, the CHMP agreed that no further non-clinical studies are required.

2.3.2. Ecotoxicity/environmental risk assessment

An Environmental Risk Assessment (ERA) has been submitted.

According to the Guideline on the environmental risk assessment of medicinal products for human use (EMEA/CHMP/SWP/4447/00 Rev. 1), the applicant estimated the PEC*surfacewater* for Dimethyl Fumarate at 2.4 µg /L and phase II environmental effect analysis was performed.

Substance (INN/Invented Name): dimethyl fumarate					
CAS-number (if available):					
PBT screening		Result			**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107 or …	0.82			Potential PBT (Y/**N**)
PBT-assessment					
Parameter	**Result relevant for conclusion**				**Conclusion**
Bioaccumulation	log K_{ow}				B/not B
	BCF				B/not B
Persistence	DT50 or ready biodegradability				P/not P
Toxicity	NOEC or CMR				T/not T
PBT-statement:	The compound is not considered as PBT nor vPvB				
Phase I					
Calculation	**Value**	**Unit**			**Conclusion**
PEC $_{surfacewater}$, default or refined (e.g. prevalence, literature)	2.4	µg/L			> 0.01 threshold (**Y**/N)
Other concerns (e.g. chemical class)					(Y/N)
Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Adsorption-Desorption	OECD 106 or …	K_{oc} =			List all values
Ready Biodegradability Test	OECD 301				
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	$DT_{50, water}$ = $DT_{50, sediment}$ = $DT_{50, whole\ system}$ = % shifting to sediment =			Not required if readily biodegradable
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*Species*	OECD 201	NOEC	37	µg/L	Species: *Pseudokirchenella subcapitata*
Daphnia sp. Reproduction Test	OECD 211	NOEC	55.9	µg/L	Species *Daphnia magna*
Fish, Early Life Stage Toxicity Test/*Species*	OECD 210	NOEC	45.7	µg/L	Species *Pimephales promelas*
Activated Sludge, Respiration Inhibition Test	OECD 209	EC	2000	µg/L	

In addition, it is noted that the introduction of Dimethyl fumarate Neuraxpharm is unlikely to result in any significant increase in the combined sales volumes and exposure of the environment to dimethyl fumarate.

It is agreed that Dimethyl fumarate Neuraxpharm does not present a risk to the environment.

2.3.3. Discussion on non-clinical aspects

Pharmacodynamic (PD), PK and toxicological properties of dimethyl fumarate are well known. No new non-clinical studies were submitted by the Applicant and they were not needed.

The Applicant submitted an ERA. Based on the phase I results of a $PEC_{surfacewater}$ of dimethyl fumarate being higher than 0.01- the threshold for which it is assumed that the medicinal product is unlikely to represent a risk for the environment following its prescribed usage in patients if no other

environmental concerns are apparent- a phase II assessment was conducted by the Applicant. In this phase II assessment, the PEC $_{surfacewater}$ / $PNEC_{surfacewater}$ ratio for dimethyl fumarate was below 1. It is agreed that as per EMA guideline (EMEA/CHMP/SWP/4447/00 corr2) if the ratio PEC $_{surfacewater}$ / $PNEC_{surfacewater}$ for the drug substance is below 1, further testing in the aquatic compartment is not considered necessary and it can be concluded that the drug substance and/or its metabolites are unlikely to represent a risk to the aquatic environment. Further, logKow of dimethyl fumarate does not exceed 4.5 and then, it can also be agreed that dimethyl fumarate is not a Persistent, Bioaccumulative and Toxic substance. Based on these results, the Applicant justified that the Dimethyl fumarate Neuraxpharm is unlikely to represent a risk for the environment following its prescribed usage in patients.

Non-clinical sections of the SmPC are in line with the reference product SmPC.

2.3.4. Conclusion on the non-clinical aspects

The CHMP considers the non-clinical aspects adequate to support this application.

2.4. Clinical aspects

2.4.1. Introduction

This application is for Dimethyl fumarate Neuraxpharm 120 mg and 240 mg gastro-resistant hard capsules.

To support the marketing authorisation application the applicant conducted two pivotal bioequivalence studies [2149 and 2150] with a single-dose, randomized, open-label, two-way, crossover design under fasting (study 2149) and fed (study 2150) conditions.
For the clinical assessment the Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98), the 'Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms' (EMA/CHMP/EWP/280/96 Rev1), the 'Guideline on quality of oral modified release products' (EMA/CHMP/QWP/428693/2013) and the EMA dimethyl fumarate gastro-resistant capsules 120 mg and 240 mg product-specific bioequivalence guidance (EMA/CHMP/421315/2017) are of particular relevance. As the bioequivalence has been demonstrated for 240 mg strength, the 'Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms' requires that other strength's composition is proportional, the formulations contain identical beads or pellets (and these are produced by the same manufacturing process) and the dissolution profiles are similar in order to exempt the other strengths from BE study.

The applicant provided a clinical overview outlining the pharmacokinetics and pharmacodynamics as well as efficacy and safety of [active substance] based on published literature. The SmPC is in line with the SmPC of the reference product.

GCP aspect

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Exemption

A biowaiver is applied for the strength of 120 mg gastro-resistant hard capsules, based on the bioequivalence studies for Dimethyl fumarate 240 mg gastro-resistant hard capsules with the

Reference product Tecfidera 240 mg gastro-resistant hard capsules (Biogen Manufacturing ApS., Denmark).
According to the Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1/ Corr ** the Applicant justifies biowaiver by the following arguments:
- the pharmaceutical products are manufactured by the same process and by the same manufacturer,
- qualitative composition of the different strengths is the same (data presented in Table 1),
- quantitative composition of the different strengths is proportional (data presented in Table 1),
- *in vitro* dissolution profiles confirmed the similarity between strength used in the bioequivalence study and the additional strength (data presented in Table 2),
- linear pharmacokinetics of the active substance was confirmed.
Thus, the similarity of the dissolution profiles was shown and bioequivalence studies for additional 120 mg strength are not required.
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.

- **Tabular overview of clinical studies**

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.

Type of Study	Bioequivalence (BE) - ***fasting conditions***
Study Identifier	study no. 2149
Objective(s) of the Study	To evaluate and compare bioavailability of the test product (Dimethyl Fumarate 240 mg gastro-resistant hard capsules, Polpharma S.A.) and reference (Tecfidera 240 mg gastro-resistant hard capsules, Biogen Idec Ltd.), and therefore to assess the bioequivalence of two different formulations of dimethyl fumarate after a single oral dose administration in healthy subjects under fasting conditions.
Study Design and Type of Control	Single-Dose, Randomized, Open-Label, Four-Way, Fully Replicate, Pivotal, Bioequivalence Study in Healthy Male and Non-Pregnant Female Volunteers under Fasting Conditions
Test Product(s); Dosage Regimen; Route of Administration	***Dimethyl Fumarate, 240 mg****, gastro-resistant hard capsules* (test product, Polpharma S.A.) and ***Tecfidera, 240 mg*** *gastro-resistant, hard capsules* (reference product, Biogen Mfg. ApS, purchased in DK); One capsule of the Test or Reference products was administered orally to volunteers during each study period. Each capsule was taken concomitantly with approximately 240 mL of water
Healthy Subjects or Diagnosis of Patients	Healthy, males and females (non-pregnant), aged ≥ 18
Duration of Treatment	25/06/2017 - 08/07/2017
Study Status; Type of Report	Complete

Type of Study	Bioequivalence (BE) - ***fed conditions***
Study Identifier	study no. 2150
Objective(s) of the Study	To evaluate and compare bioavailability of the test product (Dimethyl Fumarate 240 mg gastro-resistant hard capsules, Polpharma S.A.) and reference (Tecfidera 240 mg gastro-resistant hard capsules, Biogen Idec Ltd.), and therefore to assess the bioequivalence of two different formulations of dimethyl fumarate after a single oral dose administration in healthy subjects under fed conditions.
Study Design and Type of Control	Single-Dose, Randomized, Open-Label, Four-Way, Fully Replicate, Pivotal, Bioequivalence Study in Healthy Male and Non-Pregnant Female Volunteers under Fed Conditions
Test Product(s); Dosage Regimen; Route of Administration	***Dimethyl Fumarate, 240 mg****, gastro-resistant hard capsules* (test product, Polpharma S.A.) and ***Tecfidera, 240 mg*** *gastro-resistant, hard capsules* (reference product, Biogen Mfg. ApS, purchased in DK); One capsule of the Test or Reference products was administered orally to volunteers during each study period. Each capsule was taken concomitantly with approximately 240 mL of water
Healthy Subjects or Diagnosis of Patients	Healthy, males and females (non-pregnant), aged ≥ 18
Duration of Treatment	25/08/2017 - 30/08/2017
Study Status; Type of Report	Complete

2.4.2. Clinical pharmacology

2.4.2.1. Pharmacokinetics

Study 2149

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

Methods

- **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) or Treatment B (1 x 240 mg Tecfidera gastro-resistant hard capsules).
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 at least 3 days.

- **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**

An analytical method, using a high-performance liquid chromatography with tandem mass spectrometry (LC-MS/MS), was developed for analysing the metabolite monomethyl fumarate in human plasma.

Validation report MoFuV4 - analysis of monomethyl fumarate in human plasma using high performance liquid chromatography with tandem mass spectrometry (LC-MS/MS) (Studies 2149 and 2150)

The validation report for the analytical method was provided. The acceptance criteria were met for the relevant parameters such as specificity, sensitivity, precision, accuracy, linearity, matrix effect, and dilution integrity.
The validation method is performed according to the procedure recommended with the guidelines. No questions arise according to the documentation supplied.

Bioanalysis - determination of monomethyl fumarate in human plasma using high performance liquid chromatography with tandem mass spectrometry (LC-MS/MS) (validation protocol MoFuV4) was performed to support clinical study - Study Number: 2149 (RDW431/0085/5).

Bioanalysis is acceptable.

- **Pharmacokinetic variables**

The following parameters were calculated:

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: Maximal observed plasma concentration.

Residual Area or AUC(res%) Extrapolated area under the curve, (AUCinf - AUCt)/AUCinf.

T1/2: Terminal elimination half-life, estimated as ln(2)/λ.

Tmax: Time when the maximal plasma concentration is observed.

λ: Terminal elimination rate constant, estimated by linear regression analysis of the terminal portion of the lnconcentration vs. time plot.

- **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 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 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

- **Safety data**

A total of 102 mild AEs was experienced by the subjects after treatment with the Test product. A total of 117 mild AEs was experienced by the subjects after treatment with the Reference product.
The safety profiles of the Reference and the Test Product were comparable.

Study 2150

Title: A Single-Dose, Randomized, Open-Label, Two-Way, Crossover, Pivotal, Bioequivalence Study of Dimethyl Fumarate 240 mg Gastro-Resistant Hard Capsules (Pharmaceutical Works Polpharma S.A.) and Tecfidera® (dimethyl fumarate) 240 mg Gastro-Resistant Hard Capsules (Biogen Manufacturing ApS) 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 38 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.

Drug Concentration Measurements
Blood samples were collected from 24 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 × 240 mg Dimethyl Fumarate Polpharma gastro-resistant hard capsules) or Treatment B (1 × 240 mg Tecfidera gastro-resistant hard capsules).
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.

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

- **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).

Bioanalysis - determination of monomethyl fumarate in human plasma using high performance liquid chromatography with tandem mass spectrometry (LC-MS/MS) (validation protocol MoFuV4) was performed to support clinical study - Study Number: 2150 (RDW431/0085/6).

Bioanalysis is acceptable.

- **Pharmacokinetic variables and statistical methods**

Similar to the Study 2149 (see above).

Results

Table 3. 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)	3468.81 3545.86 (21.09)	3509.22 3601.21 (22.52)	98.85	95.62 - 102.19	
AUCinf (ng.h/mL)	3703.23 3780.10 (20.45)	3745.12 3805.26 (19.16)	98.88	95.07 - 102.85	
Cmax (ng/mL)	1372.61 1469.81 (37.04)	1528.82 1649.22 (36.72)	89.78	80.79 - 99.77	
Tmax* (h)	7.50 (5.00 - 10.50)	7.26 (4.50 - 10.63)			
Lambda** (1/h)	0.9089 (37.82)	1.1126 (40.68)			
T1/2** (h)	0.92 (50.61)	0.83 (76.47)			
AUCt/AUCinf**	0.9840 (1.14)	0.9799 (3.05)			
AUC(res%)**	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:

Table 4. 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% to 125%.

- **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.

2.4.2.2. Pharmacodynamics

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

2.4.3. Discussion on clinical aspects

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

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 studies 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.

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.

2.4.4. Conclusions on clinical aspects

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

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.

2.5. Risk Management Plan

2.5.1. 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 and herpes zoster) 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 moderate to severe renal impairment Safety profile in patients with hepatic impairment Safety profile in patients in patients with severe active GI disease Increased risk of infection in patients concomitantly taking antineoplastic or immunosuppressive therapies

2.5.2. Pharmacovigilance plan

No additional pharmacovigilance activities.

2.5.3. Risk minimisation measures

None.

2.5.4. Conclusion

The CHMP and PRAC considered that the risk management plan version 1.0 is acceptable.

2.6. Pharmacovigilance

2.6.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.6.2. 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.

2.7. Product information

2.7.1. User consultation

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Tecfidera 120 mg and 240 mg gastro-resistant hard capsules, and Atorvadypina 5 mg + 10 mg and 10 mg + 10 mg coated tablets. The bridging report submitted by the applicant has been found acceptable.

3. Benefit-risk balance

This application concerns a generic version of Dimethyl fumarate Neuraxpharm 120 mg and 240 mg gastro-resistant capsule. The reference product Tecfidera is indicated for the treatment of adult and paediatric patients aged 13 years and older with relapsing remitting multiple sclerosis (RRMS). 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.

Based on the submitted ERA, the Dimethyl fumarate Neuraxpharm is unlikely to represent a risk for the environment following its prescribed usage in patients.

From a clinical perspective, this application does not contain new data on 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.
A benefit/risk ratio comparable to the reference product can therefore be concluded.

The CHMP, having considered the data submitted in the application and available on the chosen reference medicinal product, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Dimethyl fumarate Neuraxpharm is favourable in the following indication:

Dimethyl fumarate Neuraxpharm is indicated for the treatment of adult and paediatric patients aged 13 years and older with relapsing remitting multiple sclerosis (RRMS).

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

- ***Periodic Safety Update Reports***

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.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.