COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Dimethylfumaraat MSN 120 mg and 240 mg, gastro-resistant hard capsules (dimethyl fumarate)

NL/H/5715/001-002/DC

Date: 30 December 2025

This module reflects the scientific discussion for the approval of Dimethylfumaraat MSN 120 mg and 240 mg, gastro-resistant hard capsules. The procedure was finalised on 11 April 2024. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
EMA	European Medicines Agency
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
QC	Quality Control
RH	Relative Humidity
RMP	Risk Management Plan
RMS	Reference Member State
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Dimethylfumaraat MSN 120 mg and 240 mg, gastro-resistant hard capsules, from Vivanta Generics s.r.o.

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

A comprehensive description of the up-to-date indications and posology is given in the SmPC.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC, which concerns a generic application.

In this decentralised procedure, essential similarity is proven between the new product and the innovator product Tecfidera 120 and 240 mg gastro-resistant hard capsules, which has been registered by Biogen Netherlands B.V. in the EEA via a centralised procedure (EU/1/13/837) since 30 January 2014.

The concerned member states (CMS) involved in this procedure were Bulgaria, Croatia, Czechia, Estonia, Hungary, Latvia, Lithuania, Poland, Romania, Slovakia and Slovenia.

II. QUALITY ASPECTS

II.1 Introduction

Dimethylfumaraat MSN is a gastro-resistant hard capsule. Each capsule contains as active substance 120 mg or 240 mg of dimethyl fumarate, depending on the strength.

The capsules come in two strengths, which can be distinguished by colour and printing text:

- The 120 mg capsules have a green opaque cap imprinted “M” along with band in black ink and white opaque body imprinted "120 mg" in black ink, containing white to off-white coloured enteric-coated microtablets.
- The 240 mg capsules have a green opaque cap imprinted “M” along with band in black ink and green opaque body imprinted "240 mg" in black ink, containing white to off-white coloured enteric-coated microtablets.

The excipients are:
Capsule content (enteric-coated microtablets) - microcrystalline cellulose, (E460), croscarmellose sodium, colloidal hydrated silica, magnesium stearate (E470b), methacrylic acid methyl methacrylate copolymer (1:1) (contains sodium laurilsulfate), methacrylic acid - ethyl acrylate copolymer (1:1) dispersion 30% (contains sodium laurilsulfate and polysorbate 80), triethyl citrate (E1505) and talc (E553b).

Capsule shell – gelatin, purified water, titanium dioxide (E171), FD&C blue 1 (E133), iron oxide black (E172) and iron oxide yellow (E172).
Printing ink - shellac (E904), potassium hydroxide (E525) and iron oxide black (E172).

The two capsules are dose proportional.

The gastro-resistant hard capsules are packed in polyvinyl chloride/ polyethylene/ polyvinylidene chloride – aluminium (PVC/PE/PVdC-Alu) blisters.

II.2 Drug Substance

The active substance is dimethyl fumarate, an established active substance not described in the European Pharmacopoeia (Ph.Eur.). The active substance is an white to off-white colour powder and slightly soluble in water. Dimethyl fumarate is a trans-isomer. The other isomer, the cis-isomer (dimethyl maleate), is controlled in the drug substance specification. For this product, polymorphic form I is consistently produced.

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacturing process
The manufacturing process is a simple one-step process. Adequate specifications have been adopted for starting materials, solvents and reagents. The active substance has been adequately characterised and the manufacturing process is described in sufficient detail. The solvents are adequately controlled in the active substance. The control strategy for potentially genotoxic impurities is acceptable.

Quality control of drug substance
The active substance specification is considered adequate to control the quality. Batch analytical data demonstrating compliance with this specification have been provided for three batches.

Stability of drug substance
The active substance is stable for five years when stored under the stated conditions. A re-test period of 60 months is acceptable in combination with the statement that the substance will be tested prior to use in the drug product manufacturing process (due to absence of stability data for the test parameter of Particle Size Distribution).

II.3 Medicinal Product

Pharmaceutical development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The choice of excipients is in principle justified and their functions are explained. The QC dissolution method has been adequately justified. The *in vitro* dissolution studies complementary to the BE studies conducted with paddle operated at 100 rpm are acceptable and include a sufficient number of points at buffer stage to allow comparison of profiles, which are considered sufficiently comparable. The requested biowaiver for the addition of the 120 mg strength is acceptable. *In vitro* alcohol dose dumping studies have been conducted; no significant difference is present between test and reference product with respect to the effect of alcohol on the dissolution profile. The same SmPC warning on consumption of alcohol as for the reference product is acceptable.

Manufacturing process

The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for three batches of each strength at full commercial scale, in accordance with the relevant European guidelines.

Control of excipients

The excipients comply with the Ph.Eur., NF or in-house requirements. These specifications are acceptable, including the additional in-house tests for the copolymers.

Quality control of drug product

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for description, identification, average mass of capsule, filled mini tablet average mass, uniformity of dosage units, water determination, disintegration time, dissolution, assay, related substances, dimer impurity, residual solvents and microbial enumeration. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. An adequate nitrosamines risk evaluation report has been provided. No risk for presence of nitrosamines in the drug product was identified.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data three batches of each strength from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product have been provided from at least three batches of each strength, stored at 25°C/ 60% RH (48 months) and 40°C/75% RH (6 months) in accordance with applicable European guidelines. Photostability has been investigated in accordance with ICH Q1B and the drug product was found to be photostable. On basis of the data submitted, a shelf life was granted of three years. No specific storage conditions needed to be included in the SmPC or on the label.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

Scientific data and/or certificates of suitability issued by the EDQM for gelatin have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Dimethylfumaraat MSN has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Dimethylfumaraat MSN is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment was therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a generic formulation of Tecfidera which is available on the European market. Reference was made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which was 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. Therefore, the member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Dimethyl fumarate is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The member states agreed that no further clinical studies are required, besides two bioequivalence studies, which are discussed below. In addition, a biowaiver for the lower 120 mg strength was requested.

IV.2 Pharmacokinetics

The MAH conducted two bioequivalence studies in which the pharmacokinetic profile of the test product Dimethylfumaraat MSN 240 mg, gastro-resistant hard capsules (Vivanta Generics s.r.o., Czechia) was compared with the pharmacokinetic profile of the reference product Tecfidera 240 mg gastro-resistant hard capsules (Biogen Netherlands B.V., the Netherlands).

The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution study results and composition. The formula and preparation of the bioequivalence batch was identical to the formula proposed for marketing.

Biowaiver

The following general requirements for a waiver for the 120 mg strength were met, according to the EMA Bioequivalence guideline:

a. the pharmaceutical products are manufactured by the same manufacturing process,
b. the qualitative composition of the different strengths is the same,
c. the composition of the strengths are quantitatively proportional, i.e. the ratio between the amount of each excipient to the amount of active substance(s) is the same for all strengths (for immediate release products coating components, capsule shell, colour agents and flavours are not required to follow this rule),
d. appropriate *in vitro* dissolution data confirm the adequacy of waiving additional *in vivo* bioequivalence testing.

The comparison of dissolution profiles between the two strengths has been done in two media (pH 1.2 for two hours, followed by pH 6.8, and pH 4.5 for two hours followed by pH 6.8), and sufficient time points at buffer stage have been included. The calculated f_2 similarity factor values were within criteria (>50%). An f_2 value between 50 and 100% suggests that the two dissolution profiles are similar.

Bioequivalence studies

Study 1 (013-BE-2021): Dimethyl fumarate 240 mg under fasted conditions

Design

An open label, balanced, single-dose, randomised, two-period, two-treatment, two-sequence, two way crossover bioequivalence study was carried out under fasted conditions in 72 healthy subjects, aged 21-42 years. Each subject received a single dose (240 mg) of one of the two dimethyl fumarate formulations. After an overnight fast of at least 8 hours and 30 minutes before investigational drug product administration, one aspirin tablet (Ecosprin gastro-resistant 75 mg tablet) was co-administered with 100 ml water. After that, a single dose of the test formulation was orally administered with 240 ml water. There were two dosing periods, separated by a washout period of two days. The subjects received test product once and reference product once by the end of the study.

Blood samples were collected pre-dose and at 0.33, 0.67, 1, 1.33, 1.67, 2, 2.25, 2.5, 2.75, 3, 3.33, 3.67, 4, 5, 6, 7, 8, 10 and 12 hours after administration of the products.

The design of the study is acceptable.

Analytical/statistical methods
The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results
72 Subjects enrolled in the study. One subject was withdrawn from the study in period I due to an adverse event (itching all over the body). 71 Subjects were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of the active metabolite of dimethyl fumarate (monomethyl fumarate), 240 mg under fasted conditions.

Treatment N=71	**AUC_{0-t} (h.ng/mL)**	**$AUC_{0-\infty}$ (h.ng/mL)**	**C_{max} (ng/mL)**	**t_{max} (h)**
Test	3871 ± 1008	3900 ± 1011	2056 ± 655	2.75 (1.33-5.00)
Reference	3833 ± 1052	3864 ± 1048	2115 ± 785	3.00 (1.33 –6.00)
***Ratio (90% CI)**	1.01 (0.96 -1.06)	1.01 (0.96 -1.06)	0.98 (0.91 – 1.06)	--

$AUC_{0-\infty}$	Area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t}	Area under the plasma concentration-time curve from time zero to t = 12 hours
C_{max}	Maximum plasma concentration
t_{max}	Time after administration when maximum plasma concentration occurs
CI	Confidence interval

**ln-transformed values*

<u>Study 2 (014-BE-2021):</u> Dimethyl fumarate 240 mg under fed conditions
Design
An open label, balanced, single oral dose, randomised, two-period, two-treatment, two-sequence, two-way crossover bioequivalence study was carried out under fed conditions in 72 healthy subjects, aged 18-43 years. Each subject received a single dose (240 mg) of one of the two dimethyl fumarate formulations. The tablet was orally administered with 240 ml water after a fasting period of 8 hours and 30 minutes after a high-fat, high calorie breakfast (919 calories). There were two dosing periods, separated by a washout period of two days. The subjects received test product once and reference product once by the end of the study.

Blood samples were collected pre-dose and at 0.5, 1, 1.5, 2, 2.33, 2.67, 3, 3.33, 3.67, 4, 4.33, 4.67, 5, 5.33, 5.67, 6, 7, 8, 9, 10, 12 hours after administration of the products.

The design of the study is acceptable.

Dimethyl fumarate should be taken with food. For those patients who may experience flushing or gastrointestinal adverse reactions, taking dimethyl fumarate with food may improve tolerability.

Analytical/statistical methods
The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results
72 Subjects completed the study. One subject was excluded from statistical analysis due to low plasma drug concentrations. 71 Subjects were eligible for pharmacokinetic analysis.

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of the active metabolite of dimethyl fumarate (monomethyl fumarate), 240 mg under fed conditions.

Treatment N=71	**AUC_{0-t} (h.ng/mL)**	**$AUC_{0-\infty}$ (h.ng/mL)**	**C_{max} (ng/mL)**	**t_{max} (h)**
Test	4368 ± 940	4708 ± 2148	2243 ± 963	5.00 (2.00 - 9.00)
Reference	4531 ± 973	4644 ± 1022	2131 ± 995	4.67 (1.50 – 8.00)
***Ratio (90% CI)**	0.96 (0.94 -0.99)	0.99 (0.94 -1.04)	1.03 (0.95 -1.12)	--

$AUC_{0-\infty}$	Area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t}	Area under the plasma concentration-time curve from time zero to t = 12 hours
C_{max}	Maximum plasma concentration
t_{max}	Time after administration when maximum plasma concentration occurs
CI	Confidence interval

**ln-transformed values*

Conclusion on bioequivalence studies:
The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence studies Dimethylfumaraat MSN 240 mg is considered bioequivalent with Tecfidera 240 mg.

The results of the two BE studies with the 240 mg formulation (013-BE-2021 and 014-BE-2021) can be extrapolated to the 120 mg strength, according to conditions in Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1/Corr*, section 4.1.6.

The MEB has been assured that the bioequivalence study has been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

IV.3 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to

Dimethylfumaraat MSN. At the time of approval, the most recent version of the RMP was version 1.1, sign off date 17 August 2023.

Table 3. Summary table of safety concerns as approved in RMP

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 with severe active GI disease • Increased risk of infection in patients concomitantly taking antineoplastic or immunosuppressive therapies

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Tecfidera. The MAH demonstrated through two bioequivalence studies that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report making reference to Tecfidera 120 mg and 240 mg gastro-resistant hard capsules (EMEA/H/C/002601) for the content and to Rosuvastatin Vivanta 5 mg, 10 mg, 20 mg and 40 mg, film-coated tablets (NL/H/4158/001-004/DC) for the design and layout. The bridging report submitted by the MAH has been found acceptable; bridging is justified for both content and layout of the leaflet.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Dimethylfumaraat MSN 120 mg and 240 mg, gastro-resistant hard capsules have a proven chemical-pharmaceutical quality and are generic forms of Tecfidera 120 and 240 mg gastro-resistant hard capsules. Tecfidera is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Dimethylfumaraat MSN with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 11 April 2024.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
NL/H/5715/001 -002/IB/001	Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet of a generic/hybrid/biosimilar medicinal products following assessment of the same change for the reference product - Implementation of change(s) for which no new additional data are submitted by the MAH	Yes	12 March 2025	Approved	N.A.
NL/H/5715/001 -002/IB/002	Change in the manufacturing process of the finished product , including an intermediate used in the manufacture of the finished product - Other variation	No	7 July 2025	Approved	N.A.