COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

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

NL/H/5631/001-002/DC

Date: 17 December 2024

This module reflects the scientific discussion for the approval of Dimethylfumaraat Macleods 120 mg and 240 mg gastro-resistant hard capsules The procedure was finalised on 25 January 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
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 Macleods 120 mg and 240 mg gastro-resistant hard capsules, from Macleods Pharma España S.L.U.

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 mg and 240 mg gastro-resistant hard capsules, which has been registered 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 Germany, Italy and Spain.

II. QUALITY ASPECTS

II.1 Introduction

Dimethylfumaraat Macleods are gastro-resistant hard capsules. Each capsule contains as active substance 120 mg or 240 mg dimethyl fumarate. The two strengths of the gastro-resistant capsules can be distinguished by the colour of the body and imprinting and are as follows:

<u>Dimethylfumaraat Macleods 120 mg</u>
The capsules have a light green opaque cap and white opaque body with "I 65" and "120 mg" imprinted on body in black ink, containing white to off-white film-coated minitablets.

<u>Dimethylfumaraat Macleods 240 mg</u>
The capsules have a light green opaque cap and light green opaque body with "I 66" and "240 mg" imprinted on body in black ink, containing white to off-white film-coated minitablets.

The excipients are: microcrystalline cellulose (E460), croscarmellose sodium (E468), colloidal anhydrous silica (E551), magnesium stearate (E470b), methacrylic acid - ethyl acrylate copolymer (1:1) dispersion 30% (sodium laurilsulfate and polysorbate 80), triethyl citrate, talc (E553b), gelatin, titanium dioxide (E171), iron oxide yellow (E172), iron oxide black (E172), brilliant blue FCF (E133), shellac (E904) and potassium hydroxide (E525).

The two capsule strengths are dose proportional.

The gastro-resistant hard capsules are packed in white opaque polyvinyl chloride/polyethelyne/polyvinylidene chloride (PVC/PE/PVdC) blisters with aluminium foil.

II.2 DrugSubstance

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

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 consists of one-step, in which fumaric acid is reacted with methanol in an esterification reaction.Both solvents are adequately controlled in the active substance. 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 control strategy for potentially genotoxic impurities has been adequately discussed and a detailed evaluation in accordance with ICH M7 has been shown.

Quality control of drug substance

The active substance specification is considered adequate to control the quality. Additional requirements for particle size have been set by the MAH. Batch analytical data demonstrating compliance with this specification have been provided for three batches.

Stability of drug substance

Stability data on the active substance have been provided for three batches in accordance with applicable European guidelines demonstrating the stability of the active substance for five years. Based on the data submitted, a retest period could be granted of two years when stored under the stated conditions.

II.3 Medicinal Product

Pharmaceutical development

The product is an established pharmaceutical form. The development of the product has been described, the choice of excipients is justified and their functions explained. The development of the dissolution test method is adequately discussed and the discriminatory power of the

method has been demonstrated. The development is adequately described in accordance with the relevant European guidelines.

The *in vitro* dissolution studies complementary to the bioequivalence (BE) studies have been conducted in line with the EMA PKWP Q&A on gastro-resistant formulations.

Manufacturing process

The manufacturing process consists of the following steps: sifting of the dry blend ingredients, dry mixing, lubrication, compression, coating (seal coating and enteric/delayed release coating), capsule filling and packaging. The manufacturing process of modified release preparation is considered non-standard. Sufficient details of the process are included in the description.

The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for three full scale batchesin accordance with the relevant European guidelines. Capsules filling has also been adequately validated for three batches of each strength at the minimum commercial batch size.

Control of excipients

The excipients comply with their Ph.Eur., NF or in-house requirements. These specifications are acceptable.

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 net content, water, dissolution, uniformity of dosage units, residual solvents, related substances, assay and microbiological quality. 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 from eight batches (as per approved section) 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 for four batches of each strength stored at 25°C/60% RH (60 months), 30°C/65% RH (12 months) and 40°C/75% RH (6 months). Photostability studies were performed in accordance with ICH recommendations and showed that the product is stable when exposed to light. On basis of the data submitted, a shelf life was granted of five years. The labelled storage conditions are “Do not store above 30°C”.

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

Scientific data and/or certificates of suitability issued bythe EDQM for gelatinehave 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 Macleods 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 Macleods 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 the two bioequivalence studies, which are discussed below.

IV.2 Pharmacokinetics

The MAH conducted two bioequivalence studies in which the pharmacokinetic profile of the test product Dimethylfumaraat Macleods 240 mg gastro-resistant hard capsules (Macleods Pharma España S.L.U., Spain)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 are met for a biowaiver for the additional 120 mg strength, 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 should confirm the adequacy of waiving additional *in vivo* bioequivalence testing.

The dissolution was investigated according to the EMA Bioequivalence guideline (at pH 4.5 and pH 6.8 for 24 individual units). 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 study, under fasted conditions

Design

A balanced, open label, analyst blind, single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 40 healthy male subjects, aged 19-43 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 an overnight fasting period of at least 10 hours. There were two dosing periods, separated by a washout period of 7days.

Blood samples were collected pre-dose and at 0.33, 0.5, 0.67, 1, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 2.75, 3, 3.33, 3.67, 4, 4.33, 4.67, 5, 5.5, 6, 6.5, 7, 8 and 10 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

All 40subjects 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=40	AUC_{0-t} (ng.h/mL)	$AUC_{0-\infty}$ (ng.h/mL)	C_{max} (ng/mL)	t_{max} (h)
Test	4000 ± 1151	4040 ± 1152	2618 ± 965	2.13 (1.00 – 4.67)
Reference	3945 ± 870	3991 ± 867	2444 ± 604	2.64 (1.27 – 4.69)
***Ratio (90% CI)**	1.00 (0.94 – 1.05)	1.00 (0.94 – 1.05)	1.03 (0.94 – 1.13)	-

$AUC_{0-\infty}$	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 the last measurable plasma concentration / to t = 10 hours
C_{max}	Maximum plasma concentration
t_{max}	Time after administration when maximum plasma concentration occurs
CI	Confidence interval

**ln-transformed values*

Bioequivalence study, under fed conditions

Design

A balanced, open label, analyst blind, single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fed conditions in 72 healthy male subjects, aged 20-44 years. Each subject received a single dose (240 mg) of one of the two dimethyl fumarate formulations. After an overnight fasting period of at least 10 hours, the subjects received an high fat, high calorie breakfast (comprising of 800 to 1000 Kcal) 30 minutes prior to administration. The tablet was orally administered with 240 mL water. There were two dosing periods, separated by a washout period of 7 days.

Blood samples were collected pre-dose and at 0.25, 0.5, 1, 1.5, 2, 2.5, 3,3.5, 4, 4.25, 4.5, 4.75, 5, 5.25, 5.5, 5.75, 6, 6.5, 7, 7.5, 8, 9, 10, 11,12, 13, 14, 15, 16, 18, 20 and 24hours 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

One subject was withdrawn from the study in period 1 due to adverse event (nausea and episode of vomiting). Two subjects were withdrawn in period 2 due to adverse events (fever in one subject and rash and boils over facial, truck, neck, back regions associated with itching for the other subject). Three subjects withdrew due to personal reasons. 66 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=66	AUC_{0-t} (ng.h/mL)	$AUC_{0-\infty}$ (ng.h/mL)	C_{max} (ng/mL)	t_{max} (h)
Test	4131±846	4264±878	2084 ± 868	4.75 (1.50 – 10.00)
Reference	4077± 836	4292±1047	2179±900	4.75 (1.50 – 15.00)
***Ratio (90% CI)**	1.01 (0.99 – 1.04)	1.00 (0.97 – 1.03)	0.96 (0.86 – 1.07)	-

$AUC_{0-\infty}$	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 the last measurable plasma concentration / to t = 24 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 Dimethyl fumaraat Macleods 240 mg is considered bioequivalent with Tecfidera 240 mg.

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 Macleods.

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 anti-neoplastic 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 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

The package leaflet (PL) has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PL was English.

The test consisted of: a pilot test with 4 participants, followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability.The results show that the PL meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Dimethylfumaraat Macleods 120 mg and 240 mg gastro-resistant hard capsules have a proven chemical-pharmaceutical quality and are generic forms of Tecfidera 120 mg and 240 mg gastro-resistant hard capsules. Tecfiderais 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 Macleodswith the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 25 January 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/5631/001-2/IA/001	Change in the address of the marketing authorisation holder	Yes	30 August 2024	Approved	N.A.