LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Dimethyl fumarate Glenmark
(dimethyl fumarate)

SE/H/2227/01-02/DC

This module reflects the scientific discussion for the approval of Dimethyl fumarate Glenmark. The procedure was finalised on 2023-04-26. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, a marketing authorisation has been granted for Dimethyl fumarate Glenmark, 120 mg, 240 mg, Gastro-resistant capsule, hard.

The active substance is dimethyl fumarate. A comprehensive description of the indication and posology is given in the SmPC.

For recommendations to the marketing authorisation not falling under Article 21a/22a/22 of Directive 2001/83/EC and conditions to the marketing authorisation pursuant to Article 21a/22a/ 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

The application for Dimethyl fumarate Glenmark, 120 mg, 240 mg, gastro-resistant capsule, hard, is a generic application submitted according to Article 10(1) of Directive 2001/83/EC. The applicant applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and DK, FI, DE, NL, NO, ES, CZ, PL, IT, SK as concerned member states (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Tecfidera, 120 mg, gastro-resistant capsule, hard authorised in the Union since 2014, with Biogen Netherlands B.V. as marketing authorisation holder.

The reference product used in the bioequivalence studies is Tecfidera, 240 mg, gastro-resistant capsule, hard from NL with Biogen Netherlands B.V.as marketing authorisation holder.

Potential similarity with orphan medicinal products
According to the application form and a check of the Community Register of orphan medicinal products there is no medicinal product designated as an orphan medicinal product for a condition relating to the indication proposed in this application.

II. QUALITY ASPECTS

II.1 Drug Substance

The structure of the drug substance has been adequately proven and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

II.2 Medicinal Product

The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

III. NON-CLINICAL ASPECTS

Pharmacology/Pharmacokinetics/Toxicology
Pharmacodynamic, pharmacokinetic and toxicological properties of dimethyl fumarate are well known. As dimethyl fumarate is a widely used, well-known active substance, no further studies are required and the applicant provides none. Overview based on literature review is, thus, appropriate.

Environmental Risk Assessment (ERA)
Since Dimethyl fumarate Glenmark is a generic product, it will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

There are no objections to approval of Dimethyl fumarate Glenmark from a non-clinical point of view.

IV. CLINICAL ASPECTS

Pharmacokinetics
To support the marketing authorisation application the applicant has conducted two bioequivalence studies comparing Dimethyl fumarate Glenmark with the reference product Tecfidera.

Pharmacokinetic properties of the active substance
Orally administered dimethyl fumarate undergoes rapid presystemic hydrolysis by esterases and is converted to its primary metabolite, monomethyl fumarate, which is also active. Dimethyl fumarate is not quantifiable in plasma following oral administration.

Absorption: The t_{max} of monomethyl fumarate is 2 to 2.5 hours. As dimethyl fumarate gastro-resistant hard capsules contain mini tablets, which are protected by an enteric coating, absorption does not commence until they leave the stomach (generally less than 1 hour). Following 240 mg twice a day administered with food, the median peak (C_{max}) was 1.72 mg/l and overall area under the curve (AUC) exposure was 8.02 h.mg/l in subjects with multiple sclerosis.

Food does not have a clinically significant effect on exposure of dimethyl fumarate. However, dimethyl fumarate should be taken with food due to improved tolerability with respect to flushing or gastrointestinal adverse events.

Linearity: Dimethyl fumarate exposure increases in an approximately dose proportional manner with single and multiple doses in the 120 mg to 360 mg dose range studied.

Study C1B01187 (240 mg fasting)
Methods
This was a randomised, two-period, two-treatment, two-sequence crossover single-dose study conducted in 48 healthy volunteers, comparing Dimethyl fumarate 240 mg, gastro-resistant capsule, hard with Tecfidera, 240 mg, gastro-resistant capsule, hard under fasting conditions. Blood samples for concentration analysis were collected pre-dose and up to 24 hours post-dose. Plasma concentrations of the metabolite monomethyl fumarate were determined with a LC-MS/MS method.

Analysis of variance (ANOVA) was performed on the Ln-transformed data for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max}. The study was conducted between 09 September 2021 and 22 September 2021.

Results
The results from the pharmacokinetic and statistical analysis are presented in Table 1 below.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for monomethyl fumarate, n=48.

Treatment	AUC_{0-t} ng*h/ml	$AUC_{0-\infty}$ ng*h/ml	C_{max} ng/ml	t_{max} h
Test	**3400.659 ± 1151.405**	**3415.156 ± 1147.767**	**2015.835 ± 685.688**	**3.000 (1.500 - 5.017)**
Reference	**3453.455 ± 873.558**	**3630.115 ± 1270.984**	**1739.615 ± 529.317**	**3.000 (1.500 - 5.500)**
***Ratio (90% CI)**	**95.12 (88.55-102.16)**	**92.38 (84.59-100.88)**	**113.04 (103.24-123.76)**	**-**

AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
C_{max} maximum plasma concentration
t_{max} time for maximum plasma concentration

**calculated based on ln-transformed data*

For AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00%.

Study C1B01188 (240 mg fed)
Methods
This was a randomised, four-period, two-treatment, two-sequence, fully replicate, crossover single-dose study conducted in 48 healthy volunteers, comparing Dimethyl fumarate, 240 mg, gastro-resistant capsule, hard with Tecfidera, 240 mg, gastro-resistant capsule, hard under fed conditions. Blood samples for concentration analysis were collected pre-dose and up to 24 hours post-dose. Plasma concentrations of the metabolite monomethyl fumarate were determined with a LC-MS/MS method. Analysis of variance (ANOVA) was performed on the Ln-transformed data for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max}. The study was conducted between 02 September 2021 and 25 September 2021.

Results
The results from the pharmacokinetic and statistical analysis are presented in Table 2 below.

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for monomethyl fumarate, Test n=84, Reference n=84^.

Treatment	AUC_{0-t} ng*h/ml	$AUC_{0-\infty}$ ng*h/ml	C_{max} ng/ml	t_{max} h
Test	**4306.682 ± 899.229**	**4320.027 ± 897.842**	**2473.919 ± 853.910**	**5.000 (3.000 - 8.000)**
Reference	**4305.570 ± 885.251**	**4357.542 ± 899.293 (^n=83)**	**2466.051 ± 832.513**	**5.000 (2.500 - 12.000)**
***Ratio (90% CI)**	**99.64 (97.50-101.84)**	**99.00 (96.84-101.21)**	**99.33 (93.33-105.71)**	**-**

AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
C_{max} maximum plasma concentration
t_{max} time for maximum plasma concentration

**calculated based on ln-transformed data*

For AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00%.

A biowaiver was sought for the additional strength of 120 mg.

Discussion and overall conclusion
Dimethyl fumarate Glenmark is a delayed-release formulation (gastro-resistant hard capsule containing enteric-coated mini tablets). According to the product-specific bioequivalence guidance for dimethyl fumarate gastro-resistant capsule 120 mg and 240 mg (EMA/CHMP/421315/2017), a single-dose fasting study and a single-dose fed bioequivalence study in healthy subjects for the 240 mg strength are adequate for gastro-resistant multiple unit formulations.

The bioequivalence studies and the statistical evaluation were in accordance with accepted standards for bioequivalence testing, as stated in the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1) and the product-specific bioequivalence guidance for dimethyl fumarate gastro-resistant capsule 120 mg and 240 mg. The bioanalytical method was adequately validated. The bioequivalence is assessed based on the active metabolite monomethyl fumarate, which is adequate.

Absence of studies with the additional strength of 120 mg is acceptable, as all conditions for biowaiver for additional strength(s), as described in the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1) are fulfilled and since the pharmacokinetics of dimethyl fumarate is linear between 120 and 240 mg and as both test and reference products are multiple-unit formulations.

S*tudy C1B01188 (240 mg fed):* In the study, four subjects had not completed all four periods of the study and were excluded from statistical analysis as per study protocol. As requested by the RMS, the applicant provided an additional statistical analysis including data from all subjects who had received both test and reference at least once and the conclusion that bioequivalence was shown remained unchanged.

Based on the submitted bioequivalence studies, Dimethyl fumarate Glenmark is considered bioequivalent with Tecfidera.

Pharmacodynamics/Clinical efficacy/Clinical safety
No new studies on pharmacodynamics, clinical efficacy or clinical safety have been submitted. Provided that bioequivalence with the originator product is demonstrated, additional data is not necessary.

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 Dimethyl fumarate Glenmark.

Safety specification
The MAH has submitted the version 0.2 RMP dated 2022-09-15 and proposed the following summary safety concerns:

Important identified risk(s)	• Progressive Multifocal Leukoencephalopathy (PML) • Decreases in leukocyte and lymphocyte counts • Drug-induced liver injury
Important identified risk(s)	• 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 gastro-intestinal disease • Increased risk of infection in patients concomitantly taking anti-neoplastic or immunosuppressive therapies

Assessor's comments: The summary of safety concerns is in line with the summary of safety concerns for the reference product Tecfidera RMP v. 14.0. The proposed summary of safety concerns is endorsed.

Pharmacovigilance Plan
Routine pharmacovigilance is suggested and in accordance with the originator the applicant has proposed questionnaires, included in Annex 4, concerning PML, decreases in leukocyte and lymphocyte counts, drug-induced liver injury, serious and opportunistic infections (other than PML and herpes zoster), malignancies, which is acknowledged. No additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Risk minimisation measures
Routine risk minimisation is suggested and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

Summary of the RMP
The submitted Risk Management Plan, version 0.2 signed 2022-09-15 is considered acceptable.

The 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 RMS;
- 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.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

V. USER CONSULTATION

The package leaflet 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 results show that the package leaflet 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

The quality of the generic product, Dimethyl fumarate Glenmark, is found adequate. There are no objections to approval of Dimethyl fumarate Glenmark, from a non-clinical and clinical point of view. Bioequivalence between the test and reference product has been adequately demonstrated. The product information is acceptable. The benefit/risk is considered positive, and the application is therefore recommended for approval.

List of recommendations not falling under Article 21a/22a/22 of Directive 2001/83/EC in case of a positive benefit risk assessment

N/A

List of conditions pursuant to Article 21a/22a or 22 of Directive 2001/83/EC

N/A

VII. APPROVAL

The decentralised procedure for Dimethyl fumarate Glenmark, 120 mg, 240 mg, Gastro-resistant capsule, hard was positively finalised on 2023-04-26.

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Public Assessment Report – Update

Procedure number*	Scope	Product Information affected (Yes/No)	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)

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