LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Zeimem
(dimethyl fumarate)

SE/H/2488/01-02/DC

This module reflects the scientific discussion for the approval of Zeimem. The procedure was finalised on 2025-02-12. 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 Zeimem, 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 Zeimem, 120 mg and 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 the following concerned member states (CMS):

SE/H/2488/01-02/DC: RO

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.

Potential similarity with orphan medicinal products
N/A

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, nor does the applicant provide any. Overview based on literature review is, thus, appropriate.

Environmental Risk Assessment (ERA)
Since Zeimem 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 Zeimem from a non-clinical point of view.

IV. CLINICAL ASPECTS

Pharmacokinetics
To support the marketing authorisation application the applicant has conducted two bioequivalence studies (fasted and fed) comparing Zeimem 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 of dimethyl fumarate. Therefore, all pharmacokinetic analyses related to dimethyl fumarate were performed with plasma monomethyl fumarate concentrations.

Absorption: The tmax of monomethyl fumarate is 2 to 2.5 hours. As dimethyl fumarate gastro-resistant hard capsules contain microtablets, which are protected by an enteric coating, absorption does not commence until they leave the stomach (generally less than 1 hour).

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.

Elimination: The terminal half-life of monomethyl fumarate is short (approximately 1 hour) and no circulating monomethyl fumarate is present at 24 hours in the majority of individuals.

Study DIM07821(fasted)
Methods
This was a single-dose, two-way crossover study conducted in 48 healthy volunteers, comparing Zeimem, 240 mg, gastro-resistant hard capsules with Tecfidera, 240 mg, gastro-resistant hard capsule under fasting conditions. Aspirin was administered orally prior to administration of dimethyl fumarate. Blood samples for concentration analysis were collected pre-dose and up to 12 hours post-dose. Plasma concentrations of the main active metabolite monomethyl fumarate were determined with an UHPLC/MS/MS method. Analysis of variance (ANOVA) was performed on the log-transformed data for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max}. The study was conducted between 25th April 2023 and 11th May 2023.

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

Treatment	AUC_{0-t} ng*h/ml	$AUC_{0-\infty}$ ng*h/ml	C_{max} ng/ml	t_{max} h
Test 1 n=48	**4323 ± 1021**	**4347 ± 1020**	**2572 ± 897**	**1.75 (1.00-4.50)**
Test 2 n=46	**4107 ± 1078**	**4132 ± 1077**	**2405 ± 1110**	**2.25 (1.00-4.50)**
Reference 1 n=48	**3851 ± 1015**	**3876 ± 1014**	**2286 ± 804**	**2.88 (1.50-5.00)**
Reference 2 n=45	**3807 ± 924**	**3831 ± 922**	**2242 ± 696**	**3.00 (2.00-4.75)**
***Ratio (90% CI)**	**110.54 (107.04 - 114.15)**	**110.45 (106.99-114.02)**	**108.11 (100.48 - 116.33)**	**-**

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 DIM07921 (fed)
Methods
This was a single-dose, two-way crossover study conducted in 48 healthy volunteers, comparing Zeimem, 240 mg, gastro-resistant hard capsules with Tecfidera, 240 mg, gastro-resistant hard capsule under fed conditions. Blood samples for concentration analysis were collected pre-dose and up to 18 hours post-dose. Plasma concentrations of the main active metabolite monomethyl fumarate were determined with an UHPLC/MS/MS method. Analysis of variance (ANOVA) was performed on the log-transformed data for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max}. The study was conducted between 13th April 2023 and 29th April 2023.

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

Treatment	AUC_{0-t} ng*h/ml	$AUC_{0-\infty}$ ng*h/ml	C_{max} ng/ml	t_{max} h
Test 1	**3543 ± 929**	**3511 ± 851**	**1653 ± 727**	**4.50 (2.33-14.00)**
Test 2	**3495 ± 919**	**3574 ± 1029**	**1663 ± 705**	**4.67 (1.50-14.00)**
Reference 1	**3776 ± 851**	**3881 ± 859**	**2102 ± 1018**	**5.33 (2.33-14.00)**
Reference 2	**3846 ± 1039**	**3868 ± 1024**	**2046 ± 972**	**5.17 (2.33-14.00)**
***Ratio (90% CI)**	**92.28 (89.82 - 94.82) n=96**	**90.89 (88.59-93.26) n=90****	**82.27 (*75.30* - 89.90) n=96**	**-**

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*
***A few subjects did not have enough data points to calculate extrapolated AUC and $AUC_{0-\infty}$.*

For AUC_{0-t} and $AUC_{0-\infty}$ the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00%. The lower limit of the 90% confidence interval for C_{max} fell outside the conventional acceptance range but was within the widened acceptance limits of 70.70-141.44%, which was based on calculated intra-subject variability for C_{max} for the reference product which was greater than 30%, (48.09%).

The applicant has pre-specified in the study protocol that they wish to use widened acceptance limits for $_{Cmax}$ and the replicate study design allows for calculation of intra-subject variability for the reference product. The applicant provided a clinical justification that the wider difference in C_{max} is clinically irrelevant. The applicant showed results of a statistical analysis for both reference periods, which confirm that no outliers were observed based on the widely accepted criterion defining outliers as having a studentized residual > 3. As requested, detailed results were provided.

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

Discussion and overall conclusion
The bioequivalence studies and its 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/Corr) and the Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms (EMA/CPMP/EWP/280/96 Corr 1). The metabolite monomethyl fumarate was determined in plasma, in line with the product-specific bioequivalence guidance for dimethyl fumarate (EMA/CHMP/421315/2017). Administration of Aspirin in order to reduce flushing in the fasted study is also in line with the recommendation in the product-specific bioequivalence guidance. The bioanalytical methods were adequately validated. The bioequivalence is assessed based on the active metabolite monomethyl fumarate, which is adequate.

The results of studies DIM07821(fasted) and DIM07921(fed) 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/Corr **, section 4.1.6, Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms (EMA/CPMP/EWP/280/96

Corr 1) and in line with the product-specific bioequivalence guidance for dimethyl fumarate gastro-resistant capsules (EMA/CHMP/421315/2017).

Based on the submitted bioequivalence studies, Zeimem 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 Zeimem.

Part II Safety specification
The MAH has submitted the version 0.1 RMP dated 19-Sep-2023 and proposed the following summary safety concerns:

Summary of safety concerns	
Important identified risks	• 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 nehrotoxic 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

Assessor´s comment: Having considered the data in the safety specification the assessor agrees that the safety concerns listed by the MAH are appropriate. It is in line with the RMP of the reference product.

Part III Pharmacovigilance Plan
Routine pharmacovigilance is suggested and in accordance with the originator the applicant has proposed data collection forms concerning PML, drug-induced liver injury, serious and opportunistic infections (other than PML and herpes zoster), malignancies, moderate lymphopenia, and severe

lymphopenia , which is acknowledged. No additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

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

It is noted that the RMP of the reference product includes a DHPC as aRMM. However, this is not stated as a condition in section D of the EPAR-Product information. This DHPC was sent in Nov 2020 to inform HPCs about cases of PML in the settings of lymphopenia. This is already done by the originator, why this information does not have to be sent again by generics.

Part VI Summary of the RMP
The Summary of the RMP is endorsed.

Conclusion RMP assessment
The submitted Risk Management Plan, version 0.1 signed 19-Sep-2023 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

A user consultation with target patient groups on the package information leaflet (PL) has been performed on the basis of a bridging report making reference to Tecfidera, EMA/800904/2013, regarding content and the MAH´s own product Morphine 1 mg/ml solution for infusion in pre-filled syringe, regarding layout.
The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the generic products, Zeimem, are found adequate. There are no objections to approval of Zeimem, 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 applications are 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 Zeimem, 120 mg, 240 mg, Gastro-resistant capsule, hard was positively finalised on 2025-02-12.

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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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