LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Dimethyl fumarate Reddy
(dimethyl fumarate)

SE/H/2386/01-02/DC

This module reflects the scientific discussion for the approval of Dimethyl fumarate Reddy. The procedure was finalised on 2024-06-11. For information on changes after this date please refer to the module 'Update'.

Postadress/Postal address: P.O. Box 26, SE-751 03 Uppsala, SWEDEN
Besöksadress/Visiting address: Dag Hammarskjölds väg 42, Uppsala
Telefon/Phone: +46 (0)18 17 46 00 Fax: +46 (0)18 54 85 66
Internet: www.lakemedelsverket.se E-mail: registrator@lakemedelsverket.se

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, a marketing authorisation has been granted for Dimethyl fumarate Reddy, 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 Reddy, 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 AT, CZ, DE, ES, IT, NL, PL, PT, RO and SK as concerned member states (CMS). DK was withdrawn at Day 160.

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Tecfidera 120 mg, 240 mg, gastro-resistant capsule, hard, authorised in EU since 2014, with Biogen Netherlands B.V. as marketing authorisation holder.

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

Potential similarity with orphan medicinal products
Not applicable

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 (DMF) are well known. As DMF is a widely used, well-known active substance, no further studies are required, and the applicant provides none. An Overview based on literature review is, thus, appropriate.

Shortly, literature references have only been provided for the pharmacological properties. Both the parent compound, DMF, and its bioactive metabolite monomethyl fumarate (MMF) are pharmacological active. Non-clinical studies indicate that dimethyl fumarate pharmacodynamic responses appear to be primarily mediated through activation of the Nuclear factor (erythroid-derived 2)-like 2 (Nrf2) transcriptional pathway (believed to have immunomodulatory effects such as reduced pro-inflammatory cytokine production) but the precise pharmacological mechanism of action remains unclear.

The applicant has used European and Australian public assessment reports for the non-clinical pharmacokinetics and toxicology section – which is not formally acceptable. On the condition that the quality assessment determines that the reference product is acceptable for DMF Reddy, this issue is not pursued.

Environmental Risk Assessment (ERA)
The applicant has submitted an ERA for DMF (120mg and 240mg capsules, maximum dose of 480mg/day). An historical consumption comparison (spanning 2019-2022) has been provided for the relevant member states. On average, and across relevant member states, there was a trend of increased DMF consumption (2019: 10340kg/year, 2020: 11872kg/year, 2021: 12511kg/year, and 2022: 13021kg/year). The trend of increased DMF consumption could also be seen as far back as 2015 – making it clear that a regular ERA alternatively a Letter of Access ERA ('LeA-ERA') is necessary. The applicant has stated that a LeA-ERA has been asked for from Biogen but the response is yet unknown. As such, no formal conclusion about ERA status can be drawn at this time**.**

The applicant has committed to provide either a LeA-ERA or formal communication on refusal as soon as received. In the event that neither of them is received from the MAH/innovator, Dr. Reddy's commits to perform the standard Phase II ERA studies and submit an updated ERA.

Summary of main study results

Substance (INN/Invented Name): Dimethyl fumarate			
CAS-number (if available):			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107 or …		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		

	The compound is considered as vPvB The compound is considered as PBT				
Phase I					
Calculation	**Value**	**Unit**			**Conclusion**
PEC $_{surface\ water}$, default or refined (e.g. prevalence, literature)		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		µg/L	species
Daphnia sp. Reproduction Test	OECD 211	NOEC		µg/L	
Fish, Early Life Stage Toxicity Test/*Species*	OECD 210	NOEC		µg/L	species
Activated Sludge, Respiration Inhibition Test	OECD 209	EC		µg/L	
Phase IIb Studies					
Bioaccumulation	OECD 305	BCF		L/kg	%lipids:
Aerobic and anaerobic transformation in soil	OECD 307	DT50 $\%CO_2$			for all 4 soils
Soil Micro organisms: Nitrogen Transformation Test	OECD 216	%effect		mg/ kg	
Terrestrial Plants, Growth Test/*Species*	OECD 208	NOEC		mg/ kg	
Earthworm, Acute Toxicity Tests	OECD 207	NOEC		mg/ kg	
Collembola, Reproduction Test	ISO 11267	NOEC		mg/ kg	
Sediment dwelling organism		NOEC		mg/ kg	species

Conclusions on ERA:
No conclusion can presently be drawn on the environmental risk. A commitment has been made to provide relevant documentation in future procedures.

IV. CLINICAL ASPECTS

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

Pharmacokinetic properties of the active substance

Absorption: Following an oral dose of dimethyl fumarate maximal plasma concentrations of monomethyl fumarate occur at approximately 2-2.5 hours.

Food effect: For tolerability reasons the product is recommended to be administered with food.

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.

Elimination: The terminal half-life of monomethyl fumarate is approximately one hour.

Study C22143 (FASTING)

Methods

This was a single-dose, two-way crossover study conducted in 60 healthy volunteers, comparing Dimethyl Fumarate Reddy, 240 mg, gastro resistant capsule with Tecfidera, 240 mg, gastro resistant capsule under fasting conditions. Blood samples for concentration analysis were collected pre-dose and up to 10.0 hours post-dose. Plasma concentrations of the primary metabolite monomethyl fumarate were determined with an LC-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 12 December 2022 and 23 December 2022.

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=57. (C22143, FASTING)

Treatment	AUC_{0-t} ng*h/ml	$AUC_{0-\infty}$ ng*h/ml	C_{max} ng/ml	t_{max} h
Test	**3541.3 ± 937.1**	**3563.7 ± 943.1**	**2234.0 ± 699.2**	**2.75 (1.00 - 5.00)**
Reference	**3705.9 ± 966.4**	**3733.9 ± 965.5**	**2170.3 ± 698.7**	**2.75 (1.25 - 5.00)**
***Ratio (90% CI)**	**95.51 (91.36 - 99.86)**	**95.34 (91.12 - 99.76)**	**103.22 (95.56 - 111.50)**	**-**

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 C22144 (FED)

Methods

This was a single-dose, two-way crossover study conducted in 60 healthy volunteers, comparing Dimethyl Fumarate Reddy, 240 mg, gastro resistant capsule with Tecfidera, 240 mg, gastro resistant capsule under fed conditions. Blood samples for concentration analysis were collected pre-dose and up to 24 hours post-dose. Plasma concentrations of the primary metabolite monomethyl fumarate were determined with an LC-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 10 January 2023 and 27 January 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, n=58. (C22144, FED)

Treatment	AUC_{0-t} ng*h/ml	$AUC_{0-\infty}$ ng*h/ml	C_{max} ng/ml	t_{max} h
Test	**3388.7 ± 788.5**	**$3510.6 ± 789.4**	**1592.9 ± 726.5**	**5.25 (2.5-10.0)**
Reference	**3465.7 ± 931.2**	**$$3566.9 ± 914.2**	**1654.9 ± 753.4**	**5.0 (2.0-10.0)**
***Ratio (90% CI)**	**98.64 (93.94 - 103.57)**	**98.76 (93.65 - 104.14)**	**97.68 (86.60 - 110.18)**	**-**

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*
$ n=55 since subject numbers 9, 22 and 44 did not fit with linear regression in the terminal phase for test.
$$ n=54 since subject 32, 33, 59 and 60 did not fit with linear regression in the terminal phase for reference.

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
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/Corr **). In the product-specific bioequivalence guidance for dimethyl fumarate gastro-resistant capsules (EMA/CHMP/421315/2017), it is stated that conclusions on bioequivalence should be based on levels of the main active metabolite monomethyl fumarate, and that for gastro-resistant multiple unit formulations, single-dose bioequivalence studies of the 240 mg strength in the fasting and fed states are adequate. The bioanalytical methods were adequately validated.

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

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/Corr **) are fulfilled and it is in line with the product-specific bioequivalence guidance for dimethyl fumarate in case of multiple unit formulation.

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 Applicant 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 Reddy.

Part II Safety specification
The safety concerns are aligned with those of the originator product. The tabulated Summary of safety concerns (Part II: Module SVIII) is presented here below:

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 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

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

Of note, there are ongoing category 3 post-authorisation safety-studies (PASS) with the originator product. No such study is proposed for Dimethyl fumarate Reddy, which is considered acceptable for a generic application.

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

Part VI Summary of the RMP
The Applicant has adequately summarised the RMP.

Conclusion RMP assessment
The MAH has satisfactorily responded to the questions raised and updated the RMP accordingly.
Issue resolved.

The submitted **Risk Management Plan, version 0.3, signed 18 April 2024, 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 Sitagliptin 25/50/100 mg film-coated tablets, approved through decentralised procedure DE/H/6648/001-003/DC (and, for CMS DE, a bridging report making reference to Naratriptan 2.5 mg film-coated tablets, approved through decentralised procedure DE/H/6390/001/DC).
The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the generic product, Dimethyl fumarate Reddy, is found adequate. There are no objections to approval of Dimethyl fumarate Reddy, 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 ratio 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 Reddy, 120 mg, 240 mg, gastro-resistant capsule, hard was positively finalised on 2024-06-11.

LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

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)

Postadress/Postal address: P.O. Box 26, SE-751 03 Uppsala, SWEDEN
Besöksadress/Visiting address: Dag Hammarskjölds väg 42, Uppsala
Telefon/Phone: +46 (0)18 17 46 00 Fax: +46 (0)18 54 85 66
Internet: www.lakemedelsverket.se E-mail: registrator@lakemedelsverket.se