LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Dimethyl fumarate STADA Nordic
(dimethyl fumarate)

SE/H/2566/01-02/DC

This module reflects the scientific discussion for the approval of Dimethyl fumarate STADA Nordic. The procedure was finalised on 2025-02-17. 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 STADA Nordic, 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 STADA Nordic, 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, BE, CY, CZ, DK, EE, EL, FI, HR, HU, IE, IS, LT, LU, LV, MT, NO, PL, PT, SI, 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 hard capsules centrally authorised in the European 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 hard capsules from Germany with Biogen Netherlands B.V. as marketing authorisation holder.

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 STADA Nordic 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 STADA Nordic 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 Dimethyl fumarate STADA Nordic (Dimethyl Fumarate) with the reference product Tecfidera.

Pharmacokinetic properties of the active substance
Orally administered dimethyl fumarate undergoes rapid pre-systemic 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 are performed with plasma monomethyl fumarate concentrations.

Absorption: The t_{max} of monomethyl fumarate is 2 to 2.5 hours. As dimethyl fumarate gastro-resistant hard capsules contain minitablets, 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.

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. Accumulation of parent drug or monomethyl fumarate does not occur with multiple doses of dimethyl fumarate at the therapeutic regimen.

Study DIFU5117 (fasted)
Methods
This was a single-dose, two-way crossover study conducted in 60 healthy volunteers, comparing Dimethyl Fumarate, 240 mg, gastro-resistant hard capsule with Tecfidera, 240 mg, gastro-resistant hard capsule under fasting conditions. 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 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 2017-10-26 and 2018-01-02.

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=60.

Treatment	AUC_{0-t} ng*h/ml	$AUC_{0-\infty}$ ng*h/ml	C_{max} ng/ml	t_{max} h
Test	**2766.246 ± 697.369**	**2803.710 ± 703.248**	**1689.408 ± 626.548**	**2.00 (0.50-5.00)**
Reference	**2643.167 ± 755.843**	**2689.282 ± 752.948**	**1617.963 ± 541.230**	**2.75 (1.25-5.00)**
***Ratio (90% CI)**	**105.53 (101.14-110.12)**	**104.99 (100.66-109.51)**	**103.21 (94.47-112.75)**	**-**

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 DIFU1717 (fed)
Methods
This was a single-dose, three-period, semi-replicate crossover study conducted in 36 healthy volunteers, comparing Dimethyl Fumarate, 240 mg, gastro-resistant hard capsule with Tecfidera, 240 mg, gastro-resistant hard capsule under fed conditions. Blood samples for concentration analysis were collected pre-dose and up to 16 hours post-dose. Plasma concentrations of the main active 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 2017-04-21 and 2017-09-14.

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=35, Reference: n=70.

Treatment	AUC_{0-t} ng*h/ml	$AUC_{0-\infty}$ ng*h/ml	C_{max} ng/ml	t_{max} h
Test	**2756.812 ± 940.632**	**2795.369 ± 961.352****	**1746.000 ± 741.036**	**3.67 (0.67-8.00)**
Reference	**2819.629 ± 1024.959**	**2879.853 ± 1029.424*****	**1919.049 ± 834.537**	**4.75 (1.67-8.00)**
***Ratio (90% CI)**	**98.77 (92.49-105.49)**	**97.06 (91.81-102.61)**	**92.38 (78.33-108.95)**	**-**

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=34, since one subject didn't have enough data points in the elimination phase to estimate $AUC_{0-\infty}$*

**** n=68, since two subjects didn't have enough data points in the elimination phase to estimate $AUC_{0-\infty}$*

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 75.49-132.47%, which was based on calculated intra-subject variability for the reference product which was >30%, (38.29%).

The applicant has pre-specified in the study protocol that they wish to use widened acceptance limits and the semi-replicate study design allows for calculation of intra-subject variability for the reference product. The applicant has provided a clinical justification that the wider difference in C_{max} is clinically irrelevant. The applicant has also showed results of a statistical analysis for reference product, which confirm that no outliers were observed. The estimate of the intraindividual variation of CV = 38.29% is accepted.

One subject (Subject 5; T/R/R) was excluded from statistical analysis since the subject's AUC in period III was less than 5% of reference geometric mean. With respect to inclusion of subject in the statistical analysis, the bioequivalence guideline states *"(…) Ideally, all treated subjects should be included in the statistical analysis. However, subjects in a crossover trial who do not provide evaluable data for both of the test and reference products (or who fail to provide evaluable data for the single period in a parallel group trial) should not be included."*. The applicant has presented an updated statistical analysis including Subject 5 and the conclusion that bioequivalence was shown remained unchanged.

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 method was adequately validated.

Absence of studies with the additional strength of 120 mg is acceptable, as all conditions for biowaiver for additional strength, as described in the Guideline on the investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/Corr **) are fulfilled and since the pharmacokinetics of dimethyl

fumarate is linear between 120 mg and 240 mg. Further, this is in accordance with the product-specific bioequivalence guidance for dimethyl fumarate gastro-resistant capsules (EMA/CHMP/421315/2017).

Based on the submitted bioequivalence studies, Dimethyl fumarate STADA Nordic 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 STADA Nordic.

Part II Safety specification

The MAH has submitted the version 0.3 RMP dated 2024-12-19 and proposed the following summary safety concerns:

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	• PML
Important potential risks	• Malignancies • Effects on pregnancy outcome
Missing information	• Long term efficacy and safety • Safety profile in patients with moderate to severe renal impairment

Assessor's comments: The summary of safety concerns is in line with the summary of safety concerns for the reference product Tecfidera RMP, version 17.0.
The proposed summary of safety concerns is endorsed.

Part III Pharmacovigilance Plan

Routine pharmacovigilance is suggested. The originator has updated the RMP to version 17.0 which has resulted in that the applicant's proposed questionnaires, included in Annex 4, has been updated and is consistent with the originator.
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.

Part VI Summary of the RMP

The Summary of the RMP is endorsed.

Conclusion RMP assessment

The submitted Risk Management Plan, version 0.3 signed 2024-12-19 is considered acceptable.
The MAH has satisfactorily responded to the questions raised and updated the RMP accordingly.
Issue is resolved.

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 STADA Nordic, is found adequate. There are no objections to approval of Dimethyl fumarate STADA Nordic, 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 STADA Nordic, 120 mg, 240 mg, Gastro-resistant capsule, hard was positively finalised on 2025-02-17.

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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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