COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Scleryda 120 mg and 240 mg, gastro-resistant hard capsules
(dimethyl fumarate)

NL/H/5610/001-002/DC

Date: 8 October 2025

This module reflects the scientific discussion for the approval of Scleryda 120 mg and 240 mg, gastro-resistant hard capsules. The procedure was finalised on 25 October 2023. 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 Scleryda 120 mg and 240 mg, gastro-resistant hard capsules, from European Regulatory Affairs Limited (trading as Ivowen).

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 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 Cyprus, Greece, Italy and Malta.

II. QUALITY ASPECTS

II.1 Introduction

Scleryda 120 mg and 240 mg are gastro-resistant hard capsules. The capsules of the different strengths can be distinguished by their colour and printed text and are as follows:

Scleryda 120 mg are hard capsules with a blue-green cap and a white body, printed with 'MYLAN' over 'DF-120', containing white to off-white enteric coated pellets. Each capsule contains as active substance 120 mg dimethyl fumarate.

Scleryda 240 mg are blue-green hard capsules, printed with 'MYLAN' over 'DF-240', containing white to off-white enteric coated pellets. Each capsule contains as active substance 240 mg dimethyl fumarate.

The excipients are:
Capsule contents (enteric-coated pellets): microcrystalline cellulose, croscarmellose sodium, colloidal anhydrous silica, magnesium stearate, methacrylic acid - methyl methacrylate copolymer (1:1), methacrylic acid - ethyl acrylate copolymer (1:1) dispersion 30%, triethyl citrate and talc

Capsule shell: gelatine, titanium dioxide (E171), FD&C Blue#2 (E132), yellow iron oxide (E172), black iron oxide (E172) and (only for 240 mg capsules) purified water

Capsule print (black ink): partially esterified shellac glaze, propylene glycol, ammonium hydroxide and black iron oxide (E172)

The two capsule strengths are fully dose proportional.

The capsules are packed in blister packs, made from a combination of polyvinyl chloride (PVC), with polyethylene (PE), polyvinylidene chloride (PVdC) and aluminium (Al).

II.2 Drug Substance

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 practically insoluble in water. Dimethyl fumarate is not hygroscopic. Dimethyl fumarate is a trans-isomer and the cis-isomer (dimethyl maleate), is controlled in the drug substance specification. For this product, crystalline form I of dimethyl fumarate is consistently produced.

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 is a simple one-step process. Adequate specifications have been adopted for starting materials, solvents and reagents. Both solvents are adequately controlled in the active substance. The active substance has been adequately characterised and the manufacturing process is described in sufficient detail. The control strategy for potentially genotoxic impurities is acceptable.

Quality control of drug substance
The specifications adopted by the MAH are in line with the specification of the drug substance manufacturer. The active substance specifications are considered adequate to control the quality. Additional requirements for particle size have been set by the MAH. The tests and their acceptance criteria are acceptable. The analytical procedures are described and were adequately validated.

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 when stored under the stated conditions.

II.3 Medicinal Product

Pharmaceutical development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The choice of excipients is justified and their functions explained. The QC dissolution method is adequately justified.

The *in vitro* dissolution studies complementary to the BE studies and the biowaiver of additional strengths have been conducted in line with the *EMA PKWP Q&A on gastro-resistant formulations*. Similar *in vitro* dissolution was demonstrated in the biowaiver of additional strengths and the 120 mg strength can therefore be accepted. The dissolution data in the presence of alcohol shows that the dissolution of the proposed product is equivalent to (and not worse than) that of the reference product. Overall, the pharmaceutical development of the product has been adequately performed.

Manufacturing process

The manufacturing process consists of the following steps: sifting, blending, compression into pellets, coating (sub coating and enteric coating), blending of the coated pellets, encapsulation and packaging. The manufacturing process of modified release preparation is considered non-standard.

The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data have been presented for three commercial scale batches of the common blend.; Capsule filling has also been adequately validated for three batches of each strength at the commercial batch size.

Control of excipients

The excipients comply with their Ph.Eur. or in-house requirements. The functionality-related characteristics were adequately addressed.

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 appearance, identification, colour identification, dissolution, uniformity of dosage units, assay, related substances, water and microbiological quality. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. The release and shelf-life limits are identical for all parameters, with the exception of one related substance. The release and shelf-life specifications are acceptable.

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 have been presented for six batches per strength (three at site I and three at site II), in accordance with the relevant European guidelines.

Stability of drug product

Stability data on the product have been provided for six full commercial scale batches of finished product per strength, stored at 25°C/ 60% RH (up to 24 resp. 36 months), 30°C/65% RH (12 months, one site) and 40°C/75% RH (6 months). The stability was tested in accordance with applicable European guidelines demonstrating the stability of the product for three years below 30°C.

A photo stability study has been performed on the product as per ICH Q1B Guideline- "Photo stability testing of new drug substances and products". Based on this study it is concluded that the product is not photosensitive.

On basis of the data submitted, a shelf life was granted of 3 years. The labelled storage conditions are "Do not store above 30ºC".

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

Scientific data and/or certificates of suitability issued by the EDQM for gelatine have 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 Scleryda 120 mg and 240 mg have a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished products.

No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Scleryda 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 three bioequivalence studies, which are discussed below.

IV.2 Pharmacokinetics

The MAH conducted three bioequivalence studies. In study 1, three formulations (A, B and C) of the test product differing in the particle size of the active substance (milled, un-milled), coating equipment (rotor, pan), size of pellets and batches were tested against the US and EU reference products. Based on the study results, formulation B was selected for further assessment in the pivotal studies 2 and 3. In those studies, the pharmacokinetic profile of the test product Scleryda 240 mg, gastro-resistant hard capsules (Viatris Limited, Ireland) was compared with the pharmacokinetic profile of the EU reference product Tecfidera 240 mg, gastro-resistant hard capsules (Biogen Netherlands B.V., the Netherlands). For the 120 mg strength, a biowaiver was requested.

The package of bioequivalence studies complies with the product-specific bioequivalence guidance on dimethyl fumarate which recommends one single dose bioequivalence study of subjects under fasting conditions (study 1 and pivotal study 2) and one single dose bioequivalence study of subjects under fed conditions (study 1 and pivotal study 3).

The choice of the reference product in the bioequivalence studies has been justified by comparison of dissolution study results (at 0.1N HCL followed by pH 6.8) and composition. The formula and preparation of the bioequivalence batch was identical to the formula proposed for marketing.

Biowaiver

The following general requirements were met for the waiver for additional 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 criteria a, b and c are met. As for criterium d, since the test and reference product batches used in the bioequivalence studies have expired the MAH used new batches of the products for the dissolution comparison. As with to the *in vitro* dissolution studies in support of biowaiver of strength, given the high %RSD values (>20%) in the first time point of the test product at 0.1N HCl for two hours followed by pH 6.8 it is unclear why the dissolution comparison was not done using the confidence intervals of the f2 based on the bootstrap methodology. Several factors could have contributed to the difference observed as discussed by MAH. As *in vivo* data prevail this will not be pursued further. The biowaiver of the 120 mg strength is acceptable.

Bioequivalence studies

Study 1: dimethyl fumarate 240 mg under fasting and fed conditions

Design

A single-dose, randomised, five-period, five-treatment, five-sequence, crossover, two group, bioequivalence study was carried out under fasting and fed conditions in 50 healthy male (48) and female (2) subjects, aged 18-60 years. The 50 subjects were equally divided between a fasting and a fed group. Subjects in both groups were administered a single dose (240 mg) of one of five dimethyl fumarate formulations. The tablet was orally administered with 240 ml water.

There were five dosing periods, separated by a washout period of 1 day (24 hours).

Fasted group

Subjects received the tablet after an overnight fast of at least ten hours. On the day of dosing the subject received a standard low-fat meal about four hours post dose followed by an evening meal about ten hours post dose.

Blood samples were collected pre-dose and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 7, 8 and 10 hours after administration of the products.

Fed group

Subjects received the tablet after an overnight fast of at least ten hour and 30 minutes after the start of a standardised high-fat breakfast. On the day of dosing the subject received a standard low-fat meal about five hours post dose followed by an evening meal about ten hours post dose.

Blood samples were collected pre-dose and at 0.5, 1, 2, 3, 4, 4.5, 5, 5.5, 6, 6.5, 7, 8, 10 and 12 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
50 Subjects enrolled in the study. There were two drop-outs. One subject in the fasted group was discontinued post period I dosing due to adverse events (flushing, feeling hot, pruritus, erythema and rash). One subject in the fed group withdrew consent post period I dosing due to an adverse event (nausea).
As a result, 48 subjects were eligible for pharmacokinetic analysis, 24 subjects per group.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of monomethyl fumarate, following a single, oral dose of 240 mg dimethyl fumarate, fasted conditions.

Treatment N=24	AUC_{0-t} (ng.h/mL)	$AUC_{0-\infty}$ (ng.h/mL)	C_{max} (ng/mL)	t_{max} (h)
Test A	4310 ± 1114	4325 ± 1156[1]	2456 ± 717	2.5 (1.5, 5.0)
Test B	4175 ± 941	4225± 938[1]	2252 ± 767	2.0 (1.0, 7.1)
Test C	4203 ± 1039	4236 ± 1041	2434 ± 747	2.0 (1.0, 5.0)
Reference US (D)	4087 ± 807	4103 ± 834[2]	2139 ± 728	3.0 (1.5, 8.0)
Reference EU (E)	4142 ± 1008	4232 ± 1035[1]	2239 ± 572	2.5 (1.5, 5.0)
***Ratio Test A/Reference US (D) (90% CI)**	1.04 (0.98-1.10)	1.04 (0.98-1.10)	1.17 (1.05-1.32)	**N.A**
***Ratio Test B/Reference US (D) (90% CI)**	1.02 (0.96-1.08)	1.04 (0.98-1.10)	1.07 (0.95-1.20)	**N.A**
***Ratio Test C/Reference US (D) (90% CI)**	1.02 (0.97-1.08)	1.03 (0.97-1.09)	1.17 (1.04-1.31)	**N.A**
***Ratio Test A/Reference EU (E) (90% CI)**	1.04 (0.98-1.10)	1.04 (0.98-.1.10)	1.09 (0.97-1.22)	**N.A**
***Ratio Test B/Reference EU (E) (90% CI)**	1.02 (0.96-1.07)	1.04 (0.98-1.11)	0.99 (0.88-1.11)	**N.A**
***Ratio Test C/Reference EU (E) (90% CI)**	1.02 (0.96-1.08)	1.03 (0.97-1.09)	1.08 (0.97-1.22)	**N.A**

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

[1]N = 22, [2] N = 20

**ln-transformed values*

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of monomethyl fumarate, following a single, oral dose of 240 mg dimethyl fumarate, fed conditions.

Treatment N=24	AUC_{0-t} (ng.h/mL)	$AUC_{0-\infty}$ (ng.h/mL)	C_{max} (ng/mL)	t_{max} (h)
Test A	3416 ± 832	3496 ± 797[1]	1343 ± 505	6.000 (3.000, 10.00)
Test B	3211 ± 750	3352 ± 817[2]	1389 ± 612	5.500 (2.000, 8.000)
Test C	3401 ± 1464	3505 ± 818[3]	1668 ± 817	8.000 (2.000, 10.00)
Reference US (D)	3444 ± 1045	3827 ± 765[4]	1355 ± 646	7.500 (4.000, 10.00)
Reference EU (E)	3434 ± 1179	3327 ± 545[5]	1395 ± 640	6.250 (2.000, 12.00)
***Ratio Test A/Reference US (D) (90% CI)**	1.00 (0.89-1.12)	1.03 (0.89-1.20)	1.04 (0.87-1.24)	N.A.
***Ratio Test B/Reference US (D) (90% CI)**	0.95 (0.85-1.06)	0.95 (0.82-1.10)	1.07 (0.89-1.27)	N.A
***Ratio Test C/Reference US (D) (90% CI)**	0.93 (0.83-1.04)	1.22 (0.98-1.52)	1.23 (1.03-1.46)	N.A
***Ratio Test A/Reference EU (E) (90% CI)**	1.03 (0.92-1.15)	1.15 (0.98-1.33)	1.00 (0.84-1.19)	N.A
***Ratio Test B/Reference EU (E) (90% CI)**	0.97 (0.87-1.09)	1.15 (1.00-1.33)	1.03 (0.86-1.23)	N.A
***Ratio Test C/Reference EU (E) (90% CI)**	0.95 (0.85-1.06)	1.36 (1.13-1.64)	1.19 (0.99-1.41)	N.A

$AUC_{0-\infty}$ 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 t = 12 hours
C_{max} Maximum plasma concentration
t_{max} Time after administration when maximum plasma concentration occurs
CI Confidence interval

[1]N = 9, [2]N = 14, [3]N = 4, [4]N = 6, [5]N = 8

**ln-transformed values*

Conclusion bioequivalence study 1: fasting and fed

The 90% confidence intervals of monomethyl fumarate calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} in study 1 (fasted and fed) are not within the bioequivalence acceptance range of 0.80 – 1.25 as no single formulation (A, B and C of the test product) was bioequivalent with both the US and EU reference products for subjects in both fasting and fed conditions. However, the ratios for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} for monomethyl fumarate of test formulation B were between 0.95 and 1.07 (rounded up) compared to both the US and EU reference products in both fasting and fed condition. Test formulation B was therefore selected for further bioequivalence assessment in the pivotal studies 2 and 3.

Study 2: pivotal, dimethyl fumarate 240 mg under fasted conditions

Design

A single-dose, randomised, three-period, three-treatment, crossover bioequivalence study was carried out under fasted conditions in 48 healthy male (26) and female (22) subjects, aged 18-63 years. Each subject received a single dose (240 mg) of one of three dimethyl fumarate formulations. There are two reference formulations involved: the US Tecfidera 240 mg delayed-release capsules (Biogen) and the EU approved Tecfidera 240 mg, gastro-resistant hard capsules (Biogen). The tablet was orally administered with 240 ml water after an overnight fast of at least 10 hours. There were three dosing periods, separated by a washout period of one day (24 hours).

Blood samples were collected pre-dose and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 7, 8, 9, 10 and 12 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

48 Subjects enrolled in the study. Four subjects were withdrawn from the study. Two subjects were discontinued post Period I dosing due to an adverse event (vomiting), one subject was discontinued post Period III dosing due to an adverse event (diarrhoea) and one subject withdrew consent post Period I dosing due to an adverse event (nausea). Therefore, 44 subjects completed the entire clinical portion of the study. For comparison with the US reference, 45 subjects are included in the pharmacokinetic and statistical analyses for the determination of bioequivalence.

For comparison with the EU reference, 44 subjects are included in the pharmacokinetic and statistical analyses for the determination of bioequivalence.

Table 3. Pharmacokinetic parameters (non-transformed values; arithmetic mean, t_{max} (median, range)) of monomethyl fumarate, following a single, oral dose of 240 mg dimethyl fumarate under fasted conditions.

Treatment N=45	AUC_{0-t} (ng.h/mL)	$AUC_{0-\infty}$ (ng.h/mL)	C_{max} (ng/mL)	t_{max} (h)
Test B	4223 ± 1124	4350[1] ± 1191	2462± 917.6	3.00 (1.50 – 9.00)
Reference US	4149 ± 1130	4124 ± 1100	2268 ± 886.6	3.00 (1.50 – 4.50)
***Ratio Test B /Reference US (90% CI)**	1.00 (0.94-1.06)	1.02[2] (0.97-1.07)[3]	1.07 (0. 97-1.18)	N.A.

$AUC_{0-\infty}$ 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 t = 12 hours
C_{max} Maximum plasma concentration
t_{max} Time after administration when maximum plasma concentration occurs
CI Confidence interval

[1]N = 39, [2]N = 35, [3]N = 35

**ln-transformed values*

Table 4. Pharmacokinetic parameters (non-transformed values; arithmetic mean, t_{max} (median)) of monomethyl fumarate, following a single, oral dose of 240 mg dimethyl fumarate under fasted conditions.

Treatment N=44	AUC_{0-t} (ng.h/mL)	$AUC_{0-\infty}$ (ng.h/mL)	C_{max} (ng/mL)	t_{max} (h)
Test B	4256 ± 1217	4391[4] ± 1179	2495 ± 900.6	3.00 (1.50 - 9.00)
Reference EU	4368 ± 1214	4470[5] ± 1206	2357 ± 869.9	3.00 (1.50 – 5.00)
***Ratio Test B/Reference EU (90% CI)**	0.97 (0.91-1.03)	0.98[6] (0.94-1.02)[7]	1.06 (0.96-1.17)	N.A.

$AUC_{0-\infty}$ 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 t = 12 hours
C_{max} Maximum plasma concentration
t_{max} Time after administration when maximum plasma concentration occurs
CI Confidence interval

[4]N = 38, [5]N = 41, [6]N = 35, [7]N = 35

Study 3: pivotal, dimethyl fumarate 240 mg fed conditions

Design

A single-dose, four-period, two-treatment, two-sequence, crossover, randomised, open-label bioequivalence study was carried out under fed conditions in 36 healthy male (23) and female (13) subjects, aged 19-57 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 fast of at least 10 hours and 30 minutes after the start of a standardised high fat breakfast.
There were four dosing periods, separated by a washout period of 1 day (24 hours).

Blood samples were collected pre-dose and at 0.5, 1, 2, 3, 4, 4.5, 5, 5.5, 6, 6.5, 7, 8, 9, 10, 11, 12, 14, 16 and 18 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
36 Subjects enrolled in the study. One subject withdrew consent due to personal reasons post Period II dosing. A total of 35 subjects completed the entire clinical portion of the study. However, the data for one other subject was excluded from the statistical analysis due to predose concentrations greater than 5% of C_{max} in Periods II and III.
Therefore, 34 subjects were eligible for pharmacokinetic analysis.

Table 5. Pharmacokinetic parameters (non-transformed values; arithmetic mean, t_{max} (median)) of monomethyl fumarate, following a single, oral dose of 240 mg dimethyl fumarate under fed conditions.

Treatment N=34	**AUC_{0-t} (ng.h/mL)**	**$AUC_{0-\infty}$ (ng.h/mL)**	**C_{max} (ng/mL)**	**t_{max} (h)**
Test B	3568 ± 927	3803[1] ± 846	1545 ± 735	7.00 (4.50 – 14.00)
Reference EU	3434 ± 842	3426[2] ± 666	1469 ± 593	8.00 (2.00 – 14.00)
***Ratio (90% CI)**	1.03 (0.99-1.07)	1.10 (1.06-1.15)	1.01 (0.92-1.11)	N.A.

$AUC_{0-\infty}$ 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 t = 18 hours
C_{max} Maximum plasma concentration
t_{max} Time after administration when maximum plasma concentration occurs
CI Confidence interval

[1]N = 41. Each subject received each treatment twice on two separate occasions; total observations used in analysis n=68
[2]N = 38. Each subject received each treatment twice on two separate occasions; total observations used in analysis n=68

**ln-transformed values*

Conclusion on bioequivalence studies:
Study 1: fasting and fed
The 90% confidence intervals of monomethyl fumarate calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} in study 1 (fasted and fed) are not within the bioequivalence acceptance range of 0.80 – 1.25 as no single formulation (A, B and C of the test product) was bioequivalent with both the US

and EU reference products for subjects in both fasting and fed conditions. However, the ratios for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} for monomethyl fumarate of test formulation B were between 0.95 and 1.07 (rounded up) compared to both the US and EU reference products in both fasting and fed condition. Test formulation B was therefore selected for further bioequivalence assessment in the pivotal studies 2 and 3.

Studies 2 (pivotal fasting) and 3 (pivotal fed)
The 90% confidence intervals of monomethyl fumarate 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 three bioequivalence studies Scleryda 240 mg is considered bioequivalent with Tecfidera 240 mg.

The results of the bioequivalence studies with the 240 mg strength can be extrapolated to the 120 mg strength, according to conditions in Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1/Corr*, section 4.1.6.

The MEB has been assured that the bioequivalence studies have 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 Scleryda. At the time of approval, the most recent version of the RMP was version 0.3 dated 28 July 2023.

Table 4. 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) • Malignancies • Effects on pregnancy outcome • Interactions 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 renal impairment

	• Safety profile in patients with hepatic impairment • Safety profile in patients with severe active GI disease • Increased risk of infections 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. No new clinical studies were conducted. 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

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report making reference to Duloxetine Mylan 30 mg hard gastro-resistant capsules (EMEA/H/C/003981) for the visual presentation and to Tecfidera 120 mg and 240 mg gastro-resistant hard capsules (EMEA/H/C/002601) for the content. The bridging report submitted by the MAH has been found acceptable; bridging is justified for both content and layout of the leaflet.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Scleryda 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. Tecfidera is 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 Scleryda with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 25 October 2023.

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/5610/001/IB/001	Change in the manufacturing process of the finished product, including an intermediate used in the manufacture of the finished product - Other variation	No	2-5-2024	Approved	N.A.
NL/5610/001-2/IA/002	Change in the name and/or address of a manufacturer/importer of the finished product (including batch release or quality control testing sites) - The activities for which the manufacturer/importer is responsible do not include batch release	No	1-7-2024	Approved	N.A.
NL/5610/001-2/IA/003/G	Submission of a new or updated Ph. Eur. certificate of suitability or deletion of Ph. Eur. certificate of suitability: For an active substance For a starting material/reagent/intermediate used in the manufacturing process of the active substance For an excipient. - European Pharmacopoeial TSE Certificate of suitability for an active substance/starting material/reagent/ intermediate/or excipient o New certificate for a starting material/reagent/ intermediate /or excipient	No, No	30-10-2024	Approved	N.A.

	from a new or an already approved manufacturer Submission of a new or updated Ph. Eur. certificate of suitability or deletion of Ph. Eur. certificate of suitability: For an active substance For a starting material/reagent/intermediate used in the manufacturing process of the active substance For an excipient. - European Pharmacopoeial TSE Certificate of suitability for an active substance/starting material/reagent/ intermediate/or excipient o Updated certificate from an already approved manufacturer				
NL/5610/001-2/IB/004	Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet of a generic/hybrid/biosimilar medicinal products following assessment of the same change for the reference product - Implementation of change(s) for which no new additional data is required to be submitted by the MAH	Yes	13-3-2025	Approved	
NL/5610/002/IB/005	Change in the shape or dimensions of the pharmaceutical form - Gastro-resistant, modified or prolonged release	Yes	27-5-2025	Approved	N.A.

	pharmaceutical forms and scored tablets intended to be divided into equal doses				
NL/5610/001-2/IB/006/G	Change in the name and/or address of: a manufacturer (including where relevant quality control testing sites); or an ASMF holder; or a supplier of the active substance, starting material, reagent or intermediate used in the manufacture of the active substance (where specified in the technical dossier) where no Ph. Eur. Certificate of Suitability is part of the approved dossier; or a manufacturer of a novel excipient (where specified in the technical dossier) Change in manufacture of the active substance - Other variation	No, No	28-5-2025	Approved	N.A.