COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

# Public Assessment Report

# Scientific discussion

# Fingolimod Devatis 0.25 mg and 0.5 mg, hard capsules (fingolimod hydrochloride)

## NL/H/5326/001-002/DC

## Date: 2 March 2022

**This module reflects the scientific discussion for the approval of Fingolimod Devatis 0.25 mg and 0.5 mg, hard capsules. The procedure was finalised at 13 December 2021. 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 |
| ERA | Environmental Risk Assessment |
| ICH | International Conference of Harmonisation |
| MAH | Marketing Authorisation Holder |
| Ph.Eur. | European Pharmacopoeia |
| PL | Package Leaflet |
| PML | Progressive Multifocal Leukoencephalopathy |
| RH | Relative Humidity |
| RMP | Risk Management Plan |
| SmPC | Summary of Product Characteristics |
| TSE | Transmissible Spongiform Encephalopathy |
| VZV | *Varicella Zoster* Virus |

# I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Fingolimod Devatis 0.25 mg and 0.5 mg, hard capsules, from Devatis GmbH.

The product is indicated as single disease modifying therapy in highly active relapsing remitting multiple sclerosis for the following groups of adult patients and paediatric patients aged 10 years and older:

- Patients with highly active disease despite a full and adequate course of treatment with at least one disease modifying therapy (for exceptions and information about washout periods see SmPC sections 4.4 and 5.1).

or

- Patients with rapidly evolving severe relapsing remitting multiple sclerosis defined by 2 or more disabling relapses in one year, and with 1 or more Gadolinium enhancing lesions on brain MRI or a significant increase in T2 lesion load as compared to a previous recent MRI.

A comprehensive description of the indications and posology is given in the SmPC.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Gilenya 0.25 mg and 0.5 mg hard capsules, which has been registered in the EEA by Novartis Europharm Limited since 17 March 2011 through a centralised procedure (EU/1/11/677).

The concerned member state (CMS) involved in this procedure was Germany.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

# II. QUALITY ASPECTS

## II.1 Introduction

Fingolimod Devatis are hard gelatin capsules, containing white to off-white powder mixture.

- The 0.25 mg strength has an ivory opaque cap and body and is imprinted with black ink “F 0.25” on cap. Each capsule contains as active substance 0.25 mg fingolimod (as hydrochloride).
- The 0.5 mg strength has a yellow opaque cap and white opaque body and is imprinted with black ink “F 0.5” on cap. Each capsule contains as active substance 0.5 mg fingolimod (as hydrochloride).

The capsules are packed in transparent PVC/PE/PVDC-aluminium blister packs.

The excipients are:
*Capsule fill* – carmellose calcium and sodium stearyl fumarate (both strengths)
*Capsule shell* – 0.25 mg strength: gelatine, titanium dioxide (E171) and yellow iron oxide E172)
*Capsule shell* – 0.5 mg strength: gelatine, titanium dioxide (E171), tartrazine (E102) and sunset yellow FCF (E110)
*Printing ink* – shellac, black iron oxide, propylene glycol and concentrated ammonia solution (E527) (both strengths)

The two capsule strengths are dose proportional.

## II.2 Drug Substance

The active substance is fingolimod hydrochloride, an established active substance described in the European Pharmacopoeia (Ph.Eur.). Fingolimod hydrochloride is a white to off-white crystalline powder. The active substance is soluble in dimethylsulfoxide and freely soluble in methanol. Fingolimod hydrochloride shows polymorphism Batch analytical data showed that the desired polymorphic form is produced consistently. Combined with the control for the polymorphic form as included in the drug substance specification, this is acceptable.

Manufacturing process
The manufacturing process of fingolimod hydrochloride is carried out in two stages, which are adequately described according to the requirements of the EMA Guideline on the chemistry of active substances. Adequate specifications have been adopted for starting materials, solvents and reagents at both manufacturing sites. The specification of the intermediates is acceptable and all in-process controls have been adequately established. The active substance has been adequately characterised.

Quality control of drug substance
The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. Additional parameters for identification of polymorphic forms and particle size as applied by the manufacturer are adequately justified. Absence of a control for microbial quality and elemental impurities is also justified. The possible formation of N-nitrosamines is adequately discussed. Batch analytical data demonstrating compliance with this specification have been provided for three process validation batches.

Stability of drug substance
Stability data on the active substance have been provided for six batches in accordance with applicable European guidelines. All results are provided and comply to the proposed specifications, no significant change or trends are observed. Based on the data submitted, a retest period could be granted of 60 months when stored in the original package.

## II.3 Medicinal Products

Pharmaceutical development

The products are an established pharmaceutical form and their development is adequately described in accordance with the relevant European guidelines. The choice of excipients is justified and their functions are explained. Sufficient information has been provided on the manufacturing process development for both strengths. The suitability of the products for the paediatric population is adequately discussed. Also the development of the routine dissolution method has been adequately described. The dissolution limit is adequate in view of the dissolution profile of the biobatch of the test products.

Manufacturing process

The manufacturing process, which comprises dry mixing followed by encapsulation, has been validated according to relevant European/ICH guidelines. Although the manufacturing is not a complex manufacturing process, due to the low content of the drug substance in the drug product (≤ 2%), it is considered a non-standard process. Process validation data on the product have been presented with three batches of each strength in accordance with the relevant European guidelines. The presented validation results comply with the predefined acceptance criteria.

Control of excipients

The excipients comply with Ph. Eur. For sodium stearyl fumarate, additional control of particle size distribution is included in the specification. These specifications are acceptable.

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 description, capsule filling weight, identification by HPLC and UV-PDA, water content, disintegration, assay, uniformity of dosage units by content uniformity, dissolution, related substances and microbiological controls. Limits for water content and total impurities in the specification have been justified and are considered appropriate for adequate quality control of the products. Satisfactory validation data for the analytical methods have been provided. Batch analytical data of three batches per strength from the production sites have been provided, demonstrating compliance with the specification.

An acceptable risk evaluation on the presence of nitrosamine impurities in the drug products has been provided. No risk mitigation is deemed necessary.

Stability of drug product

Stability data on the product have been provided for three batches of Fingolimod Devatis 0.5 mg capsules stored at 25°C/60% RH (36 months) and 40°C/75% RH (6 months). For the lower strength, results from three batches are available up to 12 months at long term and 6 months at accelerated conditions. The conditions applied and parameters tested in the stability studies are according to the ICH stability guideline. The batches were stored in

transparent PVC/PE/PVdC – Al blisters. No significant changes have been observed, except for the water content. A decrease is observed for the assay, but all results are within specifications. Photostability studies have been conducted, the results confirm that the drug products are not sensitive to light. On basis of the data submitted, a shelf life was granted of 36 months for the 0.5 mg strength and 24 months for the 0.25 mg strength. The labelled storage conditions are: "Store below 30°C".

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

Scientific data and/or certificates of suitability issued by the EDQM for the gelatine capsules 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 Fingolimod Devatis has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

No post-approval commitments were made.

## III. NON-CLINICAL ASPECTS

### III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Fingolimod Devatis is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

### III.2 Discussion on the non-clinical aspects

These products are generic formulations of Gilenya 0.5 mg hard capsules which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is 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

Fingolimod hydrochloride is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

For this generic application, the MAH has submitted one bioequivalence study for the 0.5 mg strength, which is discussed below. For the 0.25 mg strength, a biowaiver is requested.

## IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Fingolimod Devatis 0.5 mg, hard capsules (Devatis GmbH, Germany) is compared with the pharmacokinetic profile of the reference product Gilenya 0.5 mg hard capsules (Novartis Europharm Limited, Ireland).

The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution results and compositions of the EU reference product. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Biowaiver

The MAH applied for a biowaiver for the lower strength of 0.25 mg. Both products were manufactured by the same process and the composition of the different strengths is qualitatively the same. The composition of the different strengths is dose proportional. Comparative dissolution profiles between the biobatch and two representative batches of the lower strength have been provided at three pH levels, with and without surfactant. The results with surfactant are all above 85% in 15 minutes, therefore the dissolution profiles can be considered similar. The results without surfactant showed a too high variability. Therefore, the MAH performed an additional statistical analysis of these results, demonstrating similarity of the dissolution profiles between the two strengths in the conditions required by the Guideline on investigation of bioequivalence.
Overall, the criteria for a biowaiver were met and a waiver was granted.

Bioequivalence studies

*Design*

A single-dose, randomised, single-period, two-treatment, parallel bioequivalence study was carried out under fasted conditions in 40 healthy male subjects, aged 18-42 years. Each subject received a single dose (0.5 mg) of one of the two fingolimod formulations. The tablet was orally administered with 240 ml water after an overnight fast. As this was a study with a parallel study design, no washout period was necessary. Blood samples were collected at

pre-dose and at 1, 3, 6, 8, 10, 11, 12, 13, 14, 15, 16, 20, 24, 28, 32, 36, 48 and 72 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*
All 40 subjects completed the study. The data of all 40 subjects were eligible for pharmacokinetic analysis.

**Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, $t_{max}$ (median, range)) of fingolimod hydrochloride under fasted conditions.**

| **Treatment N=40** | **$AUC_{0-72}$ (pg.h/ml)** | **$C_{max}$ (pg/ml)** | **$t_{max}$ (h)** |
|---|---|---|---|
| **Test** | 31730 ± 4766 | 559 ± 73 | 30.0 (15.0 – 32.0) |
| **Reference** | 29653 ± 5447 | 524 ± 94 | 20.0 (13.0 – 32.0) |
| ***Ratio (90% CI)** | 1.08 (0.98 – 1.18) | 1.08 (0.99 - 1.17) | -- |
| **CV (%)** | 16.8 | 16.1 | -- |

**$AUC_{0-72}$** area under the plasma concentration-time curve from time zero to 72 hours
**$C_{max}$** maximum plasma concentration
**$t_{max}$** time for maximum concentration
**CV** coefficient of variation

**ln-transformed values*

Conclusion on bioequivalence study:
The 90% confidence intervals 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 submitted bioequivalence study Fingolimod Devatis is considered bioequivalent with Gilenya.

The MEB has been assured that the bioequivalence study has 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 Fingolimod Devatis.

**Table 2. Summary table of safety concerns as approved in RMP**

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|---|---|
| Important identified risks | • Bradyarrhythmia (including conduction defects and bradycardia complicated by hypotension) occurring post-first dose<br>• Liver transaminase elevation<br>• Macular oedema<br>• Opportunistic infections including Progressive Multifocal Leukoencephalopathy (PML), *Varicella zoster* virus (VZV), herpes viral infections other than VZV, fungal infection<br>• Reproductive toxicity<br>• Skin cancer (basal cell carcinoma, Kaposi's sarcoma, malignant melanoma, Merkel cell carcinoma, squamous cell carcinoma)<br>• Convulsions<br>• Lymphoma |
| Important potential risks | • Other malignant neoplasms |
| Missing information | • Long term use in paediatric patients, including impact on growth and development (including cognitive development) |

Next to routine pharmacovigilance activities and routine risk minimisation measures, the MAH committed to perform additional risk minimisation measures pursuant to Article 21a/22 of Directive 2001/83/EC. The MAH will provide additional risk minimisation measures in the form of educational material for all risks and missing information listed in Table 1, except for the listed important identified risk of liver transaminase elevation and lymphoma, and the listed important potential risk of other malignant neoplasms. It is agreed that implementation of the additional risk minimisation measures and the details of the controlled distribution system will be agreed with the competent authority of each individual member state in the EU.
The risk management plan was considered acceptable.

## IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Gilenya. No new clinical studies were conducted. The MAH demonstrated through a bioequivalence study 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 Gilenya 0.5 mg hard capsules for content (EU/1/11/677), and to Hydroxycarbamid Devatis 500 mg Hartkapseln (DE/H/5243/001/DC) for lay-out and design. 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

Fingolimod Devatis 0.25 mg and 0.5 mg, hard capsules have a proven chemical-pharmaceutical quality and are generic forms of Gilenya 0.25 mg and 0.5 mg hard capsules. Gilenya 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 Fingolimod Devatis with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 13 December 2021.

## 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 |
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