COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Fingolimod Denk 0.5 mg, hard capsules (fingolimod hydrochloride)

NL/H/5012/001/DC

Date: 13 August 2021

This module reflects the scientific discussion for the approval of Fingolimod Denk 0.5 mg, hard capsules. The procedure was finalised at 12 February 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
RH	Relative Humidity
RMP	Risk Management Plan
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 Fingolimod Denk 0.5 mg, capsules hard, from Denk Pharma GmbH & Co. KG.

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 0.5 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 states (CMS) involved in this procedure were Germany and Malta.

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

II. QUALITY ASPECTS

II.1 Introduction

Fingolimod Denk is a hard capsule with yellow opaque cap and white opaque body, imprinted with black ink “FD 0.5 mg” on the cap. Each capsule contains as active substance 0.5 mg of fingolimod (as hydrochloride).

The capsules are packed in transparent PVC/PVDC/aluminium blisters or transparent PVC/PE/PVDC/aluminium blisters packs.

The excipients are:
Capsule fill - calcium hydrogen phosphate dihydrate, croscarmellose sodium, hydroxypropylcellulose, purified water and magnesium stearate
Capsule shell - gelatin, titanium dioxide (E171) and yellow iron oxide (E172)
Printing ink - shellac, anhydrous ethanol, isopropyl alcohol, n-butanol, propylene glycol, concentrated ammonia solution, black iron oxide, potassium hydroxide and water purified

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 or almost white powder. The active substance is freely soluble in water and in ethanol (96 per cent), but practically insoluble in heptane. Fingolimod hydrochloride exhibits polymorphism between three forms (Form I, II and III). The transformation is reversible and subject to temperature. Polymorphism is not relevant since it has no effect on drug substance's properties such as solubility. Polymorphic form I has been demonstrated by X-ray diffraction.

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 of fingolimod hydrochloride is carried out in three stages. Adequate specifications have been adopted for starting materials, solvents and reagents. 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, with additional requirements for residual solvents. A justification for not including a validated test for the control of the microbiological quality of the drug substance has been provided. The specification of the drug substance is considered acceptable. Batch analytical data have been provided for three full scaled batches. All results are found within the specification limits.

Stability of drug substance
Stability data on the active substance have been provided for three batches in accordance with applicable European guidelines. Based on the data submitted, a retest period could be granted of two 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 is explained. The choices of packaging and manufacturing process are justified in relation to the innovator. The manufacture and composition of the bio-batch used in bioequivalence studies is similar to the marketed product. Comparative dissolution profiles at three pH have been included, being one of them used for the proposed quality control dissolution method. *In vitro* dissolution studies do not support the observed *in vivo* bioequivalence. Nevertheless, the MAH has discussed the potential clinical consequences of this mismatch. The discriminatory power of the dissolution method has been demonstrated. The pharmaceutical development of the product has been adequately performed and information regarding the suitability for paediatric patients has been included.

Manufacturing process

The hard capsules are manufactured by wet granulation followed by filling of empty capsule shells. The product is manufactured using conventional manufacturing techniques but the process is a non-standard manufacturing process due to the specialised pharmaceutical form. The MAH has provided a detailed process description. The manufacturing process has been adequately validated according to relevant European guidelines and reports have been provided for three batches of the capsules at the proposed batch size. The prolonged bulk holding time that has been proposed for the bulk product has been properly justified.

Control of excipients

The excipients comply with Ph.Eur. requirements. Their 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 identification, disintegration, dissolution, assay, related substances, uniformity of dosage unit, microbiological quality, appearance, average weight, average fill weight and water content. The specification of the drug product is acceptable. A risk evaluation concerning the presence of nitrosamine impurities in the drug product has been provided in line with the Notice EMA/409815/2020 and, thus, is acceptable. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. The analytical methods have been adequately described and validated. A justification for performing microbiological testing as not routinely method has been provided and is in line with the ICH Q6A Guideline. Batch analytical data from the proposed production site have been provided on three full scaled batches demonstrating compliance with the proposed release specification.

Stability of drug product

Stability data on the product have been provided for three batches stored at 25°C/60% RH (24 months), 30°C/75% RH (12 months) and 40°C/75% RH (6 months) for product packed in

PVC/PVDC-aluminium blisters; and for three batches stored at 25°C/60 RH (24 months) and 40°C/75% RH (6 months) for product packed in PVC/PE/PVDC-aluminium blisters. The conditions used in the stability studies are according to the ICH stability guidelines. Compliance with amended specification during shelf-life has been demonstrated. The proposed shelf life of 24 months is without any storage condition for the product packed in PVC/PE/PVDC/Aluminium blister, and below 30°C for the product packed in PVC/PVDC/Aluminium blister.
Photostability studies were performed for one full scaled batch in accordance with ICH recommendations and showed that the product is stable when exposed to light.

Certificates of suitability issued by the EDQM 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 Denk 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 Denk is intended for generic substitution, this product 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

This product is a generic formulation 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, which is discussed below.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Fingolimod Denk 0.5 mg, hard capsules (Denk Pharma GmbH & Co. KG., 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.

Bioequivalence study
Design
A single-dose, randomised, open label, single-period, balanced two-treatment, parallel bioequivalence study was carried out under fasting conditions in 36 healthy male subjects, aged 18-44 years. Each subject received a single dose (0.5 mg) of one of the 2 fingolimod formulations. The tablet was orally administered with 240 ml of drinking water after an overnight fast of at least 10 hours.

Blood samples were collected pre-dose and at 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17 18, 20, 22, 24, 30, 36, 48 and 72 hours after administration of the products.

The design of the study is acceptable. The procedures followed for a fasting study are according to the bioequivalence guideline. In general, a crossover study design is preferable as this would limit variability. Nonetheless, the use of a parallel design is acceptable considering the relatively long half-life of fingolimod (i.e. 6 -9 days).

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 36 subjects completed the study and 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=36	**AUC_{0-72} (pg/ml/h)**	**C_{max} (pg/ml)**	**t_{max} (h)**
Test	23114 ± 4512	404 ± 77	24.00 (14.00–30.00)
Reference	24996 ± 3766	442 ± 68	20.50 (9.00–36.00)
***Ratio (90% CI)**	0.92 (0.83–1.01)	0.91 (0.83 – 1.00)	-
AUC_{0-72h} area under the plasma concentration. Time curve from time zero to 72 hours **C_{max}** maximum plasma concentration **t_{max}** time for maximum concentration			

**ln-transformed values*

Conclusion on bioequivalence study
The 90% confidence intervals calculated for AUC_{0-72h} and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Fingolimod Denk 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 Denk.

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

Important identified risks	• Bradyarrhythmia (including conduction defects and bradycardia complicated by hypotension) occurring post-first dose • Hypertension • Liver transaminase elevation • Posterior Reversible Encephalopathy Syndrome (PRES) • Macular edema • Infections, including opportunistic infections (PML, VZV, herpes viral infections other than VZV, fungal infection) • Reproductive toxicity • Bronchoconstriction • Skin cancer (Basal cell carcinoma, Kaposi's sarcoma, Malignant melanoma, Merkel cell carcinoma, Squamous cell carcinoma) • Convulsions
Important potential risks	• Acute disseminated encephalomyelitis-like (ADEM-like) events • Lymphoma • Other malignant neoplasms • Thrombo-embolic events • QT interval prolongation
Missing information	• Long-term use in paediatric patients, including impact on growth and development (including cognitive development) • Elderly patients (≥65 years) • Lactating women • Patients with diabetes mellitus • Patients with cardiovascular conditions including myocardial infarction, angina pectoris, Raynaud's phenomenon, cardiac failure or severe cardiac disease, increased QTc interval, uncontrolled hypertension, patients at risk for bradyarrhythmia and who may not tolerate bradycardia, patients with second degree Mobitz type 2 or higher AV block, sick-sinus syndrome, sino-atrial heart block, history of cardiac arrest, cerebrovascular disease and severe sleep apnea • Long-term risk of cardiovascular morbidity/mortality • Long-term risk of malignant neoplasms • Unexplained death • Switch from other disease modifying therapy

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

In line with the RMP of the reference product, aRMM to minimise the following risks are accepted: bradyarrhythmia occurring post-first dose, liver transaminase elevation, macular oedema, infections including opportunistic infections (PML, VZV, herpes viral infections other than VZV, fungal infection), reproductive toxicity, skin cancer and convulsions, and for the

important missing information regarding the long-term use in paediatric patients, including impact on growth and development (including cognitive development). The proposed physician's checklist and patient/parent/caregiver reminder card are also agreed, as these materials have also been in place for the reference product.

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

The package leaflet (PL) 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 test consisted of: a pilot test with three participants, followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability.
The results show that the PL 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

Fingolimod Denk 0.5 mg, hard capsules has a proven chemical-pharmaceutical quality and is a generic form of Gilenya 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 Denk with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 12 February 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