IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Fingolimod 0.5 mg hard capsules
FINGOLIMOD HYDROCHLORIDE
PA1226/017/002

The Public Assessment Report reflects the scientific conclusion reached by the Health Products Regulatory Authority (HPRA) at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation for a specific medicinal product for human use. It is made available by the HPRA for information to the public, after deletion of commercially sensitive information. The legal basis for its creation and availability is contained in Article 21 of Directive 2001/83/EC, as amended. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the medicinal product for marketing in Ireland.

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I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the HPRA has granted a marketing authorisation for Fingolimod 0.5 mg hard capsules, from Flynn Pharma Ltd on 9th August 2024.

Fingolimod 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 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.

The legal status of this product is prescription only and is subject to restricted prescribing as detailed in Section 4.2 of the Summary of Product Characteristics.

The Summary of Product Characteristics for (SmPC) for this medicinal product is available on the HPRA's website.

Name of the product	Fingolimod 0.5mg hard capsules
Name(s) of the active substance(s) (INN)	FINGOLIMOD HYDROCHLORIDE
Pharmacotherapeutic classification (ATC Code)	L04AA27
Pharmaceutical form and strength(s)	Hard capsules, 0.5mg
Marketing Authorisation Number(s) in Ireland (PA)	PA1226/017/002
Marketing Authorisation Holder	Flynn Pharma Limited 5th Floor 40 Mespil Road Dublin 4 D04 C2N4 Ireland

II. QUALITY ASPECTS

II.1. Introduction

This application is for Fingolimod 0.25 mg hard capsules, and Fingolimod 0.5 mg hard capsules.

II.2 Drug substance

The active substance is Fingolimod hydrochloride, an established active substance described in the European Pharmacopoeia, and is manufactured in accordance with the principles of Good Manufacturing Practice (GMP)

The active substance specification is considered adequate to control the quality and meets current pharmacopoeial requirements. Batch analytical data demonstrating compliance with this specification has been provided.

II.3 Medicinal product

P.1 Composition

0.25 mg fingolimod per capsule
0.50 mg fingolimod per capsule

The excipients in the medicinal product are listed in section 6.1 of the SmPC.
A visual description of the product is included in section 3 of the SmPC.

P.2 Pharmaceutical Development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

P.3 Manufacture of the Product

The product is manufactured in accordance with the principles of good manufacturing practice (GMP) at suitably qualified manufacturing sites.

The manufacturing process has been validated according to relevant European/ICH guidelines and the process is considered to be sufficiently validated.

P.4 Control of Other Substances (Excipients/*Ancillary Substances*)

All ingredients comply with Ph. Eur. or are adequately controlled by the manufacturer's specifications.

P.5 Control of Finished Product

The Finished Product Specification is based on the pharmacopoeial monograph for a hard capsule, and the tests and control limits are considered appropriate for this type of product.

The analytical methods used are described in sufficient detail and are supported by validation data.

Batch analytical data for a number of batches from the proposed production site(s) have been provided, and demonstrate the ability of the manufacturer to produce batches of finished product of consistent quality.

P.6 Packaging material

The approved packaging for this product is described in section 6.5 of the SmPC.

Evidence has been provided that the packaging complies with Ph. Eur./EU legislation for use with foodstuffs requirements.

P.7 Stability of the Finished Product

Stability data on the finished product in the proposed packaging have been provided in accordance with EU guidelines and support the shelf-life and storage conditions listed in sections 6.3 and 6.4 of the SmPC.

Adventitious Agent Safety

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

Scientific data and/or certificates of suitability issued by EDQM have been provided for Gelatin and compliance with the Note For Guidance on Minimising the Risk if Transmitting Animal Spongiform Encephalopathy Agents via Medicinal Products has been satisfactorily demonstrated

II.4 Discussion on Chemical, Pharmaceutical and Biological Aspects

The important quality characteristics of the product are well-defined and controlled. Satisfactory chemical and pharmaceutical documentation has been provided, assuring consistent quality of Fingolimod 0.25 mg hard capsules and Fingolimod 0.5 mg hard capsules.

III. NON-CLINICAL ASPECTS

III.1 Introduction

This active substance is a generic formulation of Gilenya on the European market. No new preclinical data have been submitted. As such, no pre-clinical assessment has been made on the application. This is acceptable for this type of application.

III.2 Ecotoxicity/environmental risk assessment

The proposed product is a generic formulation and its substitution for the originator product should not increase environmental exposure and thus the absence of studies to investigate the environmental risk is acceptable.

III.3 Discussion on the non-clinical aspects
No new nonclinical studies were submitted for this application which is acceptable as it is a generic product and the pharmacology, pharmacokinetics and toxicology of the active substance, fingolimod, have been previously assessed for the originator product, Gilenya.

IV. CLINICAL ASPECTS

IV.1 Introduction
Fingolimod is a well-known active substance with established efficacy and tolerability.

The content of the SmPC approved during the national procedure is in accordance with that accepted for the reference product GILENYA® (fingolimod) 0.25 mg & 0.5 mg, marketed by Novartis Europharm Limited.

For this generic application, the applicant has submitted 2 bioequivalence studies (1 of which is pivotal) in which the pharmacokinetic profile of the test product fingolimod is compared with the pharmacokinetic profile of the reference product GILENYA.

The original BE study was discounted due to PK concerns which related to missing data in 2 subjects and so is only included in this application for information. The original study was not considered in the assessment of bioequivalence as part of this procedure.

The pivotal study was a randomized, open-label, balanced, two-treatment, single-period, single dose, parallel, bioequivalence study of Fingolimod 0.5 mg Hard Capsules and GILENYA® (Fingolimod) 0.5 mg Hard Capsules in healthy adult human subjects under fasting conditions.

In accordance with the regulatory requirements, the Test/Reference ratios and their 90% confidence intervals were within the specified limits to show bioequivalence between the test product and the reference product.

The Fingolimod 0.5 mg Hard Capsules are dose proportional with the Fingolimod 0.25 mg Hard Capsules. The pharmacokinetics of the active substance are linear in the therapeutic range. Dissolution studies conducted by the applicant comparing fingolimod 0.25mg capsules with fingolimod 0.5mg hard capsules showed that the dissolution profiles, when supported by an acceptable bootstrapping exercise, were similar.

The results of the bioequivalence study performed with the Fingolimod 0.5 mg Hard Capsules therefore apply to the 0.25mg strength, and so a biowaiver for that strength is appropriate.

The HPRA has been assured that GCP standards were followed in an appropriate manner in the studies conducted.

IV.2 Pharmacokinetics
Absorption
Fingolimod absorption is slow (tmax of 12-16 hours) and extensive (≥85%). The apparent absolute oral bioavailability is 93% (95% confidence interval: 79-111%). Steady-state-blood concentrations are reached within 1 to 2 months following once-daily administration and steady-state levels are approximately 10-fold greater than with the initial dose.

Food intake does not alter Cmax or exposure (AUC) of fingolimod. Fingolimod phosphate Cmax was slightly decreased by 34% but AUC was unchanged. Therefore, fingolimod may be taken without regard to meals (see section 4.2).

Distribution
Fingolimod highly distributes in red blood cells, with the fraction in blood cells of 86%. Fingolimod phosphate has a smaller uptake in blood cells of <17%. Fingolimod and fingolimod phosphate are highly protein bound (>99%).

Fingolimod is extensively distributed to body tissues with a volume of distribution of about 1,200±260 litres. A study in four healthy subjects who received a single intravenous dose of a radioiodolabelled analogue of fingolimod demonstrated that fingolimod penetrates into the brain. In a study in 13 male multiple sclerosis patients who received fingolimod 0.5 mg/day, the

mean amount of fingolimod (and fingolimod phosphate) in seminal ejaculate, at steady-state, was approximately 10,000 times lower than the oral dose administered (0.5 mg).

Biotransformation
Fingolimod is transformed in humans by reversible stereoselective phosphorylation to the pharmacologically active (S)-enantiomer of fingolimod phosphate. Fingolimod is eliminated by oxidative biotransformation catalysed mainly via CYP4F2 and possibly other isoenzymes and subsequent fatty acid-like degradation to inactive metabolites. Formation of pharmacologically inactive non-polar ceramide analogues of fingolimod was also observed. The main enzyme involved in the metabolism of fingolimod is partially identified and may be either CYP4F2 or CYP3A4.

Following single oral administration of [^{14}C] fingolimod, the major fingolimod-related components in blood, as judged from their contribution to the AUC up to 34 days post dose of total radiolabelled components, are fingolimod itself (23%), fingolimod phosphate (10%), and inactive metabolites (M3 carboxylic acid metabolite (8%), M29 ceramide metabolite (9%) and M30 ceramide metabolite (7%)).

Elimination
Fingolimod blood clearance is 6.3±2.3 l/h, and the average apparent terminal elimination half-life (t1/2) is 6-9 days. Blood levels of fingolimod and fingolimod phosphate decline in parallel in the terminal phase, leading to similar half-lives for both.

After oral administration, about 81% of the dose is slowly excreted in the urine as inactive metabolites. Fingolimod and fingolimod phosphate are not excreted intact in urine but are the major components in the faeces, with amounts representing less than 2.5% of the dose each. After 34 days, the recovery of the administered dose is 89%.

More detailed information can be found in Section 5.2 of the Summary of Product Characteristics.

IV.3 Pharmacodynamics
Fingolimod is a sphingosine 1-phosphate receptor modulator. Fingolimod is metabolised by sphingosine kinase to the active metabolite fingolimod phosphate. Fingolimod phosphate binds at low nanomolar concentrations to sphingosine 1-phosphate (S1P) receptor 1 located on lymphocytes, and readily crosses the blood-brain barrier to bind to S1P receptor 1 located on neural cells in the central nervous system (CNS). By acting as a functional antagonist of S1P receptors on lymphocytes, fingolimod phosphate blocks the capacity of lymphocytes to egress from lymph nodes, causing a redistribution, rather than depletion, of lymphocytes. Animal studies have shown that this redistribution reduces the infiltration of pathogenic lymphocytes, including pro-inflammatory Th17 cells, into the CNS, where they would be involved in nerve inflammation and nervous tissue damage. Animal studies and in vitro experiments indicate that fingolimod may also act via interaction with S1P receptors on neural cells.
More detailed information can be found in Section 5.1 of the Summary of Product Characteristics.

IV.4 Clinical Efficacy
No new efficacy information was provided as part of this applications, which is acceptable for applications under this legal basis.

IV.5 Clinical Safety
No new safety information was provided as part of this applications, which is acceptable for applications under this legal basis.

Risk Management Plan
A risk management plan was submitted, 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 (fingolimod hydrochloride) 0.25mg, 0.5mg hard capsules.

The following summary of safety concerns was identified:

Important identified risks	• Bradyarrhythmia (including conduction defects and bradycardia complicated by hypotension) occurring post-first dose • Liver transaminase elevation • Macular oedema • Opportunistic infections (PML, VZV, herpes viral infections other than VZV, fungal infection) • Reproductive toxicity • Skin cancer (Basal cell carcinoma, Kaposi's

	sarcoma, Malignant melanoma, Merkel cell carcinoma, Squamous cell carcinoma) • Convulsions • Lymphoma
Important potential risks	• Other malignant neoplasms
Missing information	• Long-term use in paediatric patients including impact on growth and development (including cognitive development)

Routine pharmacovigilance activities are considered sufficient to identify and characterise risks relating to the product.

Additional risk minimisation measures in the form of an educational programme are considered necessary to prevent and minimize risks associated with the product.

Prior to launch of Fingolimod the Marketing Authorisation Holder (MAH) must agree about the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority (NCA).

The MAH shall ensure that all physicians who intend to prescribe Fingolimod are provided with a Physician Information Pack, including:
1. Summary of Product Characteristics (SmPC);
2. Physician's checklist for adult and paediatric patients, to consider prior to prescribing Fingolimod;
3. Patient / Parent / Caregiver's guide, to be provided to all patients, their parents (or legal representatives), and caregivers.
4. The pregnancy-specific patient reminder card, to be provided to all patients, their parents (or legal representatives), and caregivers, as applicable.

Periodic Safety Update Reports (PSURs) shall be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal. Marketing authorisation holders shall continuously check the European medicines web-portal for the DLP and frequency of submission of the next PSUR.

IV.6 Discussion on the clinical aspects

Acceptable

V. OVERALL CONCLUSIONS

Fingolimod 0.25mg and 0.5 mg Hard Capsules are generic forms of GILENYA. GILENYA is a well-known medicinal product with a proven chemical-pharmaceutical quality and an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the CHMP guidance documents. The SmPC is consistent with that of the reference product.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The HPRA, on the basis of the data submitted considered that Fingolimod 0.25mg & 0.5 mg Hard Capsules demonstrated bioequivalence with the reference product as well as a satisfactory risk/benefit profile and therefore granted a marketing authorisation.

VI. REVISION DATE

VII. UPDATES

This section reflects the significant changes following finalisation of the initial procedure.

SCOPE	PROCEDURE NUMBER	PRODUCT INFORMATION AFFECTED	DATE OF START OF PROCEDURE	DATE OF END OF PROCEDURE
New National	N/A	SmPC, IPAR, PIL	9th August 2024	8th August 2029