COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Fingolimod Edest 0.5 mg hard capsules

(fingolimod hydrochloride)

NL/H/4807/001/DC

Date: 22 July 2020

This module reflects the scientific discussion for the approval of Fingolimod Edest 0.5 mg hard capsules. The procedure was finalised at 6 May 2020. 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 Edest 0.5 mg hard capsules, from Intas Third Party Sales 2005, S.L.

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 with body weight above 40 kg:

- patients with highly active disease despite a full and adequate course of treatment with at least one disease modifying therapy
- 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 (EMEA/H/C/002202).

The concerned member states (CMS) involved in this procedure were France, Germany and Spain.

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

II. QUALITY ASPECTS

II.1 Introduction

Fingolimod Edest is a bright yellow opaque hard gelatin imprinted with “FO 0.5 mg” on the cap and two radial bands on the capsule body with yellow ink containing white to off-white powder. Each capsule contains 0.5 mg fingolimod (as hydrochloride).

The hard capsules are packed in clear PVC/PVdC-Al blister packs or clear PVC/PVdC-Al perforated unit dose blister packs.

The excipients are:
Capsule fill – pregelatinized maize starch and magnesium stearate
Capsule shell – gelatin, titanium dioxide (E171) and yellow iron oxide (E172)
Black printing ink - shellac (E904), dehydrated alcohol (E1510), isopropyl alcohol, butyl alcohol Propylene glycol (E1520), concentrated ammonia solution (E527), black iron oxide (E172) and potassium hydroxide (E525)
Yellow printing ink - shellac (E904), dehydrated alcohol (E1510), isopropyl alcohol, butyl alcohol, propylene glycol (E1520), ammonia solution, concentrated (E527) and yellow iron oxide (E172).

II.2 Drug Substance

The active substance is fingolimod hydrochloride, an established active substance described in the European Pharmacopoeia (Ph.Eur.). Fingolimod hydrochloride is white to off-white powder and freely soluble in methanol, water and ethanol. The active substance exhibits polymorphism and form-I 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 consists of four steps. 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. 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 commercial scaled batches stored at 25°C/60% RH (36 months) and 40°C/75% RH (6 months), together with preliminary results (up to 6 months) of three commercial batches manufactured after the last ASMF update. All results are within proposed limits. The proposed retest period of 24 months is acceptable.

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. Sufficient information has been provided on manufacturing process development. The impact of particle size distribution and polymorphic form of the drug substance on quality and performance of drug product have been adequately discussed.

The description of development of the proposed routine dissolution method is sufficient.

A bioequivalence study was carried out. Comparative dissolution testing complementary to the *in vivo* bioequivalence study has been performed with the biobatches at three different pHs 1.2, 4.5 and 6.8 with and without surfactant and in QC medium. Similarity of dissolution profiles was demonstrated when using media with surfactant, however without surfactant this was not the case at pH 1.2. The MAH provided an adequate justification for this observation.

Manufacturing process

The manufacturing process compromises a mixing process followed by encapsulation. Although the manufacturing is not a complex manufacturing process, due to the low content of the drug substance in the drug product, it is considered a non-standard process. The manufacturing process has been validated according to relevant European guidelines. Process validation data on the product have been presented for three batches in accordance with the relevant European guidelines. Additional process validation has been performed on a fourth batch of the same size after change in encapsulation equipment. The presented validation only covers final blending and encapsulation. Regarding the packaging operations, only a validation protocol has been provided, which is acceptable.

Control of excipients

The excipients comply with the Ph. Eur. and/or relevant EU Regulation. Acceptable specification for the empty gelatine capsules is provided. Functionality-related characteristics of the excipients have been identified, which are included in the excipient's specifications.

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, average net content, identification, identification of the colorants, loss on drying, assay, related substances, dissolution, uniformity of dosage units (content) and microbial examination. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. Satisfactory validation data for the analytical methods have been provided. Batch analytical data from three batches from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product have been provided for three batches stored at 25°C/60% RH (36 months) and 40°C/75% RH (6 months). The batches were stored in accordance with applicable European guidelines. Photostability studies show that the drug product is not sensitive to light. On basis of the data submitted, a shelf life was granted of 3 years. The labelled storage condition is: 'Store below 30°C'.

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

The gelatin capsules are sourced from bovine origin. No other materials of human or animal origin are present in the drug product. Adequate certification about TSE/BSE risk is provided for the capsules.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Fingolimod Edest 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 Edest 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

This product is a generic formulation of Gilenya 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 a 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 Edest 0.5 mg hard capsules (Intas Third Party Sales 2005, S.L., Spain) 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, one-period, two-treatment, two-sequence, parallel bioequivalence study was carried out under fasted conditions in 81 healthy male subjects, mean age 30.9 years. Each subject received a single dose (3 x 0.5 mg) of one of the 2 fingolimod formulations. After an overnight fast of at least 10 hours, subjects in each group were given either 3 x 0.5 mg fingolimod test or reference hard capsule formulation with 240 ml of water in the morning. The study was conducted in two groups of 41/40 subjects each.

Blood samples were collected pre-dose and at 1, 2, 4, 6, 8, 9, 10, 11, 12, 13, 14, 15, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 40, 48 and 72 hours after administration of the products.

The design of the study is acceptable. Fingolimod hydrochloride may be taken without reference to food intake. From the literature it is known that food does not interact with the absorption of fingolimod hydrochloride. Therefore, a food interaction study is not deemed necessary. The bioequivalence study under fasting conditions is in accordance with CPMP/EWP/QWP/1401/98 Note for Guidance on the investigation of bioavailability and bioequivalence.

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
Three subjects dropped out due to vomiting, personal reasons and a medical reason. A total of 78 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 under fasted conditions.

Treatment	AUC_{0-72h} (ng.h/ml)	C_{max} (ng/ml)	t_{max} (h)
Test (N=40)	100417 ± 16177	1819 ± 301	14.51 (6.00 – 48.00)
Reference (N=38)	93290 ± 16500	1713 ± 272	13.50 (9.00 – 36.02)
***Ratio (90% CI)**	1.08 1.01 – 1.15	1.06 0.99 – 1.13	--

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
CV coefficient of variation

**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 Edest 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 Edest.

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 oedema - 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 apnoea - Long-term risk of cardiovascular morbidity/mortality - Long-term risk of malignant neoplasms - Unexplained death - Switch from other disease modifying therapy

The MAH shall ensure that in each Member State where Fingolimod is marketed, all physicians who intend to prescribe finfolimod are provided with an updated Physician Information Pack, including:

- Summary of Product Characteristics (SmPC);
- Physician's checklist for adult and paediatric patients, to consider prior to prescribing fingolimod;

- The Patient / Parent / Caregiver's guide, to be provided to all patients, their parents (or legal representatives), and caregivers.
- The pregnancy-specific patient reminder card, to be provided to all patients, their parents (or legal representatives), and caregivers, as applicable.

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) and Zoledronic Acid 4 mg/ml concentrate for solution for infusion (for design and layout) 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 Edest 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 Edest with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 6 May 2020.

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