COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Fingolimod Biocon 0.5 mg, hard capsules (fingolimod hydrochloride)

NL/H/4948/001

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This module reflects the scientific discussion for the approval of Fingolimod Biocon 0.5 mg, hard capsules. The procedure was finalised at 16 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
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 Biocon 0.5 mg, hard capsules, from Biocon Pharma Malta I Limited.

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 Austria, 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 Biocon is a hard gelatine capsules with a white opaque body and bright yellow cap, imprinted with the Biocon logo on the cap and “F 0.5” on the body with black ink. Each capsule contains as active substance 0.5 mg fingolimod (as hydrochloride).

The capsules are packed in PVC/PVdC-aluminium blister pack (in a carton).

The excipients are:
Capsule fill - microcrystalline cellulose (E460), colloidal anhydrous silica (E551) and magnesium stearate (E470b)
Capsule cap – gelatine (E441), titanium dioxide (E171 and iron oxide yellow (E172)
Capsule body - gelatine (E441) and titanium dioxide (E171),
Imprinting ink - shellac (E904), strong ammonia solution (E527), black iron oxide (E172), potassium hydroxide (E525) and propylene glycol (E1520)

Excipients and container closure system are usual for this type of dosage form.

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, freely soluble in water and in ethanol 96%, and practically insoluble in heptane. Fingolimod hydrochloride exhibits polymorphism, the form claimed to be produced by Biocon is polymorphic form I.

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 carried out in three stages. Adequate specifications have been adopted for starting materials, solvents and reagents. The active substance characterisation is acceptable.

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. Particle size distribution, polymorphic form and microbiological quality are included in the specification. 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. Based on the data submitted, a retest period could be granted of 12 months years, which is shorter than the retest period in the ASMF, 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 adequately justified and their functions explained. Quality by design principles are applied in the development of the product formulation and the manufacturing process, but no design space is claimed. The Quality Target Product Profile (QTPP) should take into account the specific needs of the paediatric population, as the drug product is proposed for use in adult patients and paediatric patients of 10 years and older. 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. *In vitro* equivalence has been demonstrated. Furthermore, the proposed dissolution method is acceptable.

Manufacturing process

The manufacturing process has been validated according to relevant European/ICH guidelines. The manufacturing process of the drug product comprises direct blending 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 (≤ 2%), it is considered a non-standard process. Process validation data on the product have been presented for three batches from development site and three batches from the proposed manufacturing site for commercial batches, all in accordance with the relevant European guidelines.

Control of excipients

The excipients comply with Ph.Eur. requirements. These specifications are acceptable. Sufficient information and specifications are provided for the empty gelatine capsules.

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 by HPLC and infrared, assay, related substances, water content, dissolution, uniformity of dosage units, and microbiological quality. 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. Satisfactory validation data for the analytical methods have been provided.

Batch analytical data from three batches from the proposed production sites have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product have been provided for three batches manufactured at the site where the biobatch was produced. Samples of these batches were stored at 25°C/60% RH (36 months), 30°C/65% RH (12 months) and 40°C/75% RH (6 months). Stability data on the

product have also been provided for three batches manufactured at the site for commercial batches. Since significant changes were observed in long-term and accelerated conditions, the shelf-life is based on real time data. Photostability studies performed at ICH conditions showed that the drug product is considered as photo-stable when stored in the original package. The product has a shelf life of 2 years with the following storage conditions 'Store below 25°C. Store in the original package in order to protect from light'.

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 bovine 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. No other materials of human or animal origin are present in the drug product.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Fingolimod Biocon 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 Biocon 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 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 Biocon 0.5 mg, hard capsules (to Biocon Pharma Malta I Limited, Malta) 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 studies
Design
A single-dose, randomised, single period, two-treatment, parallel bioequivalence study was carried out under fasted conditions in 54 healthy male subjects, aged 18-45 years. Each subject received a single dose (1.5 mg by 3 x 0.5 mg tablets) of one of the 2 fingolimod formulations. The tablet was orally administered with 240 ml water after at least 8 hours overnight fasting. There was one dosing period, so there was no washing out period.

Blood samples were collected one hour prior to dosing and post-dose at 1, 2, 4, 6, 8, 10, 11, 12, 13, 14, 15, 16, 18, 20, 24, 28, 30, 32, 34, 36, 48 and 72 hours after administration of the products.

The design of the study is acceptable. The MAH selected a parallel design because the half-life of fingolimod is very long. A parallel design is appropriate for comparative bioavailability studies.

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
One subject was self-withdrawn from the study prior to dosing. Fifty three 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=53	**AUC_{0-72} (pg.h/ml)**	**C_{max} (ng/ml)**	**t_{max} (h)**
Test	76547 ± 14968	1381 ± 249	18 (10 - 34)
Reference	74639 ± 11872	1340 ± 241	20 (10 - 34)
***Ratio (90% CI)**	1.02 (0.94 -1.11)	1.03 (0.95 -1.12)	--
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}, $AUC_{0-\infty}$ and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Fingolimod Biocon 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 Biocon.

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 • Liver transaminase elevation • Macular edema • Opportunistic infections including 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)

The member states agreed that routine pharmacovigilance activities, including specific adverse reactions follow-up questionnaires, routine risk minimisation measures (RMM) and educational material as additional RMM, 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 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 MAH has compared the package leaflet (PL) of Fingolimod Biocon 0.5 mg, hard capsules, submitted in the United Kingdom and for which a user test was performed, to the PL of the reference product, Gilenya. The same level of information is given and practically the same wording is used: only few minor stylistic/typographic changes have been made. As the test product belongs to the same class of medicinal products as the reference product, has a PL with common design, layout and style and as testing is available for the reference product, this is acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Fingolimod Biocon 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 Biocon with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 16 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