COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Inzolfi 0.25 mg, hard capsules (fingolimod (as hydrochloride))

NL/H/4848/002/DC

Date: 12 December 2022

This module reflects the scientific discussion for the approval of Inzolfi 0.25 mg, hard capsules. The procedure was finalised on 11 August 2022. 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 Inzolfi 0.25 mg, hard capsules, from Sandoz B.V.

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 sections 4.4 and 5.1 of the SmPC).

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 line extension application claiming essential similarity with the reference product Gilenya 0.25 mg hard capsules by Novartis Europharm Limited, registered in the EEA since 22 November 2018 (EU/1/11/677/007-008). Sandoz is the generic division of the Novartis group. As the Inzolfi 0.25 mg hard capsules will be produced with the same qualitative and quantitative composition, at the same manufacturing site, using the same manufacturing procedure and the same source of active substances as the currently manufactured reference products Gilenya 0.5 mg/0.25 mg, hard capsules (EU/1/11/677/001-008), this is a so-called “auto-generic”, where no bioequivalence study is needed.

The concerned member states (CMS) involved in this procedure were Austria, Belgium, Czechia, Croatia, Estonia, Hungary, Italy, Latvia, Lithuania and Slovakia.

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

II. QUALITY ASPECTS

II.1 Introduction

Inzolfi is a hard capsule with an ivory opaque cap and body, with black radial imprint “FTY 0.25 mg” on cap and black radial band on body. Each hard capsule contains 0.28 mg of fingolimod hydrochloride, corresponding to 0.25 mg of fingolimod.

The capsules are packed in transparent PVC/PVDC-aluminium blister packs (which can be packed in wallets), or transparent PVC/PVDC-aluminium perforated unit dose blister packs.

The excipients are:
Capsule fill – mannitol, hydroxypropyl cellulose (E463), hydroxypropyl betadex and magnesium stearate (E470b)
Capsule shell – gelatin, titanium dioxide (E171) and yellow iron oxide (E172)
Printing ink – shellac (E904), black iron oxide (E172) and propylene glycol (E1520)

II.2 Drug Substance

The active substance is fingolimod hydrochloride, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is a white to practically white powder and is freely soluble in water. The drug substance exhibits polymorphism; Form I is used consistently in the product. The MAH has submitted full information regarding the drug substance, no ASMF or CEP procedure was used.

Manufacturing process
The manufacturing process of fingolimod hydrochloride, performed in 11 steps, is described by the MAH in sufficient details. 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. The in-house method of measuring impurities and the other analytical methods are equivalent to the requirements of the monograph in the Ph.Eur. Batch analytical data demonstrating compliance with this specification have been provided for three commercial scale batches.

The MAH has provided a toxicological justification for impurities A-F. This is acceptable because the proposed limits and justifications are identical to those of the accepted innovator product Gilenya 0.25 mg hard capsules, for which this new product is an auto-generic. A commitment was made to tighten the limits for these impurities.

Furthermore, a commitment was made to validate the gas chromatography analytical method for one residual solvent and to amend the description of the analytical method accordingly.

Stability of drug substance
Stability data on the active substance have been provided for six full scale batches in accordance with applicable European guidelines demonstrating the stability of the active substance for 60 months long-term and 6 months at accelerated conditions. Based on the data submitted, a retest period could be granted of 5 years.

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. No bioequivalence study was carried out since it is a generic product of the reference product and produced with the same qualitative and quantitative composition, at the same manufacturing site, using the same manufacturing procedure and the same source of active substance. The choice of excipients is adequately justified and their functions explained. The selection of the dissolution method has been explained. The description of the manufacturing process development has been provided and is acceptable.

Manufacturing process

The manufacturing process has been validated according to relevant European guidelines. The process includes preparation of solutions including solution with drug substance, granulation and drying, pre-blending and blending, and encapsulation steps. This is satisfactorily described with in-process controls. Process validation data on the product have been presented for three commercial scale batches in accordance with the relevant European guidelines.

Control of excipients

The excipients comply with Ph. Eur. or international standards. 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 appearance, identity, mean mass of contents, assay, degradation products, water content, dissolution, content uniformity, and microbiological testing. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product.

A commitment was made by the MAH that tightening of the dissolution limit to Q=85% in 15 minutes will be evaluated once data from 15 batches are available (June 2023 at the latest). Wider shelf-life limits were applied for assay and degradation products, which are acceptable.

The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on three full scale batches, demonstrating compliance with the proposed release specification. The risk assessment on elemental impurities indicate that no additional monitoring is required.

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

Stability of drug product

Stability data on the product has been provided for three registration batches stored at 25°C/60% RH (36 months), 30°C/75% RH (36 months) and 40°C/75% RH (6 months). These batches are manufactured with 2% overage of the active substance. Statistical shelf life evaluation has been performed using normalized assay results to support the proposed shelf life and storage conditions of the proposed drug product manufactured without overage. In addition, stability data is provided on three commitment batches stored at 25°C/60% RH (24 months), 30°C/65% RH (24 months), 30°C/75% RH (24 months) and 40°C/75% RH (6 months). The proposed shelf life of 24 months is supported by the stability data. Photostability studies show that the drug product is not sensitive to light. The temperature storage condition "Do not store above 25°C" is accepted.

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

The gelatin capsules are sourced from bovine origin. 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. 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 Inzolfi has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

The following post-approval commitments were made:

- Tighten the limits for impurities A-F,
- Validate the gas chromatography analytical method for one residual solvent and amend the description of the analytical method accordingly,
- Tighten the dissolution limit to Q=85% in 15 minutes (once data from 15 batches are available, June 2023 at the latest).

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Inzolfi 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

Fingolimod hydrochloride is a well-known active substance with established efficacy and tolerability. Pharmacodynamic, pharmacokinetic and toxicological properties of fingolimod hydrochloride are well known. 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.

IV.1 Pharmacokinetics

As the Inzolfi 0.25 mg hard capsules will be produced with the same qualitative and quantitative composition, at the same manufacturing site, using the same manufacturing procedure and the same source of active substances as the currently manufactured reference products Gilenya 0.5 mg/0.25 mg, hard capsules (EU/1/11/677/001-008), no bioequivalence studies are needed.

IV.2 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 Inzolfi.

Table 1. Summary 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 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)

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

IV.3 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Gilenya. No bioequivalence study was needed and no new clinical studies were conducted. 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 and 0.25 mg hard capsules (EU/1/11/677/001-008). 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

Inzolfi 0.25 mg, hard capsules has a proven chemical-pharmaceutical quality and is a generic form of Gilenya 0.25 mg hard capsules. Gilenya is a well-known medicinal product with an established favourable efficacy and safety profile. Since both the reference and current product are manufactured in identical manner, with identical composition, no bioequivalence study is deemed necessary.

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 Inzolfi with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 11 August 2022.

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
N/A	N/A	N/A	N/A	N/A	N/A