COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Inzolfi 0.5 mg, hard capsules (fingolimod hydrochloride)

NL/H/4848/001/DC

Date: 13 October 2021

This module reflects the scientific discussion for the approval of Inzolfi 0.5 mg, hard capsules. The procedure was finalised at 27 May 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
PML	Progressive Multifocal Leukoencephalopathy
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy
VZV	Varicella Zoster Virus

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Inzolfi 0.5 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 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, Belgium, Bulgaria, Croatia, Czechia, Denmark, Estonia, Finland, Greece, Hungary, Iceland, Italy, Latvia, Lithuania, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Sweden and the United Kingdom (Northern Ireland).

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 bright yellow opaque cap and white opaque body, imprinted with black ink “FTY 0.5 mg” on the cap and two radial bands imprinted on the body with yellow ink. Each capsule contains as active substance 0.5 mg of fingolimod (as hydrochloride).

The capsules are packed in transparent PVC/PVDC-aluminium blister packs.

The excipients are:
Capsule content - mannitol and magnesium stearate
Capsule shell - gelatine, titanium dioxide (E171) and yellow iron oxide (E172)
Printing ink - shellac (E904), propylene glycol (E1520), potassium hydroxide, black iron oxide (E712), yellow iron oxide (E172), titanium dioxide (E171) and dimethicone

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 to almost white crystalline powder and freely soluble in water. The drug substance exhibits polymorphism.
The provided general information corresponds with the information in the monograph and is therefore acceptable. Polymorphism is adequately discussed and the employed form I is controlled by an X-ray powder diffraction (XRPD) in the drug substance specification.

Manufacturing process
The manufacturing process consists of 11 steps, which are adequately described according to the requirements of the EMA Guideline on the chemistry of active substances. Adequate specifications have been adopted for starting materials, solvents and reagents. The specification of the intermediates is acceptable and all in-process controls have been adequately established. 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 commercial scale batches.

Stability of drug substance
Stability data on the active substance have been provided for three sets of stability data originating from different production dates and sites, in accordance with applicable European guidelines. Based on the data submitted, a retest period could be granted of five years when stored in sealed flat bag of quadruple laminated foil below 30°C.

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. The selection of the dissolution method has been explained. The omission of bioequivalence studies is justified, as the drug product under review is identical to the originator's product with respect to composition, manufacturing site, manufacturing process and origin of drug substance. The description of

the manufacturing process development lacks of details, but no issue is raised as sufficient information is provided in the process validation.

Manufacturing process

The manufacturing process, which includes screening, dry blending and encapsulating steps, is satisfactorily described with in-process controls and has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for three full scale batches in accordance with the relevant European guidelines.

Control of excipients

The excipients comply with Ph. Eur. or international standards. Requirements on functionality characteristics for mannitol are included in the specification. 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, assay, degradation, dissolution, content uniformity, microbiological testing. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. Wider shelf life limits were applied for assay and degradation products, which is acceptable. Satisfactory validation data for the analytical methods have been provided. Batch analytical data from three full scale batches from the proposed production site have been provided, demonstrating compliance with the specification.

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 have been provided for three registration batches stored at 25°C/60% RH (36 months) and 40°C/75% RH (6 months), and for five commitment batches stored at 25°C/60% RH (24 months) and 40°C/75% RH (6 months). The batches were stored in PVC/PVDC blister with aluminium lidding foil or HDPE bottles. Stability data from two additional batches manufactured with amended manufacturing process has been provided. Photostability studies performed at ICH conditions showed that the drug product is not sensitive to light. On basis of the data submitted, a shelf life was granted of two years. The labelled storage conditions are: “Do not store above 25 °C. Store in the original package in order to protect from moisture.”.

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

Scientific data and/or 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 Inzolfi 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 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 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 no bioequivalence study. This lack has been justified based on the statement that the proposed generic Fingolimod 0.5 mg hard capsules have the same qualitative and quantitative composition as the currently manufactured reference products Gilenya, are manufactured at the same manufacturing site according to the same manufacturing process and using the same sources of the active ingredient. The justification not to perform bioequivalence studies is considered acceptable.

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 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 (Progressive Multifocal Leukoencephalopathy (PML), *Varicella zoster* virus (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

Next to routine pharmacovigilance activities and routine risk minimisation measures, the MAH committed to perform additional risk minimisation measures pursuant to Article 21a/22 of Directive 2001/83/EC.

The MAH shall ensure that in each member state where Inzolfi is marketed, all physicians who intend to prescribe fingolimod 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.3 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. As the product applied for is identical to the reference product, with respect to composition, manufacturing site, manufacturing process and origin of drug substance, it is agreed that no clinical studies have been performed. 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 (EU/1/11/677), and to Alendronate/Colecalciferol 70 milligrams/140 micrograms tablets for layout and design. 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 0.5 mg, hard capsules have a proven chemical-pharmaceutical quality and are 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.

No bioequivalence study was deemed necessary, as the medicinal product is identical to the originator's product with respect to composition, manufacturing site, manufacturing process and origin of drug substance.

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 27 May 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