COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Posaconazol Mylan 100 mg, gastro-resistant tablets (posaconazole)

NL/H/6040/001/DC

Date: 16 July 2024

This module reflects the scientific discussion for the approval of Posaconazol Mylan 100 mg, gastro-resistant tablets. The procedure was finalised at 2 October 2019 in Germany (DE/H/5575/001/DC). After a transfer on 23 November 2023, the current RMS is the Netherlands. 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
EMA	European Medicines Agency
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
RMS	Reference Member State
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 Posaconazol Mylan 100 mg, gastro-resistant tablets, from Mylan Pharmaceuticals Limited.

Posaconazole inhibits the enzyme lanosterol 14α-demethylase (CYP51), which catalyses an essential step in ergosterol biosynthesis.

Posaconazole has been shown in vitro to be active against the following microorganisms: *Aspergillus* species (*Aspergillus fumigatus, A. flavus, A. terreus, A. nidulans, A. niger, A. ustus*), *Candida* species (*Candida albicans, C. glabrata, C. krusei, C. parapsilosis, C. tropicalis, C. dubliniensis, C. famata, C. inconspicua, C. lipolytica, C. norvegensis, C. pseudotropicalis*), *Coccidioides immitis, Fonsecaea pedrosoi*, and species of *Fusarium, Rhizomucor, Mucor*, and *Rhizopus*.
The microbiological data suggest that posaconazole is active against *Rhizomucor, Mucor,* and *Rhizopus*; however, the clinical data are currently too limited to assess the efficacy of posaconazole against these causative agents.

Pharmacotherapeutic group: Antimycotics for systemic use, triazole derivatives, ATC code: J02AC04.

Posaconazole is indicated for use in the treatment of the following fungal infections in adults:

- Invasive aspergillosis in patients with disease that is refractory to amphotericin B or itraconazole or in patients who are intolerant of these medicinal products;
- Fusariosis in patients with disease that is refractory to amphotericin B or in patients who are intolerant of amphotericin B;
- Chromoblastomycosis and mycetoma in patients with disease that is refractory to itraconazole or in patients who are intolerant of itraconazole;
- Coccidioidomycosis in patients with disease that is refractory to amphotericin B, itraconazole or fluconazole or in patients who are intolerant of these medicinal products.

Refractoriness is defined as progression of infection or failure to improve after a minimum of 7 days of prior therapeutic doses of effective antifungal therapy.

and indicated for **prophylaxis** of invasive fungal infections in the following patients:

- Patients receiving remission-induction chemotherapy for acute myelogenous leukemia (AML) or myelodysplastic syndromes (MDS) expected to result in prolonged neutropenia and who are at high risk of developing invasive fungal infections;
- Hematopoietic stem cell transplant (HSCT) recipients who are undergoing high-dose immunosuppressive therapy for graft versus host disease and who are at high risk of

developing invasive fungal infections.

Dosing and duration of therapy is based on type and severity of the fungal infection.

A comprehensive description of the up-to-date indications and posology is given in the SmPC. Of note: The tablet and oral suspension are not to be used interchangeably due to the differences between these two formulations in frequency of dosing, administration with food and plasma drug concentration achieved. Therefore, follow the specific dosage recommendations for each formulation.

The decentralised applications concern a generic version of Noxafil® (100 mg gastro-resistant tablets). The legal basis for this application is article 10(1) of Directive 2001/83/EC (generic application). The originator product is Noxafil® 100 mg gastro-resistant tablets by Merck Sharp & Dohme Ltd, UK, registered within the EU since 25 October 2005.

The concerned member states (CMS) involved in this procedure were Croatia, France, Ireland, Italy, United Kingdom (Northern Ireland), Norway, Poland, Portugal, Romania and Sweden.

The applicant has submitted two single dose bioequivalence studies under fed and fastening conditions with the Posaconazole 100 mg gastro-resistant tablets.

The RMS has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for this product type at all sites responsible for the manufacture and assembly of this product prior to granting its national authorisation.
The GCP/GLP aspects of the clinical phases of the study are sufficiently documented.
A statement on the application of appropriate GCP and GLP standards in the submitted studies has been provided.

The applicant submitted module 1.7.1 as part of this application. In conclusion, with respect to Article 8 of Regulation (EC) No 141/2000, Posaconazol Mylan 100 mg, gastro-resistant tablets is considered not similar (as defined in Article 3 of Commission Regulation (EC) No. 847/2000) to Cresemba.

II. QUALITY ASPECTS

II.1 Drug Substance

Posaconazole is an established drug substance; however, it is not subject of a monograph in the Ph.Eur. The ASMF procedure is used. A letter of access for procedure is provided.

Manufacturing process
The active substance is controlled according to the general requirements of Ph. Eur., EU/ICH guidance including Q6A, Q3A and Q3C as well as EDQM guidance.
The in-house analytical methods are adequately described and validated.

Quality control of drug substance
Batch analysis data are provided to confirm that the active substance of the required quality can be obtained consistently by the proposed manufacturing process.
Stability of drug substance
Stability studies are performed with the active substance in line with ICH guidance. Based on the presented stability studies, an appropriate re-test period has been set.

II.2 Medicinal Product

Pharmaceutical development
Gastro-resistant tablets were formulated to contain 100 mg posaconazole. The product will be marketed in Triplex (PVC/PE/PVdC) white opaque-aluminium blister packs.
The drug product Posaconazol Mylan gastro-resistant tablets was developed to be identical to Merck Sharp & Dohme Ltd. from the European market. Posaconazol Mylan gastro-resistant tablets are yellow coated, capsule shaped tablets, debossed with “100P” on one side and plain on the other side.
Critical attributes of the drug substance used in the drug product that can affect the product performance or manufacturability are accordingly controlled. Posaconazole is not subject of a monograph in the Ph.Eur. There are no compatibility issues noted between the active ingredient and other ingredients present in the formulation.

Manufacturing process
The manufacturing process of Posaconazole 100 mg gastro-resistant tablets comprises different stages. The process is considered as non-standard. The presented in-process controls are considered sufficient.
Overall, the process is considered to be satisfactorily validated. The critical phases were evaluated and the process found to be well controlled producing consistent quality of the medicinal product that complies with the acceptance criteria and finished product specifications.

Control of excipients
The excipients are well known excipients used in pharmaceuticals and similar excipients are used in the reference product. The use of antioxidant propyl gallate in the generic formulation of Posaconazole gastro-resistant tablets has been justified.

Quality control of drug product
The release and shelf-life specifications include appropriate tests for this kind of dosage form. Specifications are based on ICH limits or the Ph.Eur. The Ph.Eur. and in-house methods have all been adequately described and validated.

Stability of drug product
Stability data from three commercial scale batches of finished product stored under long term conditions (25 ºC / 60% RH) and accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The batches of Posaconazole Accord 100 mg gastro-resistant tablets are identical to those proposed for marketing and were packed in the primary packaging

proposed for marketing (white opaque PVC/PE/PVdC-Alu blisters), as well as Alu-Alu blisters, white opaque PVC/PCTFE-Alu blisters and HDPE bottles.
The analytical procedures used are stability indicating.
The finished product is generally very stable and no degradational trends were observed over time. In addition, one batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. No significant degradation was observed.Based on available stability data, the proposed shelf-life of 30 months with no storage conditions is acceptable.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
No excipients of human or animal origin are used in the manufacturing of Posaconazole 100 mg gastro- resistant tablets.

III. NON-CLINICAL ASPECTS

There are no objections to approval of Posaconazol Mylan 100 mg, gastro-resistant tablets from a non-clinical point of view.

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Posaconazol Mylan 100 mg, gastro-resistant tablets are intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

IV. CLINICAL ASPECTS

IV.1 Introduction

The Applicant has submitted two single dose bioequivalence studies under fed and fastening conditions with Posaconazole 100 mg gastro-resistant tablets.

IV.2 Pharmacokinetics

The pharmacokinetic properties of posaconazole are well-known. They are adequately described in the relevant section of the SmPC regarding healthy subjects as well as specific target population.

Bioequivalence studies
Study CLCD-023-16 (Fed condition):
The study was performed as a randomized, open label, two treatment, three period, three sequence, single oral dose, crossover, partial replicate, pivotal, bioequivalence study of Posaconazole 100 mg gastro-resistant tablets, with Noxafil® 100 mg magensaftresistente

Tabletten (Noxafil® 100 mg gastro-resistant tablets) of Merck Sharp & Dohme Ltd, United Kingdom in healthy adult human male subjects under fed (high-fat) condition.

Sixty-six healthy male subjects, aged 18 - 45 years, were included in this study.
Subjects received a single dose of Posaconazol Mylan 100 mg, gastro-resistant tablets [test (T)] or Noxafil® 100 mg gastro-resistant tablets [reference (R)].
A washout period of 14 days was maintained between the dosing of each period.

Study CLCD-024-16 (Fasting condition):
The study was performed as a randomized, open label, two treatment, three period, three sequence, single oral dose, crossover, partial replicate, pivotal, bioequivalence study of Posaconazol Mylan 100 mg, gastro-resistant tablets, with Noxafil® 100 mg magensaftresistente Tabletten (Noxafil® 100 mg gastro-resistant tablets) of Merck Sharp & Dohme Ltd, United Kingdom in healthy adult human male subjects under fasting condition.

Sixty-six healthy male subjects, aged 18 - 45 years, were included in this study.
Subjects received a single dose of Posaconazole 100 mg gastro-resistant tablets [test (T)] or Noxafil® 100 mg gastro-resistant tablets [reference (R)] with 240 mL of water on an overnight fast of at least 10 hours.
A washout period of 14 days was maintained between the dosing of each period.

Based on the submitted bioequivalence studies Posaconazole 100 mg gastro-resistant tablets is considered bioequivalent with Noxafil® 100 mg gastro-resistant tablets Merck Sharp & Dohme Ltd. under fed condition as well as under fasting condition.

IV.3 Pharmacodynamics

There are no new data. The pharmacodynamic profile of posaconazole is well characterized in literature and adequately presented in the relevant section of the SmPC.

IV.4 Summary Pharmacovigilance system

The applicant has submitted a signed Summary of the Applicant's and/or Proposed Future MAH's Pharmacovigilance System. Provided that the Pharmacovigilance System Master File fully complies with the new legal requirements as set out in the Commission Implementing Regulation and as detailed in the GVP module, the RMS considers the Summary acceptable.

IV.5 Risk Management Plan

Risk management plan has been 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 the medicinal product(s) applied for authorisation.

Summary table of safety concerns as approved in RMP

Important identified risks	• Hepatic - elevated liver enzymes; hepatotoxicity; hepatic failure; hepatitis • Blood - thrombotic thrombocytopenia purpura; hemolytic uraemic syndrome • Cardiac - Torsade de Pointes • General - drug interaction
Important potential risks	• Blood - agranulocytosis; aplastic anaemia • Cardiac - QTc prolongation; heart failure; myocardial infarction • Psychiatric - depression; suicide • Endocrine - adrenal insufficiency • CNS - convulsion; cerebral ischemia; cerebral haemorrhage • Respiratory - pulmonary haemorrhage • Vascular- hypertension; venous thrombosis; arterial thrombosis • Metabolism – hypokalaemia • Visual - photopsia; visual brightness; visual disturbances • Neoplasms - occurrence of any neoplasm/malignancy, especially: hepatic adenoma; hepatic neoplasm; adrenal adenoma; adrenal neoplasm; phaeochromocytoma • Infections - fungal infections
Missing information	• Experience in children

Pharmacovigilance Plan

Not applicable. Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed, which is endorsed.

Risk minimisation measures

Not applicable. Routine risk minimisation is suggested and no additional risk minimisation activities are proposed, which is endorsed.

Summary of the RMP

Overall, the submitted RMP is considered approvable.

An updated RMP should be submitted:

- At the request of the RMS;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

Periodic Safety Update Report (PSUR)
Use the below statement in case a substance is listed in the published EURD list. With regard to PSUR submission, the MAH should take the following into account:

- 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.
- For medicinal products authorized under the legal basis of Article 10(1) or Article 10a of Directive 2001/83/EC, no routine PSURs need to be submitted, unless otherwise specified in the EURD list.
- In case the active substance will be removed in the future from the EURD list because the MAs have been withdrawn in all but one MS, the MAH shall contact that MS and propose DLP and frequency for further PSUR submissions together with a justification.

V. USER CONSULTATION

The medicinal product is subject to medical prescription. The proposed multiple bridging is justified. The submitted PL for the Posaconazol Mylan 100 mg, gastro-resistant tablets is acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

There are no objections against the approval of Posaconazol Mylan 100 mg gastro-resistant tablets. The application is approved. For intermediate amendments see current product information.

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
NL/H/6040/001 /R/001	Renewal	No	03-06-2024	Approved	N.A.