COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Posaconazol Devatis 100 mg gastro-resistant tablets
(posazonazole)

NL/H/5690/001/DC

Date: 12 November 2024

This module reflects the scientific discussion for the approval of Posaconazol Devatis 100 mg gastro-resistant tablets. The procedure was finalised on 13 February 2024. 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 Devatis 100 mg gastro-resistant tablets, from Devatis GmbH.

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

- invasive aspergillosis

The product indicated for use in the treatment of the following fungal infections in paediatric patients from 2 years of age weighing more than 40 kg and 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.

The product is also indicated for prophylaxis of invasive fungal infections in the following paediatric patients from 2 years of age weighing more than 40 kg and adults:

- patients receiving remission-induction chemotherapy for acute myelogenous leukaemia (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

A comprehensive description of the up-to-date indications and posology is given in the SmPC.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC, which concerns a generic application.

In this decentralised procedure, essential similarity is proven between the new product and the innovator product Noxafil 100 mg gastro-resistant tablets, which has been registered in the EEA via a centralised procedure (EU/1/05/320/002-003) since 25 October 2005.

The concerned member state (CMS) involved in this procedure was Germany.

Similarity assessment

According to Article 8(1) of Regulation (EC) No 141/2000, no marketing authorisation can be granted for a product similar to an orphan medicinal product for a period of ten years, when this concerns a similar medicinal product with the same therapeutic indication. A similarity assessment has been performed between Posaconazol Devatis and Cresemba, which obtained orphan market exclusivity for "Treatment of invasive aspergillosis" on 25 October 2005, based on designation EU/3/14/1284. The similarity assessment report concluded that Posaconazol Devatis is considered not similar (as defined in Article 3 of Commission Regulation (EC) No. 847/2000) to Cresemba.

II. QUALITY ASPECTS

II.1 Introduction

Posaconazol Devatis is a yellow coloured, oblong, biconvex film-coated, gastro-resistant tablet. It contains as active substance 100 mg of posaconazole.

The excipients are:
Tablet core - Hypromellose acetate succinate; cellulose, microcrystalline; hydroxypropyl cellulose; silica colloidal anhydrous; croscarmellose sodium; and magnesium stearate.

Tablet coating - polyvinyl alcohol; titanium dioxide (E171); macrogol 3350; talc; and iron oxide yellow (E172).

The gastro-resistant tablets are packed in an opaque polyvinyl chloride/polychlorotrifluoroethylene/aluminium (PVC/PCTFE/Alu) blister.

II.2 Drug Substance

The active substance is posaconazole, and is classified as a Biopharmaceutics Classification System (BCS) class II molecule and is not described in any Pharmacopoeia. Posaconazole is soluble in dichloromethane and practically insoluble in water and in isopropyl alcohol. Posaconazole contains four chiral centers and hence it exhibits stereoisomerism. However, the manufacturing process used by the ASMF-holder consistently produces the isomer. For this product, polymorphic crystalline 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 synthesising posaconazole from the three starting materials in six stages. In the last stage isopropyl alcohol and dichloromethane are used. The ASMF-holder included a specification for heavy metals in the drug substance specification. No class 1 solvents are used. Adequate specifications have been adopted for starting materials, solvents and reagents. The active substance has been adequately characterised and the manufacturing process is described in sufficient detail.

Quality control of drug substance

The active substance specification has been established in-house by the ASMF holder with tests for appearance, identification, polymorphism, sulphated ash, specific optical rotation, water by Karl Fischer titration, assay, related substances, chiral purity, residual solvents, and particle size distribution. The drug product manufacturer specification of the drug substance is identical to that of the ASMF-holder and is acceptable. An acceptable justification is provided for not including a control for microbiological quality in the drug substance specification from the drug product manufacturer. 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 small scale and three higher scale batches in accordance with applicable European guidelines demonstrating the stability of the active substance for 72 months. Based on the data submitted, a retest period could be granted of 5 years 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 product was optimised for enteric polymer concentration, impact of diluent, binder, disintegrant, lubricant and film-coating. The choices of the packaging and manufacturing process are adequately justified.

A process validation batch was used in two bioequivalence studies under fed and fasting conditions with the reference product Noxafil. The batch of the test product is acceptable as it is of commercial scale and the assay content was within 5% of the assayed content of the reference product. Comparative dissolution of the test and reference product was performed

in line with the requirements for gastro-resistant tablets, and dissolution profiles for both products were comparable.

The choice of the QC dissolution method has been discussed, and the discriminatory power thereof has been sufficiently demonstrated. Hence, the QC dissolution method is acceptable.

The alcohol dose dumping study is performed in the acid stage with different concentrations of alcohol, i.e., 5%, 10% and 20% v/v, and concluded that the test and reference product show comparable drug release behaviour under these conditions.

Manufacturing process

The drug product is manufactured with the hot melt extrusion method. The main manufacturing steps are sifting, mixing, hot melt extrusion, milling, pre-lubrication, lubrication, compression, film coating and blister packing. The manufacturing process has been validated according to relevant European/ICH guidelines. 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 the Ph.Eur. except for Hypromellose acetate succinate, which is complying with current edition of USP-NF monograph for Hypromellose acetate succinate. The components of the Opadry II Yellow 85F220219 are complying with current edition of European Pharmacopoeia except iron oxide yellow, which is complying with EU regulation 231/2012. Additional information on the functionality related characteristics of the used excipients is also provided. 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 description, identification, uniformity of dosage units, dissolution, hardness, water content, assay, degradation products and microbial limits. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. An adequate nitrosamines risk evaluation report has been provided. No risk for presence of nitrosamines in the drug product was identified.

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 from three batches stored at 25°C/ 60% RH (18 months) and 40°C/75% RH (6 months) in accordance with applicable European guidelines. Photostability study showed that the product is stable when exposed to light. On basis of the data submitted, a shelf life was granted of 30 months. No specific storage conditions needed to be included in the SmPC or on the label.

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

There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Posaconazol Devatis 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 Posaconazol Devatis is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment was therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a generic formulation of Noxafil which is available on the European market. Reference was made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which was 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

Posaconazole is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The member states agreed that no further clinical studies are required, besides the two bioequivalence studies, which are discussed below.

IV.2 Pharmacokinetics

The MAH conducted two bioequivalence studies in which the pharmacokinetic profile of the test product Posaconazol Devatis 100 mg gastro-resistant tablets (Devatis GmbH, Germany) was compared with the pharmacokinetic profile of the reference product Noxafil 100 mg gastro-resistant tablets (Merck Sharp & Dohme B.V., the Netherlands).

The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution study results and composition. The formula and preparation of the bioequivalence batch was identical to the formula proposed for marketing.

The dissolution was investigated according to the EMA Bioequivalence guideline. The calculated f_2 similarity factor values were within criteria (>50%). An f_2 value between 50 and 100% suggests that the two dissolution profiles are similar.

Bioequivalence study, fasting conditions

Design

A single-dose, randomised, three-period, two-treatment, three-sequence, open label, partial replicate bioequivalence study was carried out under fasted conditions in 36 healthy male subjects, aged 23-44 years. Each subject received a single dose (100 mg) of one of the two posaconazole formulations. The tablet was orally administered with 240 mL water after an overnight fasting period of 10 hours. There were three dosing periods. Period 1 and 2 were separated by a washout period of 16 days. Period 2 and 3 were separated by a washout period of 20 days.

Blood samples were collected pre-dose and at 1, 1.5, 2, 2.5, 3, 3.33, 3.67, 4, 4.33, 4.67, 5, 5.33, 5.67, 6, 6.5, 7, 8, 10, 12, 16, 24, 36, 48, 72, 96, 120 and 144 hours after administration of the products.

The design of the study is acceptable.

Posaconazole may be taken without reference to food intake. From the literature it is known that food does not interact with the absorption of posaconazole. 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

All 36 subjects completed at least 2 periods. Therefore, all 36 subjects were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of posaconazole, 100 mg, under fasted conditions.

Treatment N=36	**AUC_{0-t} (ng.h/mL)**	**$AUC_{0-\infty}$ (ng.h/mL)**	**C_{max} (ng/mL)**	**t_{max} (h)**
Test	9951 ± 3516	10219 ± 3719	299 ± 98	4.67 (2.00-8.00)
Reference	10099 ± 3226	10433 ± 3513	294 ± 107	5.00 (2.00-10.00)
***Ratio (90% CI)**	0.99 (0.92-1.07)	0.99 (0.92-1.06)	1.05 (0.96-1.12)	-

$AUC_{0-\infty}$	Area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t}	Area under the plasma concentration-time curve from time zero to the last measurable plasma concentration
C_{max}	Maximum plasma concentration
t_{max}	Time after administration when maximum plasma concentration occurs
CI	Confidence interval

**ln-transformed values*

Bioequivalence study, fed conditions

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, open label, balanced, crossover bioequivalence study was carried out under fed conditions in 28 healthy male subjects, aged 23-44 years. Each subject received a high-fat, high calories (approximately 800-1000 calories) breakfast 30 minutes pre-dose. Each subject received a single dose (100 mg) of one of the two posaconazole formulations. The tablet was orally administered with 240 mL water. Drinking water was not allowed from 1 hour before dosing until 1 hour post-dose. There were two dosing periods, separated by a washout period of 16 days.

Blood samples were collected pre-dose and at 1, 1.5, 2, 2.5, 3, 3.33, 3.67, 4, 4.33, 4.67, 5, 5.33, 5.67, 6, 6.5, 7, 8, 10, 12, 16, 24, 36, 48, 72, 96, 120 and 144 hours after administration of the products.

The design of the study is acceptable.

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

28 subjects enrolled in the study. Two subjects were withdrawn from the study, one due to not reporting to the facility between dosing periods and the other due to having an adverse event before dosing in the second period. 26 subjects were eligible for pharmacokinetic analysis.

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of posaconazole, 100 mg, under fed conditions.

Treatment N=26	AUC_{0-t} (ng.h/mL)	$AUC_{0-\infty}$ (ng.h/mL)	C_{max} (ng/mL)	t_{max} (h)
Test	12342 ± 3619	12840 ± 4313	376 ± 96	6.50 (3.00-16.00)
Reference	12430 ± 3642	12846 ± 4162	389 ± 81	5.50 (2.50-12.00)
***Ratio (90% CI)**	0.99 (0.97-1.02)	1.00 (0.97-1.02)	0.96 (0.89-1.05)	-

$AUC_{0-\infty}$	Area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t}	Area under the plasma concentration-time curve from time zero to the last measurable plasma concentration
C_{max}	Maximum plasma concentration
t_{max}	Time after administration when maximum plasma concentration occurs
CI	Confidence interval

**ln-transformed values*

Conclusion on bioequivalence studies:
The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence studies Posaconazol Devatis is considered bioequivalent with Noxafil.

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 Posaconazol Devatis.

Table 3. Summary table of safety concerns as approved in RMP

Important identified risks	None
Important potential risks	None
Missing information	None

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures 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 Noxafil. No new clinical studies were conducted. The MAH demonstrated

through bioequivalence studies 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 Posaconazol Devatis 40 mg/mL oral suspension, NL/H/4123/001/DC. 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

Posaconazol Devatis 100 mg gastro-resistant tablets has a proven chemical-pharmaceutical quality and is a generic form of Noxafil 100 mg gastro-resistant tablets. Noxafil 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 Posaconazol Devatis with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 13 February 2024.

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/5690/001 /IB/001	Extension of the shelf life of the finished product	Yes	24 July 2024	Refused	Cannot be accepted based on extrapolation of the available stability data
NL/H/5690/001 /IA/002	Update of product information after PSUSA	Yes	04 November 2024	Approved	N.A.