COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Posaconazol Devatis 40 mg/ml oral suspension

(posaconazole)

NL/H/4123/001/DC

Date: 1 May 2019

This module reflects the scientific discussion for the approval of Posaconazol Devatis 40 mg/ml oral suspension. The procedure was finalised at 5 September 2018. 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 Posaconazol Devatis 40 mg/ml oral suspension, from Devatis GmbH.

The product 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;
- Oropharyngeal candidiasis: as first-line therapy in patients who have severe disease or are immunocompromised, in whom response to topical therapy is expected to be poor.

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 oral suspension is also 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.

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 Noxafil 40 mg/ml, oral suspension which has been registered in the EEA by Merck Sharp & Dohme B.V. since 25 October 2015 through a centralised procedure (EU/1/05/320).

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

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

II. QUALITY ASPECTS

II.1 Introduction

Posaconazol Devatis is a white to off-white oral suspension. Each ml of suspension contains 40 mg of posaconazole.

The oral suspension is packed in a glass amber type III bottle closed with a plastic child-resistant cap (polypropylene) and a measuring spoon (propylene) with 2 graduations (2.5 ml and 5 ml).

The excipients are: polysorbate 80 (E433), xanthan gum (E415), sodium benzoate (E211) citric acid monohydrate (E330), sodium citrate (E331), glycerol (E422), liquid glucose, titanium dioxide (E171), simethicone emulsion 30 %, artificial cherry flavour containing benzyl alcohol and purified water.

II.2 Drug Substance

The active substance is posaconazole, an established active substance, however not described in any pharmacopeia. Posaconazole is a white to off-white powder and soluble in dichloromethane and practically insoluble in water. Different polymorphic forms exist; form-I is used. The active substance contains four chiral centres and is non-hygroscopic.

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 of posaconazole is described in the ASMF and is divided into six stages consisting of eight steps in total. The proposed starting materials and are acceptable. Overall, the manufacturing is acceptable and adequately described.

Quality control of drug substance

The active substance specification of the ASMF-holder is adopted with additional limits for particle size. The proposed limits for particle size are acceptable. Descriptions of all analytical procedures have been provided and the analytical methods have been adequately validated.

The specification is considered adequate to control the quality. Batch analytical data demonstrating compliance with this specification have been provided for three batches.

Stability of drug substance

No data has been provided on the stability of the active substance. Reference is made to the ASMF. The stability data provided in the ASMF support the claimed retest period and storage condition. The active substance is stable for 48 months with storage condition 'Preserve in well closed containers at controlled room temperature between 20 °C and 25 °C (excursions are allowed between 15°C and 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 justified and their functions explained. Development trials were performed to obtain a stable suspension dosage form. The following formulation development studies were performed: physical characterisation of reference product, chemical characterisation of reference product, drug substance particle size selection for product development, manufacturing process selection.

A bioequivalence study has been performed. The biobatch is manufactured conform the proposed manufacturing process and stability and validation data of the biobatch have been provided. Dissolution profiles demonstrate that rapid dissolution was observed in pH 1.2 and pH 4.5 acetate dissolution media i.e. more than 85% of drug release was observed with in 15 min of time point and thus considered to be similar. At pH 6.8 similarity factor was found to be 65.1 and thus similar. The media used in these tests included SLS. Similarity was also demonstrated by comparison of the dissolution of the biobatches at three different pHs without 0.3% SLS.

Manufacturing process

The manufacturing process of the product involves preparation of the dispersion medium, dispersion of the drug substance, homogenisation process, final compounding and packaging. The manufacturing process has been validated according to relevant European guidelines. Process validation data on the product have been presented for three pilot batches in accordance with the relevant European guidelines. The product is manufactured using conventional manufacturing techniques. Process validation for full-scale batches will be performed post authorisation.).

Control of excipients

The excipients comply with the European pharmacopoeia with the exception of the cherry flavour. These specifications are acceptable. A statement that the cherry flavor complies with regulation 178/2002 and amendment and the EU regulation 1334/2008 and amendments has been provided.

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 of posaconazole, identification of sodium benzoate, titanium dioxide, redispersibility time, deliverable volume, viscosity, pH, uniformity of dosage units by content uniformity, assay of posaconazole, assay of sodium benzoate, dissolution, related substances, particle size and microbial contamination. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. The release and shelf-life limits are identical. Satisfactory validation data for the analytical methods have been provided. Batch analytical data three pilot scaled 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 for three pilot scaled batches in upright and inverted position at 25°C/60% RH (12 months upright; 18 months inverted), 30°C/65% RH (12 months upright and inverted) and 40°C/75% RH (6 months upright and inverted). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in the proposed packaging. Between the upright and inverted batches no differences were observed under any condition. At long term, intermediate and accelerated conditions no trends are observed. The efficacy of preservatives has been established using the test for efficacy of antimicrobial preservation of the Ph.Eur. The proposed shelf life of 24 months can be granted. The storage condition “This medicinal product doesn’t require any special storage conditions. Do not freeze” and packaging are acceptable.

The same batches which are included in the stability studies are also tested for in-use stability under the same storage conditions as mentioned. The in-use stability studies justify an in use shelf life of 28 days. The efficacy of the antimicrobial preservative under simulated in-use conditions has been established.

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 is 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 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

Posaconazol 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 for Posaconazol Devatis 40 mg/ml oral suspension (Devatis GmbH, Germany) is compared with the pharmacokinetic profile of the reference product Noxafil 40 mg/ml, oral suspension (Merck Sharp & Dohme B.V., NL).

The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution results and compositions of the test product with the EU reference product. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Bioequivalence study

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fed conditions in 48 healthy male subjects, aged 21-43 years. Each subject received a single dose (400 mg; 10 ml oral suspension 40 mg/ml) of one of the 2 posaconazole formulations. The suspension was orally administered with 240 ml water 30 minutes after start intake of a high fat, high caloric breakfast (bread with cheese, whole milk with sugar, walnuts, cutlet, green chutney and tomato chutney). There were 2 dosing periods, separated by a washout period of 14 days.

Blood samples were collected at pre-dose and at 1, 2, 2.5, 3, 3.5. 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 9, 10, 12, 16, 24, 48 and 72 hours after administration of the products.

The design of the study is acceptable. A 400 mg dose (10 ml suspension) was administered, which is the maximal single dose.

A single dose, crossover study to assess bioequivalence is considered adequate. According to the SmPC, the suspension should be taken with food to enhance the oral absorption and to ensure adequate exposure. As such, the fed conditions applied in the study is considered adequate.

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

Six subjects were withdrawn from the study. One subject did not return prior to the second period, one subject was withdrawn due to adverse events, one subject consumed tobacco and three subjects had found positive in alcohol breath test. Therefore, 42 subjects completed the study and were eligible for pharmacokinetic analysis.

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

Treatment N=42	**AUC_{0-72h} (ng.h/ml)**	**C_{max} (ng/ml)**	**t_{max} (h)**
Test	18656 ± 7896	558 ± 220	6.0 (4.5 – 24.0)
Reference	18100 ± 8822	559 ± 228	5.5 (4.5 – 16.0)
***Ratio (90% CI)**	1.05 (0.98 – 1.11)	1.00 (0.93 – 1.07)	--
CV (%)	17.5	19.4	--

AUC_{0-72h}	area under the plasma concentration-time curve from time zero to t hours
C_{max}	maximum plasma concentration
t_{max}	time for maximum concentration
CV	coefficient of variation

**ln-transformed values*

Conclusion on bioequivalence study

The 90% confidence intervals calculated for AUC_{0-72h} and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study 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 2. Summary table of safety concerns as approved in RMP

Important identified risks	• Hepatic – Elevated liver enzymes; hepatotoxicity; hepatic failure; hepatitis • Blood – Thrombotic thrombocytopenia purpura; haemolytic uremic syndrome • Cardiac – Torsade de pointes • General – Drug interaction • General – Infusion site reactions after peripheral line infusion of intravenous posaconazole • Renal – Renal effects of cyclodextrin with intravenous infusion of posaconazole
Important potential risks	• Blood – Agranulocytosis; aplastic anemia • 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

	• Neoplasms – Occurrence of any neoplasm/malignancy, especially: Hepatic adenoma; hepatic neoplasm; adrenal adenoma; adrenal neoplasm; phaeochromocytoma • Infections – Fungal infections • Visual – Photopsia; visual brightness; visual disturbances • Injury, poisoning and procedural complications – Medication error – Related to potential substitution between different formulations (tablet and oral suspension) • General – Infusion site reactions after central line infusion of intravenous posaconazole • Surgical and medical procedures – Off label use of IV formulation in paediatrics
Missing information	• Experience in children

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 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 package leaflet (PL) has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The results show that the PL meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Posaconazol Devatis 40 mg/ml oral suspension has a proven chemical-pharmaceutical quality and is a generic form of Noxafil 40 mg/ml, oral suspension. 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 5 September 2018.

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