COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Posaconazol MSN 300 mg, concentrate for solution for infusion

(posaconazole)

NL/H/4234/001/DC

Date: 29 July 2019

This module reflects the scientific discussion for the approval of Posaconazol MSN 300 mg, concentrate for solution for infusion. The procedure was finalised at 20 February 2019. 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 MSN 300 mg, concentrate for solution for infusion, from Vivanta Generics s.r.o.

The product is indicated for: 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.

This product is also indicated for prophylaxis of invasive fungal infections in the following patients:

- 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 (GVHD) 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 300 mg concentrate for solution for infusion which has been registered in the EEA by Merck Sharp & Dohme B.V. since 25 October 2005 through a centralised procedure (EMEA/H/C/000610).

The concerned member states (CMS) involved in this procedure were Czech Republic, Hungary, Poland and Romania.

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

Orphan similarity

The indication for Posaconazole MSN includes “invasive aspergillosis”. Orphan market exclusivity for "Treatment of invasive aspergillosis" (based on designation EU/3/14/1284) started on 19 October 2015 for the medicinal product Cresemba (containing isavuconazole).
Having considered the arguments presented by the MAH and with reference to Article 8 of Regulation (EC) No 141/2000, Posaconazole MSN is considered not similar (as defined in Article 3 of Commission Regulation (EC) No. 847/2000) to Cresemba.
Therefore, with reference to Article 8 of Regulation (EC) No. 141/2000, the existence of any market exclusivity for Cresemba in the treatment of invasive aspergillosis, does not prevent the granting of the marketing authorisation of Posaconazole MSN. This finding is without prejudice to the outcome of the scientific assessment of the marketing authorisation application.

II. QUALITY ASPECTS

II.1 Introduction

Posaconazol MSN is a clear, colourless to yellow solution and free from visible particles. Each vial contains 300 mg of posaconazole and each ml contains 18 mg of posaconazole. The pH of the solution is between 2.0 to 3.0.

The concentrate for solution for infusion is packed in Type I glass vials, closed with a bromobutyl rubber stopper and aluminium red colour flip-off seal containing 16.7 ml of solution.

The excipients are: betadex sulfobutyl ether sodium (SBECD), disodium edetate, hydrochloric acid concentrate (for pH adjustment), sodium hydroxide (for pH adjustment) and water for injections.

II.2 Drug Substance

The active substance is posaconazole, an established active substance not described in the European Pharmacopoeia (Ph.Eur.) or any other pharmacopoeia. Posaconazole is white to off-white powder and soluble in dichloromethane and practically insoluble in water. The active substance contains four chiral centres and is non-hygroscopic. Different polymorphic forms exist, Form-I is consistently manufactured.

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 is divided into six stages and consists of eight steps in total. The active substance has been characterised and acceptable specifications have been adopted for the starting materials, the solvents and the reagents used in the process.

Quality control of drug substance

The active substance specification is considered adequate to control the quality. The MAH has adopted the specification of the ASMF holder, with additional limits for microbiological examination and bacterial endotoxins. Descriptions of all analytical procedures have been provided and the analytical methods have been adequately validated. Batch analytical data demonstrating compliance with this specification have been provided for three batches.

Stability of drug substance

No data have been provided by the MAH 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 60 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. The excipients used are identical to the excipients used in the innovator product. The main development studies performed were the characterisation of the reference product, Quality Target Product Profile (QTPP) of the drug product, prototype formulation and selection of the sterilisation method. No design space is claimed. Since the drug product is a clear solution no bioequivalence study is required. Additional compatibility data of the proposed product with reconstitution diluents have been provided demonstrating each reconstituted product can be stored at 2-8°C up to 24 hours.

Manufacturing process

The manufacturing process has been validated according to relevant European guidelines and consists of compounding, filtration, filling, stoppering, sealing, labelling and packaging. It is considered to be a non-standard process. Process validation data on the product have been presented for three production scale batches in accordance with the relevant European guidelines.

Control of excipients
With the exception of betadex sulfobutyl ether sodium, all excipients comply with their respective Ph. Eur. monograph. Betadex sulfobutyl ether sodium complies with the United States Pharmacopeia. The 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, pH, particulate matter, sterility test, assay, extractable volume, related substance and bacterial endotoxins. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. Satisfactory validation data for the analytical methods have been provided. Batch analytical data three commercial 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 production scale batches stored at 5°C (24 months) and 25°C/60% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in 20 mL Type I glass vials, upright and inverted. No significant changes or up or downward trends were observed when the vials were stored at long term conditions and accelerated conditions. All results remained well within the specifications. Results of a photostability study demonstrated that the drug product is not light sensitive. On basis of the data submitted, a shelf life was granted of 2 years when stored in a refrigerator at 2°C - 8°C.

Chemical and physical in-use stability has been demonstrated for 24 hours at 2°C - 8°C.
From a microbiological point of view, once admixed, unless the method of dilution precludes the risk of microbial contamination, the product should be used immediately. If not used immediately, in –use storage times and conditions prior to use are the responsibility of the user and would normally not longer than 24 hours at 2°C - 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

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 MSN 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 MSN 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

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 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.2 Pharmacokinetics

Biowaiver

Posaconazol MSN 300 mg, concentrate for solution for infusion is a parenteral formulation and therefore fulfils the exemption mentioned in the Note for Guidance on bioequivalence "5.1.6 parenteral solutions", which states that a bioequivalence study is not required if the product is administered as an aqueous intravenous solution containing the same active substance in the same concentration as the currently authorised reference medicinal product (NfG CPMP/EWP/QWP 1401/98). The quantitative composition of Noxafil is entirely the same as the originator. Therefore, it may be considered as therapeutic equivalent, with the same efficacy/safety profile as known for the active substance of the reference medicinal product. The current product can be used instead of its reference product.

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 MSN.

Table 1. Summary table of safety concerns as approved in RMP

Important identified risks	- Elevated liver enzymes; Hepatotoxicity, Hepatic failure, Hepatitis - Thrombotic thrombocytopenia purpura; Hemolytic uremic syndrome - Torsade de pointes - Drug interaction - Infusion site reactions after peripheral line infusion of intravenous posaconazole - Renal effects of cyclodextrin with intravenous infusion of posaconazole
Important potential risks	- Agranulocytosis, aplastic Anemia - QTc prolongation, heart Failure, myocardial infarction - Depression, suicide - Adrenal Insufficiency - Convulsion, cerebral ischemia, cerebral haemorrhage - Pulmonary haemorrhage - Hypertension; Venous thrombosis; Arterial thrombosis - Hypokalemia - Occurrence of any neoplasms/malignancy, especially: hepatic adenoma, hepatic neoplasm, adrenal adenoma, adrenal neoplasm, phaeochromocytoma - Fungal infections - Photopsia, visual brightness, visual disturbances - Infusion site reactions after central line infusion of intravenous posaconazole - Off label use of IV formulation in paediatrics
Missing information	- Experience in children - Posaconazole as a possible substrate and/or inhibitor of OATP1B1 and OATP1B3

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. A biowaiver has been granted. 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 test consisted of: a pilot test with 2 participants, followed by two rounds with 10 participants each. 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 MSN 300 mg, concentrate for solution for infusion has a proven chemical-pharmaceutical quality and is a generic form of Posaconazol MSN 300 mg, concentrate for solution for infusion. Posaconazol MSN is a well-known medicinal product with an established favourable efficacy and safety profile.

Since both the reference and current product are intended for parenteral use, no bioequivalence study is deemed necessary. A biowaiver has been granted.

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 MSN with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 20 February 2019.

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