COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Posaconazole Biocon 100 mg gastro-resistant tablets
(posaconazole)

NL/H/5346/001/DC

Date: 15 November 2022

This module reflects the scientific discussion for the approval of Posaconazole Biocon 100 mg gastro-resistant tablets. The procedure was finalised at 28 July 2022. 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 Posaconazole Biocon 100 mg gastro-resistant tablets, from Biocon Pharma Malta I Limited.

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

- Invasive aspergillosis
- 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.

Posaconazole Biocon 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 hybrid application claiming essential similarity with the innovator product Noxafil 100 mg gastro-resistant tablets which has been registered in the EEA by Merck Sharp & Dohme B.V. since 23 April 2014 via a centralised procedure (EMEA/H/C/000610).

The concerned member states (CMS) involved in this procedure were Germany and Italy.

The marketing authorisation has been granted pursuant to Article 10(3) of Directive 2001/83/EC, a hybrid application as this product is a formulation with a smaller food effect than the reference product. This difference in food effect is seen as a formulation advantage over the reference formulation and thus it is considered eligible for hybrid application.

Assessment of orphan similarity

The MAH submitted an orphan similarity assessment report to address the possible similarity between Posaconazole Biocon and the medicinal product Cresemba (containing isavuconazole). Both products are indicated for treatment of invasive aspergillosis however, Cresemba has been granted orphan market exclusivity for treatment of invasive aspergillosis since 19 October 2015.

The orphan similarity assessment found that based on the differences in the principal molecular structure Posaconazole Biocon can be 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 Biocon.

II. QUALITY ASPECTS

II.1 Introduction

Posaconazole Biocon is a pale yellow to yellow, oval, biconvex, film-coated tablet debossed with "B100" on one side and plain on the other side. Each tablet contains 100 mg of posaconazole. The film-coated tablets are packed in white opaque PVC/Aclar-Al blisters.

The excipients are:

Tablet core - hypromellose acetate succinate, hydroxy propyl cellulose, microcrystalline cellulose, croscarmellose sodium, colloidal silicon dioxide and magnesium stearate.

Film-coat Opadry II yellow – polyvinyl alcohol (E1203), titanium dioxide (E171), macrogol 3350 (E1521), talc (E553b), yellow iron oxide (E172) and ferrosoferric oxide (E172).

II.2 Drug Substance

The active substance is posaconazole, a known active substance not described in any pharmacopoeia. Posaconazole is an amorphous powder that is practically insoluble in water. The active substance has four chiral centres and is synthesised as 3R, 5R, 2S, 3S isomer. The control of the final isomer is described in sufficient detail. Posaconazole exhibits polymorphism in the form of crystalline and amorphous forms. The manufacturer consistently produces the amorphous form.

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 4-6 steps and has been adequately described. No class 1 solvents are used during the synthesis of posaconazole. No class 1 or class 2A and 2B or class 3 elements are added during the manufacturing of the active substance. The drug substance has been adequately characterised and the starting materials are acceptable.

Quality control of drug substance

The active substance specification is considered adequate to control the quality. Posaconazole is not described in any pharmacopoeia therefore the active substance specification has been established in-house. The specification is acceptable. Batch analytical data demonstrating compliance with this specification have been provided for three production scaled batches.

Stability of drug substance

Stability data on the active substance have been provided for three production scaled batches stored at 25°C/60% RH (36 months) and 40°C/75% RH (6 months) which is in accordance with applicable European guidelines. All parameters stay within the proposed acceptance limits during both storage conditions. Based on the data submitted, a retest period could be granted of 30 months when stored in an airtight container at a temperature not exceeding 25°C and excursions allowed in between 15°C to 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 initial focus of the development was to design a tablet formulation that provided monophasic release of drug with the gastro-resistant action and formulation of a tablet that would disintegrate in buffer media in a similar way to the reference product. Further, multimedia dissolution studies and comparative dissolution studies were performed. In a dose dumping study in 0.01 N HCl with 5%, 10% and 20% alcohol (750 ml; 75 rpm) the Posaconazole Biocon 100 mg gastro-resistant tablets behave similar to the reference product. To support the application two single dose bioequivalence studies were submitted, one under fasting conditions and one under fed conditions.

Manufacturing process

The manufacturing process consists of multiple steps including blending, compression, a hot melt extrusion, milling and sifting. The manufacturing process has been validated according to relevant European guidelines. Process validation data on the product have been presented for three full scaled batches in accordance with the relevant European guidelines.

Control of excipients

The excipient hypromellose acetate succinate is not described in the European Pharmacopoeia (Ph.Eur) however is described in the United States Pharmacopeia-National Formulary (USP–NF). The coating material Opadry II yellow complies with in-house specifications. The other excipients comply with Ph.Eur. requirements. Adequate information has been provided and all 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, identification, dissolution, assay, uniformity of dosage units, related substances, water content, elemental impurities and microbiological tests. Release and shelf-life specifications are similar. 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 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 production scaled batches stored at 25°C/60% RH (12 months) and 40°C/75% RH (6 months) in accordance with applicable European guidelines. At accelerated conditions a very slight increase in any unspecified degradation product was observed and a slight increase in water content was observed. No other trends are observed and all parameters remained well within the proposed specification limits. At long term conditions no trends are observed. Photostability studies were performed in accordance with ICH recommendations and showed that the product is stable when exposed to light On basis of the data submitted, a shelf life of two years was granted. No specific storage conditions need 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 Posaconazole Biocon 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 Posaconazole Biocon is intended for hybrid 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 hybrid 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. Also pharmacodynamic, pharmacokinetic and toxicological properties of posaconazole are well known. 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 hybrid application, the MAH has submitted 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 Posaconazole Biocon 100 mg gastro-resistant tablets (Biocon Pharma Malta I Limited., Malta) is 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 results and compositions of the EU reference product. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Bioequivalence studies

Two single-dose bioequivalence studies were submitted, one study under fed conditions and the other study under fasted conditions. This is in accordance with the posaconazole gastro-resistant tablet 100 mg product specific bioequivalence guidance (EMA/CHMP/800785/2017). The design of the studies is acceptable.

Analytical/statistical methods

The analytical method of both studies has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Study 1 (single dose, fed, 100 mg tablet)

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover, pivotal bioequivalence study was carried out under fed conditions in 56 healthy male subjects, aged 18-45 years. Each subject received a single dose (100 mg) of one of the two posaconazole formulations. After an overnight fast of at least 10 hours the subjects received a high calorie, high fat breakfast (consisting of bread, eggs, chicken, hashbrown potatoes and whole milk). Thirty minutes after the start of this meal the tablet was orally administered with 150 ml of water. There were two dosing periods, separated by a washout period of 14 days. Blood samples were collected at pre-dose and 1.00, 2.00, 2.50, 3.00, 3.50, 4.00, 4.50, 5.00, 5.50, 6.00, 6.50, 7.00, 7.50, 8.00, 9.00, 10, 11, 12, 14, 16, 24, 36, 48, 72, 96, 120 and 144 hours after administration of the products.

A total of 8 subjects dropped-out or were withdrawn from the study. Three subjects did not visit the facility for period two check-in, two subjects tested positive for urine drug screening, one person withdrew consent due to a personal emergency, one person was not able to consume 100% of the high calorie meal and one subject experienced a moderate adverse event. 48 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=48	AUC_{0-t} (ng.h/ml)	$AUC_{0-\infty}$ (ng.h/ml)	C_{max} (ng/ml)	t_{max} (h)
Test	16513±3468	16900±3632	568±139	6.0 (2.5-10.0)
Reference	17280±3373	17977±4138	568±139	6.0 (2.5-10.0)
***Ratio (90% CI)**	0.95 (0.93 – 0.98)	0.94 (0.91 – 0.98)	0.99 (0.94 – 1.04)	
CV (%)	7.57	10.46	14.95	

$AUC_{0-\infty}$	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 t hours
C_{max}	maximum plasma concentration
t_{max}	time for maximum concentration
CV	coefficient of variation

**ln-transformed values*

Study 2 (single dose, fasted, 100 mg tablet)

Design

A randomised, open label, two-treatment, three-period, three sequence, single dose, crossover, partial replicate, pivotal bioequivalence study was carried out under fasted conditions in 66 healthy male subjects, aged 18-45 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 fast of at least ten hours. There were three dosing periods, separated by a washout period of fourteen days. Blood samples were collected at pre-dose and at 1.00, 1.50, 2.00, 2.50, 3.00, 3.50, 4.00, 4.50, 5.00, 5.50, 6.00, 6.50, 7.00, 7.50, 8.00, 9.00, 10, 12, 14, 16, 24, 36, 48, 72, 96 and 120 hours after administration of the products.

Results

One subject did not visit the facility for period three check-in and was considered lost to follow up. Therefore, 65 subjects completed the study and were eligible for pharmacokinetic analysis.

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

Treatment N= 65	AUC_{0-t} (ng.h/ml)	$AUC_{0-\infty}$ (ng.h/ml)	C_{max} (ng/ml)	t_{max} (h)
Test	8827±2956	9456±3398	315±101	4.5 (1.5-7.5)
Reference	7775±2464	8366±2790	233±79	4.5 (3.0-10.0)
***Ratio (90% CI)**	1.12 (1.06 – 1.19)	1.12 (1.06 – 1.19)	1.35 (1.27 – 1.45)	
CV (%)	20.7	22.0	26.5	

$AUC_{0-\infty}$	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 t hours
C_{max}	maximum plasma concentration
t_{max}	time for maximum concentration
CV	coefficient of variation

**ln-transformed values*

Table 3. Additional pharmacokinetic data for study 2 (posaconazole under fasted conditions)

Plasma concentration curves where	Related information
- AUC_{0-t}/ $AUC_{0-\infty}$ < 0.8	Not applicable
- C_{max} is the first point	Nil
-Pre-dose sample > 5% C_{max}	Nil

Table 4. The difference in the fasted and fed state for both test and reference product (posaconazole)

Parameter	Geometric LS means		% Decrease
	Reference (fed)	Reference (fasting)	
C_{max} (ng/ml)	540.23	220.99	59%
AUC_{0-t} (ng.h/ml)	16951.79	7419.64	56%
	Test (fed)	**Test (fasting)**	
C_{max} (ng/ml)	533.47	299.39	44%
AUC_{0-t} (ng.h/ml)	16187.23	8344.08	48%

Table 5. Comparison of fasting study with published results from literature data (posaconazole)

Parameter	Arithmetic mean		
	Published results*	Results of fasting study	
		Reference	Test
C_{max} (ng/ml)	288-329	233.35	315.04
AUC_{0-t} (ng.h/ml)	8327 – 9202	7775.37	8826.80

*European Medicines Agency, Committee for Medicinal Products for Human Use. (2014). Assessment report. Noxafil. *Report EMA/159150/2014* (page 16-75).

Conclusion on bioequivalence studies

For the study under fed conditions 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 study Posaconazole Biocon is considered bioequivalent with Noxafil under fed conditions.

The results of the study under fasted conditions fall outside of the bioequivalence acceptance range. This is due to the known food effect of the reference product which has been shown to be 12-15% smaller for Posaconazole Biocon. The MAH has provided evidence that the behaviour of the reference product in the bioequivalence study under fasted conditions does not differ from that reported in the literature. In addition the MAH has sufficiently demonstrated that Posaconazole Biocon has a smaller food effect which is seen as a formulation advantage over the reference formulation and thus it is considered eligible for hybrid application. The posology for Posaconazole Biocon 100 mg gastro-resistant tablets remains in line with that of the Noxafil 100 mg gastro-resistant tablets thus the SmPC states that the product may be taken regardless of the food.

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 Posaconazole Biocon.

Table 6. Summary table of safety concerns as approved in RMP

Important identified risks	Hepatic	-elevated liver enzymes -hepatoxicity -hepatic failure -hepatis
	Blood	-thrombotic thrombocytopenia purpura -hemolytic uremic syndrome
	Cardiac	-Torsade de Pointes -QTc prolongation
	General	-drug interactions
	Endocrine	-adrenal insufficiency
	Metabolism	-hypokalaemia
Important potential risks	Cardiac	-heart failure -myocardial infarction
	CNS	-convulsion
	Respiratory	-pulmonary haemorrhage
	Vascular	hypertension -venous thrombosis
	Visual	-photopsia -visual brightness -visual disturbance
Missing information	Experience in children Use in patients with hepatic impairment	

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 100 mg gastro-resistant tablets. 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 hybrid 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 language used for the purpose of user testing the PL was English. The test consisted of: a pilot test with 4 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

Posaconazole Biocon 100 mg gastro-resistant tablets have a proven chemical-pharmaceutical quality and are a hybrid 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 concerned member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Posaconazole Biocon with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 28 July 2022.

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