COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Posaconazol Fresenius Kabi 100 mg gastro-resistant tablets

(posaconazole)

NL/H/4626/001/DC

Date: 25 March 2020

This module reflects the scientific discussion for the approval of Posaconazol Fresenius Kabi 100 mg gastro-resistant tablets. The procedure was finalised at 9 January 2020. 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 Fresenius Kabi 100 mg gastro-resistant tablets, from Fresenius Kabi Nederland B.V.

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.

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 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 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 25 October 2005 through a centralised procedure (EU/1/05/320/002-003).

The concerned member states (CMS) involved in this procedure were Germany, France, Italy, Spain and the United Kingdom.

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 without food effect and the reference formulation has a food effect. This difference in food effect is seen as a

formulation advantage over the reference formulation and thus it is considered eligible for hybrid application.

Orphan similarity

The indication for Posaconazole Fresenius Kabi 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 Fresenius Kabi 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 Fresenius Kabi. This finding is without prejudice to the outcome of the scientific assessment of the marketing authorisation application.

II. QUALITY ASPECTS

II.1 Introduction

Posaconazol Fresenius Kabi is a yellow coloured, capsule shaped, biconvex, film-coated, gastro-resistant tablet, embossed with ‘P100’ on one side. Each gastro-resistant tablet contains 100 mg of posaconazole.

The gastro-resistant tablets are packed in PVC/PE/PVDC aluminium foil.

The excipients are:

Tablet core - hypromellose acetate succinate, hypromellose, maize starch, silica colloidal anhydrous, croscarmellose sodium, lactose granule (lactose monohydrate spray dried), silicified microcrystalline cellulose, low substituted hydroxypropyl cellulose and magnesium stearate

Tablet coating - polyvinyl alcohol-part hydrolysed, titanium dioxide (E171), macrogol 4000, talc and iron oxide yellow (E172).

II.2 Drug Substance

The active substance is posaconazole, an established active substance, however not described in the European Pharmacopoeia (Ph.Eur.). Posaconazole is a white to off-white powder very slightly soluble in ethanol and isopropanol, sparingly soluble in methanol and acetone, slightly soluble in acetonitrile and freely soluble in dichloromethane, DMSO, N-methyl-2-pyrrolidone. Posaconazole is poorly soluble in aqueous media, in particular very

slightly soluble at pH 1 and insoluble at pH 2-14. The active substance exhibits chirality and polymorphism. The amorphous form of the stereoisomer RRSS is used.

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

Posaconazole is obtained with a convergent process which includes five synthetic steps and two purification steps. The proposed starting materials are acceptable. No class 1 organic solvents are used. The active substance has been adequately characterised and the proposed limits for impurities in the starting materials and intermediates are acceptable.

Quality control of drug substance

The active substance specification is considered adequate to control the quality and has been established in-house by the ASMF holder. The following tests are performed: appearance, identification, loss on drying, specific optical rotation, sulphated ash, palladium content, assay, related substances, chiral impurities, residual solvents and x-ray powder diffraction. Batch analytical data demonstrating compliance with this specification have been provided for three full-scale batches.

Stability of drug substance

Stability data on the active substance have been provided for three full-scale batches stored at 25°C/60% RH (36 months) and 40°C/75% RH (6 months). Based on the data submitted, a retest period could be granted of 36 months.

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 choices of the packaging and manufacturing process are justified in relation to the innovator.
To support the application, the MAH has submitted a four-period comparative bioavailability study evaluating bioequivalence under fasting and fed conditions. The pharmaceutical development of the product has been adequately performed.

Manufacturing process

The tablets are manufactured by wet granulation, spray granulation, dry granulation followed by compression. The process has been validated according to relevant European

guidelines. Process validation data on the product have been presented for three full-scale batches in accordance with the relevant European guidelines.

Control of excipients

The excipients are in accordance with the Ph. Eur. or United States Pharmacopeia with additional in-house tests. 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 appearance, identity, average weight, uniformity of mass, water content, disintegration, assay, uniformity of dosage units, dissolution, related substances, residual solvents and microbiological control. 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 production 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 production scaled batches stored at 25°C/60% RH (12 months), 30°/65% RH (12 months) and 40°C/75% RH (6 months). The conditions in the stability studies are according to the ICH stability guidelines. The batches were stored in the proposed packaging. At long term, at intermediate and at accelerated conditions an increase in total impurities was observed. However, it stayed well below the proposed shelf life limit. No other trends are observed. A photostability study demonstrated that the drug product is not light sensitive. On basis of the data submitted, a shelf life was granted of 24 months. No special storage conditions need to be included.

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

Lactose monohydrate spray dried is of animal origin. It has been produced from milk sourced from healthy cows in the same conditions as milk collected for human consumption. In addition, it has been prepared, without the use of other rudiment material than calf rennet, according to the description as published in Public Statement EMEA/CPMP/571/02 of 27 February 2002.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Posaconazol Fresenius Kabi 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 Fresenius Kabi 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. 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 a bioequivalence study, which is discussed below.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Posaconazol Fresenius Kabi 100 mg gastro-resistant tablets (Fresenius Kabi Nederland B.V., NL) is compared with the pharmacokinetic profile of the reference product Noxafil 100 mg gastro-resistant tablets (Merck Sharp & Dohme B.V., UK).

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 study

Design

A single-dose, randomised, four-period, four-treatment, four-sequence, crossover bioequivalence study was carried out. The study consisted of the following four treatments:

- Treatment-1: Test product administered under fasting conditions
- Treatment-2: Reference product administered under fasting conditions
- Treatment-3: Test product administered under fed conditions
- Treatment-4: Reference product administered under fed conditions

During Treatment-1 and Treatment-2 (under fasting conditions) a single 100 mg oral dose of the assigned formulation was administered in the morning after a supervised overnight fast.

During Treatment-3 and Treatment-4 (under fed conditions) the subjects received a standardised high-fat, high-calorie meal (consisting of whole milk, eggs, hash brown potatoes, toast, butter and bacon) 30 minutes before drug administration after a supervised overnight fast. Thirty minutes after the start of breakfast, a single 100 mg oral dose of the assigned formulation was administered in the morning.

The drug administrations were separated by a wash-out of 14 calendar days.

A total of 36 healthy male and female subjects with a mean age of 41 years were included in the study. 35 subjects received Treatment-1 (test product under fasting conditions), 35 subjects received Treatment-2 (Reference product under fasting conditions), 33 subjects received Treatment-3 (test product under fed conditions), and 34 subjects received Treatment-4 (reference product under fed conditions).

Blood samples were collected pre-dose and at 1.0, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 5.5, 6.0, 6.5, 7.0, 7.5, 8.0, 10.0, 12.0, 16.0, 24.0, 48.0, 72.0, 96.0, 120.0, and 144.0 hours after administration of the products.

The design of the study is acceptable. The washout period of 14 days sufficient considering mean elimination half-life of 29 hours.

One four-period comparative bioavailability study evaluating bioequivalence under fasting and fed conditions is considered appropriate in case of gastro-resistant coated formulation and in line with the Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms (EMA/CPMP/EWP/280/96 Corr1).

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

Four subjects discontinued the study and 32 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 fasted and fed conditions.

PARAMETER	Treatment-1 [test-fasting] (n=33)		Treatment-2 [reference-fasting] (n=33)		Treatment-3 [test-fed] (n=33)		Treatment-4 [reference-fed] (n=33)	
	MEAN	C.V. (%)	MEAN	C.V. (%)	MEAN	C.V. (%)	MEAN	C.V. (%)
C_{max} (ng/mL)	463.23	(31.0)	291.22	(35.9)	408.23	(39.0)	424.06	(43.0)
ln (C_{max})	6.0955	(4.8)	5.6181	(5.9)	5.9566	(5.4)	5.9855	(5.7)
T_{max} (hours)[a]	5.00	(2.57-8.00)	5.00	(3.50-8.00)	6.00	(2.00-12.00)	6.00	(2.00-16.00)
AUC_{0-T} (ng·h/mL)	12258.03	(36.6)	8877.65	(37.7)	12134.93	(39.1)	12358.00	(36.4)
ln (AUC_{0-T})	9.3461	(4.1)	9.0208	(4.3)	9.3367	(3.9)	9.3618	(3.7)
$AUC_{0-\infty}$ (ng·h/mL)	12561.61	(37.6)	9175.42	(38.9)	12472.38	(40.3)	12743.36	(37.5)
ln ($AUC_{0-\infty}$)	9.3673	(4.2)	9.0496	(4.4)	9.3601	(4.0)	9.3885	(3.9)
Residual Area (%)	2.08	(97.3)	2.81	(86.5)	2.29	(81.8)	2.61	(83.9)
λ_Z (hours^{-1})	0.0332	(31.8)	0.0325	(32.7)	0.0327	(30.2)	0.0321	(34.3)
T_{half} (hours)	22.85	(30.7)	23.74	(33.9)	23.01	(27.8)	24.02	(31.9)

Table 2. Summary of the statistical analysis of posaconazole (Treatment-1 [test-fasting] vs Treatment-2 [reference-fasting])

PARAMETER	INTRA-SUBJECT C.V. (%)	GEOMETRIC LSMEANS[a]		RATIO (%)	90% CONFIDENCE LIMITS (%)	
		Treatment-1 (n=33)	Treatment-2 (n=33)		LOWER	UPPER
C_{max}	15.1	445.68	275.99	161.49	151.61	172.00
AUC_{0-T}	11.5	11444.30	8246.08	138.78	132.28	145.61
$AUC_{0-\infty}$	11.7	11684.54	8487.30	137.67	131.11	144.56

Table 3. Summary of the statistical analysis of posaconazole (Treatment-3 [test-fed] vs Treatment-4 [reference-fed])

PARAMETER	INTRA-SUBJECT C.V. (%)	GEOMETRIC LSMEANS[a]		RATIO (%)	90% CONFIDENCE LIMITS (%)	
		Treatment-3 (n=33)	Treatment-4 (n=33)		LOWER	UPPER
C_{max}	13.6	380.61	390.74	97.41	91.95	103.19
AUC_{0-T}	7.5	11279.27	11574.23	97.45	94.41	100.60
$AUC_{0-\infty}$	7.7	11544.87	11892.18	97.08	93.97	100.29

Table 4. Summary of the statistical analysis of Posaconazole (Treatment-3 [test-fed] vs Treatment-1 [test-fasting])

PARAMETER	INTRA-SUBJECT C.V. (%)	GEOMETRIC LSMEANS[a]		RATIO (%)	90% CONFIDENCE LIMITS (%)	
		Treatment-3 (n=32)	Treatment-1 (n=32)		LOWER	UPPER
C_{max}	18.9	386.28	443.55	87.09	80.38	94.35
AUC_{0-T}	9.4	11424.35	11715.35	97.52	93.71	101.48
$AUC_{0-\infty}$	9.4	11693.41	11976.76	97.63	93.79	101.63

Table 5. Summary of the statistical analysis of posaconazole (Treatment-4 [reference-fed] vs Treatment-2 [reference-fasting])

PARAMETER	INTRA-SUBJECT C.V. (%)	GEOMETRIC LSMEANS[a]		RATIO (%)	90% CONFIDENCE LIMITS (%)	
		Treatment-4 (n=33)	Treatment-2 (n=33)		LOWER	UPPER
C_{max}	24.9	394.54	271.50	145.32	131.14	161.03
AUC_{0-T}	14.0	11371.42	8190.37	138.84	130.98	147.17
$AUC_{0-\infty}$	14.1	11669.96	8428.32	138.46	130.58	146.82

Conclusion on bioequivalence study

Based on the submitted bioequivalence study Posaconazol Fresenius Kabi 100 mg gastro-resistant tablets is considered bioequivalent with Noxafil 100 mg gastro-resistant tablets under fed, however not under fasting conditions. The MAH demonstrated that Posaconazole Fresenius Kabi has no 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 Fresenius Kabi 100 mg enteric coated tablet remains in line with that of the Noxafil SmPC, i.e. 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 Posaconazol Fresenius Kabi.

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

Important identified risks	- Liver problems- increased liver enzymes, liver damage, liver failure, inflammation of the liver (hepatic- elevated liver enzymes, hepatotoxicity, hepatic failure, hepatitis) - Blood related problems- extensive clots in the small blood vessels throughout the body and abnormal destruction of red blood cells (blood- thrombotic thrombocytopenic purpura, haemolytic uremic syndrome) - Heart problems- abnormal heart rhythm (cardiac- Torsades de pointes) - General- Drug interaction - Injury, poisoning and procedural complications- Medication error- related to potential substitution between different formulations (tablet and oral suspension)
Important potential risks	- Blood related problems- severely low white blood cell count, loss in the formation of new blood cells (blood- agranulocytosis, aplastic anaemia) - Heart problems- Abnormal electrocardiogram heart tracing, heart failure, heart attack (cardiac- QTc prolongation, heart failure, myocardial infarction) - Mental problems- persistent feeling of sadness and loss of interest and thought of killing own self (psychiatric- depression, suicide) - Hormonal problems- inability of adrenal glands to produce adequate amount of steroid hormones (endocrine- adrenal insufficiency) - Brain disorders- fits, insufficient blood flow to the brain, severe bleeding inside the brain tissue (CNS- convulsion, cerebral ischaemia, cerebral haemorrhage) - Lung problems- bleeding from the lungs and the respiratory tract (respiratory- pulmonary haemorrhage) - Problems in blood vessels- high blood pressure, blood clot in the vessels that carry blood toward the heart or away from the heart (vascular- hypertension, venous thrombosis, arterial thrombosis) - Problems related to chemical processes in the body- low level of potassium in the blood (metabolism- hypokalaemia) - Cancer- occurrence of any cancer especially liver cancer, cancer of adrenal glands and tumour in the cells in the middle of an adrenal gland (neoplasms- occurrence of any neoplasm/malignancy, especially hepatic adenoma, hepatic neoplasm, adrenal adenoma, adrenal neoplasm, pheochromocytoma)

	- Infections- Fungal infections - Vision related problems- presence of perceived flashes of light, visual brightness, interference with normal sight (visual- photopsia, visual brightness, visual disturbances)
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 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 test consisted of: a pilot test, 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 Fresenius Kabi 100 mg gastro-resistant tablets have a proven chemical-pharmaceutical quality and is 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 member states, on the basis of the data submitted,

considered that essential similarity has been demonstrated for Posaconazol Fresenius Kabi with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 9 January 2020.

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