CBG MEB

Public Assessment Report

Scientific discussion

Voriconazol Fresenius Kabi 200 mg, powder for solution for infusion

(Voriconazole)

NL/H/3248/001/DC

Date: 21 April 2016

This module reflects the scientific discussion for the approval of Voriconazol Fresenius Kabi 200 mg, powder for solution for infusion. The procedure was finalised on 28 July 2015. 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 Voriconazol Fresenius Kabi 200 mg, powder for solution for infusion, from Fresenius Kabi Nederland BV.

Voriconazole is a broad spectrum, triazole antifungal agent and is indicated in adults and children aged 2 years and above as follows:

- Treatment of invasive aspergillosis
- Treatment of candidaemia in non-neutropenic patients
- Treatment of fluconazole-resistant serious invasive Candida infections (including C. krusei).
- Treatment of serious fungal infections caused by *Scedosporium* spp. and *Fusarium* spp.

Voriconazol Fresenius Kabi should be administered primarily to patients with progressive, possibly life-threatening infections.

Prophylaxis of invasive fungal infections in high risk allogeneic hematopoietic stem cell transplant (HSCT) recipients.

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 Vfend 200 mg powder for solution for infusion which has been registered in the EEA by Pfizer Ltd. since 21 March 2002 through centralised procedure EMEA/H/C/000387.

The concerned member states (CMS) involved in this procedure were Belgium, Bulgaria, Cyprus, Czech Republic, Germany, Denmark, Greece, Spain, Finland, France, Croatia, Hungary, Ireland, Italy, Luxembourg, Norway, Poland, Portugal, Romania, Sweden, Slovenia, Slovakia and the UK.

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

II. QUALITY ASPECTS

II.1 Introduction

Voriconazol Fresenius Kabi 200 mg, powder for solution for infusion is a white or almost white lyophilised powder, with pH 5.5-7.0.

The lyophilised powder is packed in 25 ml clear, colourless glass type I vials with bromobutyl rubber stopper and aluminium flip cap with a blue plastic lid. One vial is used for each infusion. Each vial contains 200 mg of voriconazole powder. The reconstituted solution contains 10 mg voriconazole per ml.

The excipients are hydroxypropylbetadex, L-arginine, hydrochloric acid (for pH adjustment) and sodium hydroxide (for pH adjustment).

II.2 Drug Substance

The active substance is voriconazole, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The substance is a white or almost white powder and very slightly soluble in water and freely soluble in acetone and in methylene chloride Voriconazole has two chiral centers and hence contains four isomers. Adequate methods are used to test for enantiomeric purity.

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological

quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the European Pharmacopoeia.

Manufacturing process
A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The active substance specification is considered adequate to control the quality, and meets the requirements of the Ph.Eur. with a number of additional tests. Batch analytical data demonstrating compliance with this specification have been provided for three batches.

Stability of drug substance
The retest period is not included on the CEP. However it was confirmed by stability data on three production scaled batches stored at accelerated (40°C/75% RH) and long term conditions (25°C/60% RH) up to the proposed retest period. Based on the data submitted, a retest period of 60 months without special storage conditions is granted.

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. During development, composition and process parameters were optimised until the final formulation was obtained. Selection of a solubilizing agent (due to poor solubility of the drug substance in water) has been justified. The choice of packaging, manufacturing process and sterilisation method has been justified.

Since the product is a powder for solution for infusion no bioequivalence study is required. The chemical-physical quality characteristics of the proposed product compared with the innovator are satisfactory.

Manufacturing process
The manufacturing process involves dissolving voriconazole in a solution of excipients at the right pH, filling the solution through a filter into the final packaging followed by lyophilisation. The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for three batches.

Control of excipients
The excipients comply with the Ph.Eur. with a number of additional tests. 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 appearance, clarity of solution, colour of solution, pH, uniformity of dosage units, water content, identification of voriconazole, assay, sub-visible particles and visible particles, related substances, sterility, bacterial endotoxins and reconstitution time. 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 for three batches. Vials were stored at upright and inverted position up to 12 months (25°C/60% RH) and at accelerated conditions up to 6 months (40°C/75% RH). The conditions used in the stability studies are according to the ICH stability guideline. The product remains stable throughout the testing period. A photostability testing study was

performed according to ICH, showing that the product is not susceptible to light. On basis of the data submitted, a shelf life was granted of 18 months unopened without special storage conditions.

In-use stability of the reconstituted product has been demonstrated for 24 hours at 2°C to 8°C and of the diluted product for 7 days at 2°C to 8°C. Compatibility of the product with several diluents has been studied. The approved diluents for reconstitution and dilution are listed in the SmPC.

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 Voriconazol Fresenius Kabi 200 mg, powder for solution for infusion 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 Voriconazol Fresenius Kabi 200 mg, powder for solution for infusion 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 Voriconazol Fresenius Kabi 200 mg, powder for solution for infusion 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

Voriconazole 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
Voriconazol Fresenius Kabi 200 mg, powder 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 authorized reference medicinal product (NfG CPMP/EWP/QWP 1401/98).

Voriconazol Fresenius Kabi 200 mg powder for solution for infusion contains hydroxypropyl-β-cyclodextrin (hydroxypropylbetadex) as solubilizing agent for the active substance voriconazole, whereas Vfend 200 mg powder for solution for infusion contains sulfobutylether-β-cyclodextrin for the same purpose. Cyclodextrins are cyclic (α-1,4)-linked oligosaccharides of α-D-glucopyranose. Cyclodextrins contain a relatively hydrophobic central cavity and a hydrophilic outer surface. They can increase the equilibrium solubility of some hydrophobic molecules. Several commercial oral and injectable cyclodextrin-based products are available throughout the world. The two most common and preferred water-soluble β-cyclodextrin derivatives are hydroxypropylbetadex and sulfobutylether-β-cyclodextrin. The MAH showed that the difference in solubilizing agent does not influence the disposition of voriconazole *in vivo*. In addition, no difference in voriconazole distribution (protein binding) is expected using hydroxypropylbetadex or sulfobutylether-β-cyclodextrin. The use of hydroxypropylbetadex has also been evaluated in children. No significant age dependence was observed for AUC and C_{max} among the children evaluated. Concentrations of hydroxypropyl-β-dex fell below quantifiable limits by 12 hours. The use of hydroxypropylbetadex instead of sulfobutylether-β-cyclodextrin is acceptable. The complex is considered rapidly 'dissolved' after the blood stream.

Overall, Voriconazol Fresenius Kabi 200 mg can 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 Voriconazol Fresenius Kabi 200 mg, powder for solution for infusion.

Summary table of safety concerns as approved in RMP:

Important identified risks	• Hepatic toxicity • QTc prolongation • Visual events (including optic neuritis, papiloedema and other visual concerns) • Phototoxicity • Peripheral neuropathy • Squamous Cell Carcinoma (SCC)
Important potential risks	• Skin cancers (non-SCC) • Suicide-related events
Missing information	• Effects in pregnancy • Effects in paediatrics • Off-label use • Resistance

Additional risk minimisation measures are required relating to hepatotoxicity, squamous cell carcinoma and phototoxicity . These have been laid down in line with the reference product. It concerns the following additional risk minimisation measures for these two safety concerns:

- Health Care Professional Checklist for phototoxicity, SCC and hepatic toxicity
- Health Care Professional Question and Answer Brochure for phototoxicity, SCC and hepatic toxicity
- Patient Alert Card for SCC

The implementation of the additional measures will be agreed at a national level in each of the member states.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Vfend 200 mg powder for solution for infusion. No new clinical studies were conducted. The

MAH demonstrated equivalence based on comparative *in vitro* data. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

The package leaflet 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 4 participants, followed by two rounds with 10 participants each. A questionnaire was developed that contains 17 questions specific to Voriconazol Fresenius Kabi 200 mg, powder for solution for infusion and 3 additional questions specific to the format of the patient leaflet. The questions sufficiently cover the significant safety issues. The results show that the package leaflet 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

Voriconazol Fresenius Kabi 200 mg, powder for solution for infusion has a proven chemical-pharmaceutical quality and is a generic form of Vfend 200 mg powder for solution for infusion. Vfend 200 mg 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.

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 Voriconazol Fresenius Kabi 200 mg with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 28 July 2015.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE – SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached
Change in the name and/or address of the marketing authorisation holder	NL/H/3248/ 001/IA/001/ G	IA/G	7-2-2016	8-3-2016	Approval	No