

**Public Assessment Report**  
**Scientific discussion**

**Voriconazol betapharm 200 mg, powder for  
solution for infusion**  
**(voriconazole)**

**NL/H/3363/001/MR**

**Date: 25 May 2016**

This module reflects the scientific discussion for the approval of Voriconazol betapharm. The procedure was finalised on 18 May 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 betapharm 200 mg, powder for solution for infusion from Betapharm Arzneimittel GmbH.

The product is indicated for

Voriconazol betapharm, 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 betapharm 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 mutual recognition procedure concerns a generic application claiming essential similarity with the innovator product Vfend 200 mg powder for solution for infusion (EMA/H/C/000387), which has been registered by Pfizer since 21 March 2002 by a centralised procedure.

The concerned member state (CMS) involved in this procedure was Germany. A repeat use procedure was accepted for Spain, France and Italy (NL/H/3363/001/E/001).

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

## II. QUALITY ASPECTS

### II.1 Introduction

Voriconazol betapharm 200 mg powder for solution for infusion is white to off-white lyophilized powder. One vial is used for each infusion. After reconstitution each ml contains 10 mg of voriconazole. Once reconstituted further dilution is required before administration.

The powder for solution for infusion is packed in a clear type I glass vial that is closed with a type I rubber bromobutyl stopper and aluminium flip-off cap. One vial is used for each infusion. Each vial contains 200 mg of voriconazole.

The excipients are hydroxypropylbetadex and lactose monohydrate.

### 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 non-hygroscopic powder, which is freely soluble in acetone and in methylene chloride, and insoluble in water. Further, voriconazole exhibits polymorphism. The two active substance manufacturers produce the same polymorphic form. The substance consists of two asymmetric carbons with a configuration of (2R,3S). Isomerism has been sufficiently specified.

The Active Substance Master File (ASMF) procedure is used for both manufacturers of 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

For both manufacturers a description of the process have been given, in sufficient detail and from acceptable starting materials.

#### Quality control of drug substance

The MAH laid down a drug substance specification which complies with the Ph.Eur. monograph of voriconazole. In addition, a test for particle size is included. Sufficient batch analysis data have been provided, demonstrating compliance with the specification.

#### Stability of drug substance

A re-test period of the drug substance of 48 months is applicable for the first manufacturer. Data have been provided during storage at  $25^{\circ}\pm 2^{\circ}\text{C}/60\pm 5\% \text{RH}$  (44 months) and  $40^{\circ}\pm 2^{\circ}\text{C}/75\pm 5\% \text{RH}$  (6 months). For the second manufacturer a re-test period of 12 months has been granted based on stability data obtained at  $25^{\circ}\pm 2^{\circ}\text{C}/60\pm 5\% \text{RH}$  (6 months) and  $40^{\circ}\pm 2^{\circ}\text{C}/75\pm 5\% \text{RH}$  (6 months). No specific storage conditions apply.

### **II.3 Medicinal Product**

#### Pharmaceutical development

The development of the product has been described, the choice of excipients is justified and the difference in solubiliser with the respect to the reference product has been explained. The use of hydroxypropylbetadex instead of sulfobutylether beta-cyclodextrin is acceptable. The selection of the different solubiliser is further supported by the bioequivalence study performed.

During development, composition and process parameters were optimised until the final formulation was obtained. The stability of the formulation was demonstrated to be similar to the reference product Vfend. The choice of sterilization by aseptic processing and filtration is justified as dry heat sterilization and radiation sterilization lead to significant degradation of the drug product.

The choice of container closures system, discussion on microbiological attributes and compatibility with the list of diluents mentioned in the SmPC are acceptable.

The pharmaceutical development of the product has been adequately performed. The applied overfill of 10% is required. The overfill of 10% leads to a vial containing 220 mg of voriconazole, which needs to be reconstituted with 19 ml prior to use, thus obtaining a volume of 22 ml and a concentration of 10 mg/ml. This is the same reconstitution volume and final concentration as the reference product.

#### Manufacturing process

The manufacturing process concerns a non-standard lyophilisation process which involves the following steps: preparation of the bulk solution, filtration of the bulk solution, filling of the vials, lyophilisation, closing and capping of the vials. The manufacturing process has been validated on three full-scale batches.

#### Control of excipients

All the excipients, used in the manufacturing of the powder for solution for infusion are of pharmacopoeial grade (Ph.Eur.) and tested as per their Ph.Eur. monograph. These specifications are adequate.

#### Quality control of drug product

The product specification includes tests for appearance, reconstitution time, pH, uniformity of dosage units, water content, particulate contamination, identification, assay, impurities, sterility and bacterial endotoxins. The release and end-of shelf-life specifications are identical with the exception of the limits for assay and impurities. The analytical methods have been adequately described. The validation of the methods is adequately performed. Batch analytical data has been presented for three batches, including the bio-batch. All batches comply with the specification.

#### Stability of drug product

Stability data on the drug product has been provided on three batches stored at 25°C/60% RH (36 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in glass vial with rubber stopper as proposed for marketing. The MAH performed a photostability study in line with ICH Q1B demonstrating the photostability of the drug product. Based on the stability data provided, a shelf-life of 36 months was granted. Supported by the complying results under accelerated storage conditions, no special storage conditions are considered necessary.

Stability data after reconstitution with water for injections or 0.9% NaCl and further dilution with the list of diluents mentioned in the SmPC have been presented. The product is stable up to 24 hours at 2-8 °C.

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

Only lactose monohydrate is of animal origin. TSE statements from representative manufacturer regarding the safety and compliance of lactose monohydrate, have been provided. TSE risk for the lactose used can be considered negligible.

### **II.4 Discussion on chemical, pharmaceutical and biological aspects**

Based on the submitted dossier, the member states consider that Voriconazol betapharm 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 betapharm 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 Vfend 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.

For this generic application, the MAH has submitted two bioequivalence studies, which are discussed below.

## IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Voriconazol betapharm 200 mg, powder for solution for infusion is compared with the pharmacokinetic profile of the reference product Vfend 200 mg powder for solution for infusion (Pfizer, Poland).

The choice of the reference products in the bioequivalence studies is accepted, as Vfend has been registered through a centralised procedure. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

### Design

A single-dose, 2-period, 2-sequence, cross-over bioequivalence study was carried out in 24 healthy male subjects, aged 25-77 years. Each subject received a single dose (200 mg infusion over about 1.5 h) of one of the 2 voriconazole formulations. There were 2 dosing periods, separated by a washout period of 7 days.

Blood samples were collected pre-dose and at 0.33, 0.67, 1, 1.25, 1.5, 1.58, 1.67, 1.83, 2, 2.5, 3, 4, 6, 8, 10, 12, 16, 24 and 30 hours after administration of the products.

A single dose, crossover study to assess bioequivalence for voriconazole is considered adequate. The study was conducted to evaluate bioequivalence between the test formulation with hydroxypropylbetadex and the reference with sulfobutylether beta-cyclodextrin. Overall, the use of hydroxypropylbetadex instead of sulfobutylether beta-cyclodextrin is acceptable. The complex is considered rapidly 'dissolved' after the blood stream.

### 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

All subjects completed the study and data from 24 subjects were included in the pharmacokinetic and statistical analysis.

**Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean  $\pm$  SD,  $t_{max}$  (median, range)) of 200 mg voriconazole powder for solution for infusion.**

Treatment N=24	AUC <sub>0-t</sub> ng.h/ml	AUC <sub>0-∞</sub> ng.h/ml	C <sub>max</sub> ng/ml	t <sub>max</sub> h	t <sub>1/2</sub> h
<b>Test</b>	7139 $\pm$ 2299	7327 $\pm$ 2352	1987 $\pm$ 475	1.5 (1.25 – 6.0)	6.3 $\pm$ 1.1
<b>Reference</b>	6660 $\pm$ 1712	6879 $\pm$ 1850	1927 $\pm$ 433	1.5 (1.25 – 1.58)	6.3 $\pm$ 1.4
<b>*Ratio (90% CI)</b>	1.06 (1.00-1.12)	--	1.03 (0.97-1.10)	--	--
<b>CV (%)</b>	11.6	--	12.3	--	--
<b>AUC<sub>0-∞</sub></b> area under the plasma concentration-time curve from time zero to infinity <b>AUC<sub>0-t</sub></b> area under the plasma concentration-time curve from time zero to t hours <b>C<sub>max</sub></b> maximum plasma concentration <b>t<sub>max</sub></b> time for maximum concentration <b>t<sub>1/2</sub></b> half-life					

*\*In-transformed values*

A  $t_{max}$  of 6 h was observed in 1 subject; this was a second peak. The observed  $t_{max}$  values in the other subjects ranged from 1.25–1.58 h. The second peak may be likely explained by withdrawing blood from the administration catheter causing unusual high voriconazole plasma concentrations due to possible 'left over'.

Conclusion on bioequivalence study:

The 90% confidence intervals calculated for  $AUC_{0-t}$  and  $C_{max}$  are within the bioequivalence acceptance range of 0.80–1.25. Based on the submitted bioequivalence study Voriconazol betapharm 200 mg, powder for solution for infusion are considered bioequivalent with Vfend.

The MEB has been assured that the bioequivalence studies have 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.1 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 betapharm powder for solution for infusion.

Summary table of safety concerns as approved in RMP

Important identified risks	<ul style="list-style-type: none"> <li>• Hepatotoxicity</li> <li>• Neuropathy peripheral</li> <li>• Phototoxicity</li> <li>• QTc prolongation and torsades de pointes</li> <li>• Squamous cell carcinomas</li> <li>• Visual effects (including optic neuritis, papilloedema and other visual concerns)</li> </ul>
Important potential risks	<ul style="list-style-type: none"> <li>• Long-term treatment</li> <li>• Other skin cancer (non-SCC)</li> <li>• Suicide-related events</li> </ul>
Important missing information	<ul style="list-style-type: none"> <li>• Resistance</li> <li>• Use in children below two years of age</li> <li>• Use in patients with severe chronic hepatic cirrhosis (Child-Pugh C)</li> <li>• Use in pregnant and lactating women</li> </ul>

Additional risk minimisation measures are required relating to hepatotoxicity and squamous cell carcinoma. 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, Squamous Cell Carcinoma and hepatic toxicity
- Health Care Professional Question and Answer Brochure for phototoxicity, Squamous Cell Carcinoma and hepatic toxicity
- Patient Alert Card for Squamous Cell Carcinoma

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

**IV.2 Discussion on the clinical aspects**

For this authorisation, reference is made to the clinical studies and experience with the innovator product Vfend. 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**

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report making reference to the innovator product Vfend, which is registered through

a centralised procedure. Minor changes have been made to the PL in line with company house style, which has been subject to successful user tests for other products. These tests confirm that the MAH's house style does not affect readability of the leaflet. The bridging report submitted has been found acceptable.

## **VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION**

Voriconazol betapharm 200 mg, powder for solution for infusion have a proven chemical-pharmaceutical quality and are generic forms of Vfend 200 mg powder for solution for infusion. Vfend 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. The date of authorisation in the Netherlands was 16 December 2014.

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 betapharm with the reference product, and have therefore granted a marketing authorisation. The mutual recognition procedure was finalised with a positive outcome on 18 May 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
Secondary packaging site	NL/H/3363/1A/001/G	IA	26-8-2015	9-9-2015	Approval	No
Repeat use procedure to register the product in Spain, France and Italy	NL/H/3363/001/E/001	E	1-12-2015	29-2-2016	Approval	No
Change of the name and/or address of a manufacturer	NL/H/3363/1/1A/02	IA	12-4-2016	12-5-2016	Approval	No