CBG MEB

Public Assessment Report

Scientific discussion

Voramol 200 mg powder for solution for infusion

(Voriconazole)

NL/H/3161/001/DC

Date: 10 March 2016

This module reflects the scientific discussion for the approval of Voramol 200 mg powder for solution for infusion. The procedure was finalised at 11 February 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 Voramol 200 mg powder for solution for infusion, from Alvogen IPCo S.ar.l.

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

Voramol should be administered primarily to patients with progressive, possibly life-threatening 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 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 marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

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

II. QUALITY ASPECTS

II.1 Introduction

Voramol 200 mg powder for solution for infusion is a white to off white lyophilised powder, with pH: 5.0–7.0 and osmolality 530 mOsm/Kg ± 10%.

The lyophilised powder is packed in 25 ml transparent glass vials, sealed with chlorobutyl rubber stoppers and aluminium caps with plastic flip-off seal. One vial is used for each infusion. Each vial contains 200 mg voriconazole powder. The reconstituted solution contains 10 mg voriconazole per ml and is infused at a maximum rate of 3 mg voriconazole per kg per hour.

The excipients are hydroxypropyl beta (cyclo) dextrin (molar substitution grade 0.65), sodium chloride and hydrocloric acid (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. It has been demonstrated that the same polymorphic form is manufactured consistently. Voriconazole has two chiral centers and hence contains four isomers.

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 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 of the drug substance comprises three stages. Specifications have been adopted for the starting material, solvents, reagents and other raw materials; these are generally acceptable. The drug substance has been adequately characterized

Quality control of drug substance
The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. with a number of additional requirements. Batch analytical data demonstrating compliance with this specification have been provided for three pilot/semi-production scale batches.

Stability of drug substance
Stability data on the active substance have been provided for three batches in accordance with applicable European guidelines demonstrating the stability of the active substance for 18 months at 25°C/60%RH and 30°C/65%RH and during 6 months at 40°C/75%RH. Based on the data submitted, a retest period could be granted of 30 months without special storage conditions.

II.3 Medicinal Product

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. During the development, studies were performed such as characterization of batches of the originator, development of the formulation based on the originator's formulation, selection of a solubilizing agent (due to poor solubility of the drug substance in water), and its required concentration and manufacturing process development. Typical chemical-physical quality aspects of the product after reconstitution of the powder were compared with those of the originator (e.g. pH, specific gravity, osmolality).

The choices of the packaging and manufacturing process are justified. A bioequivalence study was performed between the proposed product and the innovator due to the difference in solubility enhancer. The quality requirements in the bioequivalence guideline are fulfilled (e.g. regarding size & composition of test batch, assay test batch & reference batch etc.). The chemical-physical quality characteristics of the proposed product compared with the innovator support the bioequivalence study.

Manufacturing process
The manufacturing process consists of the following production phases: preparation of the bulk solution, filtration of solution, filling of solution into the vials, lyophilisation and capping of lyophilised vials. The manufacturing process has been adequately validated according to relevant European guidelines. The in-process controls are adequate. Adequate process validation data on the product has been presented for three production batches.

Control of excipients
The excipients comply with the Ph.Eur.

Quality control of drug product
The product specification includes tests for appearance, clarity & colour, reconstitution time, water content, pH, osmolality, particulate contamination, identity, assay, uniformity of dosage units, related substances, sterility and bacterial endotoxins. Extractable volume of reconstituted solution is tested as in-process control. The release and shelf-life requirements are identical except for degradation products, where the release limit is tighter.
The specification is acceptable. The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on three production batches, demonstrating compliance with the release specification.

Stability of drug product

Stability data on the product have been provided for two production batches stored during 12 months at 25°C/60% RH and 30°C/65% RH and six months at 40°C/75% RH, and one production batch stored during 18 months at 25°C/60% RH and 30°C/65% RH and six months at 40°C/75% RH. The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in the proposed container closure systems. The levels of degradation products increased very slightly and remained well within the limits. Voriconazole is not susceptible to light. The proposed shelf-life of 24 months, no special storage conditions, is justified.

Compatibility/in-use stability studies have been performed with the reconstituted solution and the reconstituted diluted solution. The solvents and IV liquids stated in the SmPC were used in the studies. The results are adequate. The studies will be completed with product stored during the shelf-life.

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 Voramol 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 Voramol 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 one bioequivalence study, which is discussed below.

IV.2 Pharmacokinetics

Bioequivalence study

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Voramol 200 mg powder for solution for infusion (Pharmathen S.A., Greece) is compared with the pharmacokinetic profile of the reference product Vfend 200 mg powder for solution for infusion (Pfizer Ltd., Poland).

The choice of the reference product in the bioequivalence study has been justified. The formula and preparation of the bioequivalence batch is considered identical to the formula proposed for marketing.

The MAH has selected a different cyclodextrine, i.e. hydroxypropylbetadex, than used for Vfend, i.e. sulfobutylether beta-cyclodextrin sodium.
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 use of hydroxypropylbetadex has also been evaluated in children. No significant age dependence was observed for AUC and Cmax among the children evaluated. Concentrations of hydroxypropyl-betadex fell below quantifiable limits by 12 hours. Overall, the use of hydroxypropylbetadex instead of sulfobutylether beta-cyclodextrin is acceptable. The complex is considered rapidly 'dissolved' after the blood stream.

Design

A single-dose, two-period, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 26 healthy male subjects, aged 23-61 years. Each subject received a single dose (200 mg) of both the test and the reference formulations. Once reconstituted and diluted, the powder solution contained 4 mg/ml of voriconazole. It was then infused during 1.5 hours. There were two dosing periods, separated by a washout period of 7 days.

Blood samples were taken 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 36 hours after administration of the products.

The design of the study is acceptable.

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.

ResultsI

All 26 subjects completed the study and were eligible for pharmacokinetic analysis. Their samples were included in statistical data analysis and subsequent bioequivalence assessment.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, tmax (median, range)) of voriconazole under fasted conditions.

Treatment N=26	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	6375 ± 2080	6574 ± 2118	1686 ± 271	1.5 (1.25 – 1.67)	6.3 ± 1.6
Reference	6850 ± 2323	7054 ± 2407	1767 ± 309	1.5 (1.25 – 1.58)	6.4 ± 1.2
***Ratio (90% CI)**	0.93 (0.91-0.96)	--	0.96 (0.91-1.00)	--	--

$AUC_{0-\infty}$	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
$t_{1/2}$	half-life

**ln-transformed values*

Conclusion on bioequivalence study
The 90% confidence intervals calculated for AUC0-t and Cmax are within the bioequivalence acceptance range of 0.80–1.25. Based on the submitted bioequivalence study Voramol 200 mg with hydroxypropylbetadex is considered bioequivalent with Vfend 200 mg powder for solution for infusion with sulfobutylether beta-cyclodextrin.

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 Voramol 200 mg.

Summary table of safety concerns as approved in RMP:

Summary of safety concerns	
Important identified risks	• Hypersensitivity to the active substance, other azoles or to any of the excipients of the product • Hepatic toxicity • QTc prolongation • Visual events (including blurred vision, optic neuritis and papilloedema) • Phototoxicity • Peripheral neuropathy • Squamous cell carcinoma of the skin (SCC)
Important potential risks	• Patients with risk factors for acute pancreatitis • Stevens-Johnson syndrome • Development of resistant strains • Skin cancers (non-SCC) • Suicidal events • Off label use (especially as related to prophylactic and long-term use, i.e., hepatic toxicity, phototoxicity, and skin cancer)
Missing information	• Use of voriconazole during pregnancy and in women of child-bearing potential • Use in breastfeeding women • Safety and efficacy in children below 2 years

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 Squamous Cell Carcinoma and hepatic toxicity
- Health Care Professional Question and Answer Brochure for 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.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 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 information leaflet (PIL) has been performed on the basis of a bridging report making reference to Voriconazole 50 mg and 200 mg film-coated tablet, NL/H/3162/001-002. The bridging report submitted by the MAH has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Voramol 200 mg 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.

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 Voramol 200 mg with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 11 February 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
Introduction of a summary of pharmacovigilance system, changes in QPPV (including contact details) and/or changes in the Pharmacovigilance System Master File (PSMF) location. Change in the summary of Pharmacovigilance System (SPS) of Alvogen IPCo S.ar.l for the RMS: NL and the CMSs: HR, HU and RO due to the change of the QPPV (including contact details).	NL/H/3161/IA/001/G	IA	19-01-2016	12-02-2016	Approval	No