CBG MEB

Public Assessment Report

Scientific discussion

Voramol 50 and 200 mg film-coated tablets

(voriconazole)

NL/H/3164/001-002/DC

Date: 24 March 2016

This module reflects the scientific discussion for the approval of Voramol 50 and 200 mg, film-coated tablets. The procedure was finalised on 19 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 Voramol 50 and 200 mg, film-coated tablets from Alvogen IPCo S.àr.l.

The product is indicated for:

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.

Voramol 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 50 and 200 mg film-coated tablets (EMEA/H/C/000387) which have been registered in the EEA by Pfizer since March 21, 2002 trough a centralized procedure.
The concerned member states (CMS) involved in this procedure were Croatia, Hungary and Romania.

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

II. QUALITY ASPECTS

II.1 Introduction

Voramol 50 mg is a white to off-white, round bioconvex film-coated tablet, with code ‘V50’ on one side. Each tablet contains as active substance 50 mg of voriconazole.

Voramol 200 mg is a white to off-white, oval bioconvex film-coated tablet, with code ‘V200’ on one side. Each tablet contains as active substance 200 mg of voriconazole.

The film-coated tablets are packed in PVC transparent/Aluminium foil blisters and white opaque HDPE tablet container with (PP) screw cap.

The excipients are:
tablet core - lactose monohydrate, croscarmellose sodium, povidone K30, pregelatinized maize starch, magnesium stearate, colloidal anhydrous silica
film coating - HPMC/Hypromellose (3cP, 15cP and 50 cP) (E464), titanium dioxide (E171), lactose monohydrate, macrogol 4000/PEG (E1521)

The 50 mg and 200 mg products are fully dose proportional.

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 such as characterization of batches of the originator, *in-vitro* dissolution of originator tablets and investigations of formulations and process parameters were performed. The excipients are well known. The product is also intended for children (aged two years and above), the suitability of the formulation and safety of the excipients and their quantities for use in children is justified. The choices of the packaging and manufacturing process are justified. The bioequivalence study test batch was manufactured according to the finalized manufacturing process and composition. The dissolution profiles of the 50 mg and 200 mg strength are similar, with fast dissolution (>85% in 15 minutes) at pH 1.2, 4.5 and 6.8. As the quality criteria of the guideline have been fulfilled, from a chemical pharmaceutical point of view the requested biowaiver for the additional strength (50 mg) can be granted. The pharmaceutical development of the product has been adequately performed.

Manufacturing process
The manufacturing process of voriconazole film-coated tablets involves dispensing of the raw materials, deagglomeration, pre-blending, blending and blend lubrication, wet granulation, drying, dry granulation, lubrication, compression, and coating. The holding times at the different stages are laid down and justified with stability data.
The manufacturing process has been validated according to relevant European guidelines. Process validation data on the product have been presented for three pilot/semi-production scaled batches in accordance with the relevant European guidelines.

Control of excipients
All excipients comply with the Ph.Eur. A specification is also provided for the film-coating mixture. 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, dimensions, identity, average mass, uniformity of mass, uniformity of dosage units, loss on drying, disintegration, hardness, assay, degradation, including enantiomeric purity, dissolution, microbial quality and tightness of bottle. 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 per strength on pilot/semi production scale from the proposed production sites have been provided, demonstrating compliance with the specification.

Stability of drug product
Stability data on the product has been provided for three pilot/semi-production scale batches per strength in accordance with applicable ICH guidelines. The data demonstrates the stability of the product for 18 months (stored at 25°C/60% RH) and 6 months (stored at 40°C/75% RH). All parameters stay well within the proposed specification limits. No specific trends are seen. Photostability studies have been performed with packaged and unpackaged (petri-dish) tablets, in accordance with Note of Guidance on the Photostability testing of Medical products.The tablets have demonstrated to be light-resistant. The proposed shelf-life of 30 months, with no special storage conditions, is justified for both the PVC transparent/Aluminium foil blisters and HDPE tablet container. The product remains stable for 30 days following the first opening of the container. The in-use stability study will be repeated with batches stored during the entire shelf-life.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
The excipients do not pose a TSE risk. The only excipient from animal origin is lactose monohydrate; for this excipient it is declared that that the milk is sourced from healthy animals in the same conditions as milk for human use and that the lactose is prepared without the use of other ruminant materials than calf rennet.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Voramol 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 50 and 200 mg, film-coated tablets are 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 a bioequivalence study which is discussed below.

IV.2 Pharmacokinetics

Initially the MAH submitted a study which was carried out at a place for which critical GLP findings were identified during an inspection of another study. This has resulted in an overall declaration to consider studies carried out at this facility to be not GLP compliant.

In response, the MAH submitted a new bioequivalence study in which the pharmacokinetic profile of the test product Voramol 200 mg (Alvogen IPCo S.àr.l. Luxembourg) is compared with the pharmacokinetic profile of the reference product Vfend 200 mg (Pfizer, Germany).

The MEB has been assured that this new 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).

The choice of the reference product Vfend 200 mg in the bioequivalence study is accepted, as Vfend has been registered trough a centralised procedure. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Biowaiver
The results from the study with the 200 mg tablets can be extrapolated to the 50 mg strength, as the following conditions have been fulfilled:

- the formulations are dose proportional
- the formulations are manufactured by the same manufacturer and manufacturing process
- voriconazole shows a more than dose proportional increase in pharmacokinetics and as such the highest, most sensitive strength has been used in the bioequivalence study
- The *in vitro* dissolution results show similar profiles for the 50 and 200 mg strengths, with more than 85% dissolved after 15 minutes in pH 1.0, 4.5 and 6.8.

Bioequivalence study
Design
A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 48 healthy subjects (13 females, 35 males), aged 24-69 years. Each subject received a single dose (200 mg) of one of the 2 voriconazole formulations. The tablet was orally administered with 240 ml water after an overnight fast. Fasting was continued for 4 hours after dosing. There were 2 dosing periods, separated by a washout period of 7 days.

Blood samples were collected pre-dose and at 0.33, 0.5, 0.67, 0.83, 1, 1.25, 1.5, 1.75, 2, 2.33, 2.67, 3, 4, 6, 8, 12, 16, 24 and 36 hours after administration of the products.

A single dose, crossover study under fasting conditions to assess bioequivalence for voriconazole is considered adequate. Voriconazole should be taken without food, according to the SmPC.

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
One subject was withdrawn before dosing in Period II for safety reasons. 47 subjects completed the study and were eligible for pharmacokinetic and statistical analysis.

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

Treatment N=47	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	6133 ± 3533	6103 ± 3108**	1310 ± 531	1.0 (0.5-4.0)	7.2 ± 1.8**
Reference	5825 ± 3451	5758 ± 2834**	1315 ± 551	1.25 (0.33-6.0)	7.0 ± 1.9**
***Ratio (90% CI)**	1.05 (1.01-1.11)	--	1.00 (0.91-1.10)	--	--
CV (%)	13.6	--	28.9	--	--

$AUC_{0-\infty}$ 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
CV coefficient of variation

* *ln-transformed values*
** *n=46*

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 Voramol 200 mg tablet is considered bioequivalent with the Vfend 200 mg tablet.

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.

- Summary table of safety concerns as approved in RMP

Important identified risks	• Hepatic toxicity • QTc prolongation • Visual events (including optic neuritis, papilloedema and other visual concerns) • Phototoxicity • Peripheral neuropathy • Squamous cell carcinoma of the skin (SCC)
Important potential risks	• Skin cancers (non-SCC) • Suicide-related events
Missing information	• Effect in pregnancy • Effect in paediatrics • Off-label use • Resistance

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. 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

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 package leaflet of this product is reflecting the results of testing with patients to make sure it meets their needs and can enable the patient to use the medicinal product safely and effectively. No problems regarding comprehensibility and usefulness of information were identified.
The format, layout and design of the leaflet are considered acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Voramol 50 mg and 200 mg film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Vfend 50 mg and 200 mg film-coated tablets. 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.

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 50 and 200 mg with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 19 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
Introduction of a summary of pharmacovigilance system, changes in QPPV (including contact details) and/or changes in the Pharmacovigilance System Master File (PSMF) location	NL/H/xxxx/IA/349/G	iA	19-01-2016	12-02-2016	Approval	N