Public Assessment Report

Scientific discussion

Voricostad 200 mg, powder for solution for infusion

(voriconazole)

NL/H/2711/001/DC

Date: 22 April 2014

This module reflects the scientific discussion for the approval of Voricostad. The procedure was finalised on 4 November 2013. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Voricostad 200 mg, powder for solution for infusion from Stada Arzneimittel AG.

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).
- reatment of serious fungal infections caused by Scedosporium spp. and Fusarium spp.

Voriconazole 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 (EMEA/H/C/000387) which has been registered in the EEA by Pfizer Ltd since 21 March 2002 through a centralised procedure.

The concerned member states (CMS) involved in this procedure were Italy and Poland.

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

II. QUALITY ASPECTS

II.1 Introduction

Voricostad 200 mg powder for solution for infusion is a white lyophilized powder. After reconstitution each ml contains 10 mg of voriconazole. Once reconstituted further dilution is required before administration.

The powder is packed in clear type I glass vials that are closed with a rubber stopper and flip-off cap.
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 has been given, in sufficient detail and with 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°±2°C/60±5%RH (44 months) and 40°±2°C/75±5%RH (6 months).
For the second manufacturer a re-test period of 12 months has been granted based on stability data obtained at 25°±2°C/60±5%RH (6 months) and 40°±2°C/75±5% 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 solubilizer 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 solubilizer 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 (18 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 30 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 SPC 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
TSE statements from representative manufacturer regarding the safety and compliance of lactose monohydrate, have been provided. Only lactose monohydrate is of animal origin. 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 Voricostad powder for solution for infusion has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

The following post-approval commitments were made:
- If drug product batches are produced with active substance from one of the manufacturers, the MAH will provide the Certificates of Analysis and include these batches in the stability program.
- The on-going stability studies will be continued until the proposed shelf-life period of 30 months.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Voricostad 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 tot 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

To support the application for Voricostad 200 mg powder for solution for i.v. infusion, the MAH submitted a single-dose bioequivalence study versus Vfend 200 mg powder for solution for infusion (Pfizer, Poland).

The choice of the reference product in the bioequivalence study 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.

Bioequivalence study

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

Treatment N=24	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	7139 ± 2299	7327 ± 2352	1987 ± 475	1.5 (1.25 – 6.0)	6.3 ± 1.1
Reference	6660 ± 1712	6879 ± 1850	1927 ± 433	1.5 (1.25 – 1.58)	6.3 ± 1.4
***Ratio (90% CI)**	1.06 (1.00-1.12)	--	1.03 (0.97-1.10)	--	--
CV (%)	11.6	--	12.3	--	--

$AUC_{0-\infty}$ 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*

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 studies:
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, Voricostad 200 mg powder for solution for infusion is considered bioequivalent with Vfend.

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 Voricostad.

Summary table of safety concerns as approved in RMP

Important identified risks	Hepatotoxicity Neuropathy peripheral Pancreatitis acute Pancytopenia Phototoxicity QTc prolongation and torsades de pointes Renal failure acute Severe dermatological reactions Visual effects (including optic neuritis, papilloedema and other visual concerns)
Important potential risks	Bone disorder (fluorosis and periostitis) Long-term treatment Skin cancer (including cutaneous squamous cell carcinomas) Suicide-related events
Important missing information	Off-label use (including prophylactic use) Overdose Potential for resistance Use in children below two years of age Use in patients with severe chronic hepatic cirrhosis (Child-Pugh C) Use in pregnant and lactating women

No additional pharmacovigilance activities beyond routine pharmacovigilance are deemed necessary.

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

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 the innovator product Vfend, which is registered through a centralised procedure. Minor changes have been made to the PIL 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

Voricostad 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 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 Voricostad with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 4 November 2013.
The date of authorisation in the Netherlands was 7 January 2014.

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