

# **Public Assessment Report**

## **Scientific discussion**

**Voriconazol Sandoz 200 mg,  
powder for solution for infusion**

**(voriconazole)**

**NL/H/2835/001/DC**

**Date: 22 July 2014**

This module reflects the scientific discussion for the approval of Voriconazol Sandoz 200 mg, powder for solution for infusion. The procedure was finalised on 21 January 2014. For information on changes after this date please refer to the module 'Update'.

This report includes a summary on pages 8-10.

## I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Voriconazol Sandoz 200 mg, powder for solution for infusion from Sandoz B.V.

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.

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 (EMA/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 Austria, Belgium, Bulgaria, Croatia, Czech Republic, Denmark, France, Germany, Greece, Ireland, Italy, Luxembourg, Norway, Poland, Portugal, Romania, Slovakia, Slovenia and Spain.

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

## II. QUALITY ASPECTS

### II.1 Introduction

Voriconazol Sandoz 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 25 ml clear type I glass vials that are closed with a lyophilisation rubber stopper and sealed with an aluminium flip-off seals for single use.

The only excipient is sulfobutylether beta cyclodextrin sodium (SBECD).

### 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 to almost white non-hygroscopic powder, which is freely soluble in acetone and in methylene chloride, and insoluble in water. Further, voriconazole exhibits polymorphism, the polymorphic form produced by the manufacturer is Form-B. The substance consists of two asymmetric carbons, hence it exhibits optical isomerism with a possibility of two pairs of optical isomers, i.e. four isomers. Isomerism has been sufficiently specified. The manufacturer produces the active substance with a configuration of (2R,3S).

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 (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

The synthesis of voriconazole is described in four stages. No class 1 organic solvents are used in the manufacturing process. The active substance has been adequately characterised and acceptable specifications have been adopted for the starting material, solvents and reagents.

### Quality control of drug substance

The drug substance specification is in line with the Ph.Eur. with additional requirements for residual solvents and microbial quality. The specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with the drug substance specification have been provided for three full-scale batches.

### Stability of drug substance

Stability data on the active substance have been provided for three full-scale batches stored at 25°C/60% RH (44 months) and 40°C/75% RH (6 months). No clear trends or changes were seen in any of the tested parameters. The claimed retest period of 48 months without any special storage requirements is justified.

## **II.3 Medicinal Product**

### Pharmaceutical development

The development of the product has been described, the choice of excipient is justified and its function explained. Sulfobutylether beta cyclodextrin sodium is a well-known solubilizer used in parenteral preparations. The excipient is well known and is the same as present in the reference product. The main development studies performed were the comparative studies with the reference product for physicochemical properties, optimization of the lyophilisation process and performance of compatibility studies with the reconstitution and dilution solutions as recommended in the SmPC. The choices of the packaging and manufacturing process are justified. Sterilisation of the product is performed by sterile filtration. The choice of the sterilisation method has been justified. Several sterilisation methods were evaluated. Heat sterilisation, steam sterilisation and gamma irradiation of the solid drug substances resulted in complete destruction of the drug substance. A validation study on the integrity of the container closure system has been done to assure that the finished product is exempt from possible microbial contamination. Sterility was confirmed throughout shelf-life by the results of the formal stability studies.

The drug product is an un-buffered product with a pH of 4.5-7.5. The pH of the originator product lies within this range. Although the osmolality of the reconstituted product (430 mOsmol/KG) is higher than the physiological osmolality, the osmolality of the final solutions for infusion is determined by the further dilution factor and the diluent. The osmolality of the reconstituted test product is comparable to that of the reference product.

The drug product contains an overfill of 5.65%. This is compliant with the prescription for reconstitution in the PL and SmPC with 19.0 ml water for injection or 0.9% NaCl, which is in line with the prescription of the innovator product. For this generic product no clinical studies were performed. The pharmaceutical development of the product has been adequately performed.

### Manufacturing process

The main steps of the manufacturing process are the preparation of the solution, pre-filtration through a microbial retentive filter, sterile filtration through a microbial retentive filter, filling into vials, lyophilisation and closing of the vials. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for three full-scale batches.

### Control of excipients

The excipients, including water for injection and nitrogen that are used during the manufacturing process, comply with pharmacopoeial requirements. These specifications are acceptable.

### Quality control of drug product

The product specification includes tests for appearance, identity, water content, colour of solution, clarity of constituted solution, solubility and dissolving time of constituted solution, appearance of constituted solution, pH, particulate contamination, uniformity of dosage units, assay, related substances, sterility, bacterial endotoxins and osmolality. Except for pH and related substances the release and shelf-life limits are identical. 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 full-scale batches, demonstrating compliance with the release specification.

#### Stability of drug product

Stability data on the product has been provided two pilot-scale batches stored at 25°C/60% RH (36 months), 30°C/65% RH (12 months) and 40°C/75% RH (6 months) and on three full-scale batches stored at 25°C/60% RH (9 months), 30°C/75% RH (9 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 25 ml colourless type I glass vials with chlorobutyl rubber stopper with aluminium flip-off seal with PP disc. At all three storage conditions an increase of impurities was seen that was most pronounced at accelerated storage conditions. At accelerated storage conditions a significant change (out-of-specification) was seen for one impurity after 6 months. Results for assay were variable, but showed no clear trend. No clear trends or changes were observed in the other parameters tested. All other parameters remained within the acceptance criteria at all three storage conditions. The stability data on the production-scale batches are in line with the stability data on the pilot-scale batches. A photostability study was performed. No significant changes were seen in the tested parameters after light exposure. The proposed shelf-life of 2 years with storage condition 'Store below 30°C' is justified.

The compatibility and chemical stability with the proposed reconstitution fluids was adequately demonstrated for 24 hours when stored at 2-8°C protected from light. The compatibility and chemical stability after further dilution with the proposed infusion fluids as described in the SmPC and PL to a final concentration of 0.5 mg/ml and 5 mg/ml has been adequately demonstrated for 3 hours when stored at 30°C/75% RH. The reconstitution and dilution instructions as well as the compatible solutions for infusion listed in the SmPC are identical to those of the reference product.

#### 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 Sandoz 200 mg has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

The following post-approval commitment was made:

- Results of the on-going stability studies at least up to the claimed shelf-life will be submitted as soon as available.

## **III. NON-CLINICAL ASPECTS**

### **III.1 Ecotoxicity/environmental risk assessment (ERA)**

Since Voriconazol Sandoz 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.

## IV.2 Pharmacokinetics

### Biowaiver

Voriconazol Sandoz 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). The quantitative composition of Voriconazol Sandoz 200 mg is entirely the same as the originator. Therefore, it may 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 Sandoz 200 mg powder for solution for infusion.

Summary table of safety concerns as approved in RMP

Important identified risks	<ul style="list-style-type: none"><li>- QT prolongation and Torsades de Pointes</li><li>- Hepatic toxicity</li><li>- Visual effects (optic neuritis, papilloedema)</li><li>- Phototoxicity</li><li>- Peripheral neuropathy</li><li>- Periostitis</li></ul>
Important potential risks	<ul style="list-style-type: none"><li>- Skin cancer (including squamous cell carcinoma)</li><li>- Cardiac failure</li><li>- Suicide-related events</li><li>- Resistance</li><li>- Interaction with CYP450 inducers (Phenytoin, Efavirenz, Rifabutin, Ritonavir)</li></ul>
Missing information	<ul style="list-style-type: none"><li>- Long-term use impact focusing on hepatic toxicity, phototoxicity and skin cancer</li><li>- Off-label use in paediatric population</li><li>- Pregnancy and lactation</li></ul>

It is agreed that no additional pharmacovigilance activities beyond routine pharmacovigilance are necessary at this point. However, if additional risk management measures are laid down for the innovator product, the MAH will adopt these and update the RMP.

## 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. Similarity to the innovator has been sufficiently demonstrated based on *in-vitro* comparison. 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. The PL is in accordance with the leaflet of the innovator product Vfend, which is registered through a centralised procedure. The bridging report submitted has been found acceptable.

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

Voriconazol Sandoz 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.

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 Sandoz 200 mg with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 21 January 2014.

The date of authorisation in the Netherlands was 20 May 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

**Summary Public Assessment Report**  
**Generics**

**Voriconazol Sandoz 200 mg,  
powder for solution for infusion**

**voriconazole**

**NL/H/2835/001/DC**

**Date: 22 July 2014**



# Summary Public Assessment Report

## Generics

Voriconazol Sandoz 200 mg, powder for solution for infusion

Active substance: voriconazole

This is a summary of the public assessment report (PAR) for Voriconazol Sandoz 200 mg. It explains how this medicine was assessed and its authorisation recommended as well as its conditions of use. It is not intended to provide practical advice on how to use Voriconazol Sandoz.

For practical information about using this medicine, patients should read the package leaflet or contact their doctor or pharmacist.

### **What is Voriconazol Sandoz and what is it used for?**

Voriconazol Sandoz 200 mg is a 'generic medicine'. This means that it is similar to a 'reference medicine' already authorised in the European Union (EU) called Vfend powder for solution for infusion.

Voriconazole is an antifungal medicine. It is used for the treatment of adults and children over the age of two years with:

- invasive aspergillosis (a type of fungal infection due to *Aspergillus*);
- candidaemia (another type of fungal infection due to *Candida*) in non-neutropenic patients (patients with a normal white blood cell count);
- serious invasive *Candida* infections when the fungus is resistant to fluconazole (another antifungal medicine);
- serious fungal infections caused by *Scedosporium* or *Fusarium* (two different types of fungus).

This medicine is intended for patients with worsening, possibly life-threatening, fungal infections. The medicine can only be obtained with a prescription.

### **How is this medicine used?**

This medicine is given twice a day. The dose of voriconazole to use depends on the weight of the patient. Patients need to receive an initial higher dose (loading dose) on the first day of treatment. The aim of the loading dose is to reach stable blood levels. The loading dose is then followed by a maintenance dose that can be adjusted according to the patient's response. The dose may be increased or decreased according to how the patient responds.

### **How does this medicine work?**

The active substance voriconazole is an antifungal medicine that belongs to the 'triazole' group. It works by preventing the formation of ergosterol, which is an important part of fungal cell membranes. Without ergosterol, the fungus is killed or prevented from spreading. The list of fungi against which Voriconazol Sandoz is active can be found in the summary of product characteristics, which is available in the MRI Product Index ([http://mri.medagencies.org/download/NL\\_H\\_2835\\_001\\_FinalSPC.pdf](http://mri.medagencies.org/download/NL_H_2835_001_FinalSPC.pdf)).

### **How has this medicine been studied?**

The company provided data from the published literature on voriconazole. No additional studies were needed as Voriconazol Sandoz is a generic medicine that is given by infusion and contains the same amount of active substance as the reference medicine, Vfend 200 mg.

### **What are the benefits and risks of this medicine?**

Because Voriconazol Sandoz is a generic medicine, its benefits and risks are taken as being the same as the reference medicine.

### **Why is this medicine approved?**

It was concluded that, in accordance with EU requirements, this medicine has been shown to have comparable quality and to be comparable to Vfend. Therefore, the view was that, as for Vfend, the benefit outweighs the identified risk.

**What measures are being taken to ensure the safe and effective use of this medicine?**

A risk management plan has been developed to ensure that this medicine is used as safely as possible. Based on this plan, safety information has been included in the summary of product characteristics and the package leaflet for Voriconazol Sandoz 200 mg, including the appropriate precautions to be followed by healthcare professionals and patients.

**Other information about this medicine**

In the Netherlands, the marketing authorisation for Voriconazol Sandoz 200 mg powder for solution for infusion was granted on 20 May 2014.

The full PAR for this medicine can be found on the website <http://mri.medagencies.org/Human>. For more information about treatment with Voriconazol Sandoz 200 mg, read the package leaflet ([http://mri.medagencies.org/download/NL\\_H\\_2835\\_001\\_FinalPL.pdf](http://mri.medagencies.org/download/NL_H_2835_001_FinalPL.pdf)) or contact your doctor or pharmacist.

This summary was last updated in July 2014.