CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Voriconazol Sandoz 50 mg and 200 mg, film-coated tablets
Sandoz B.V., the Netherlands

voriconazole

This assessment report is published by the MEB pursuant Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB and its fellow –organisations in all concerned EU member states.
It reflects the scientific conclusion reached by the MEB and all concerned member states at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation.
This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand.

This assessment report shall be updated by a following addendum whenever new information becomes available.

General information on the Public Assessment Reports can be found on the website of the MEB.

To the best of the MEB's knowledge, this report does not contain any information that should not have been made available to the public. The MAH has checked this report for the absence of any confidential information.

EU-procedure number: NL/H/2583/001-002/DC
Registration number in the Netherlands: RVG 111735-111736

24 July 2013

Pharmacotherapeutic group:	antimycotics for systemic use, triazole derivatives
ATC code:	J02AC03
Route of administration:	oral
Therapeutic indication:	see next page
Prescription status:	prescription only
Date of authorisation in NL:	13 June 2013
Concerned Member States:	Decentralised procedure with AT, BE, DK, EE, ES, FI, FR, IE, IT, LU, NO, PL, PT, RO, SE, SK, UK
Application type/legal basis:	Directive 2001/83/EC, Article 10(1)

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SPC), package leaflet and labelling.

I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the member states have granted a marketing authorisation for Voriconazol Sandoz 50 mg and 200 mg, film-coated tablets from Sandoz B.V. The date of authorisation was on 13 June 2013 in the Netherlands.

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 SPC.

The primary mode of action of voriconazole is the inhibition of fungal cytochrome P-450-mediated 14 alpha-lanosterol demethylation, an essential step in fungal ergosterol biosynthesis. The accumulation of 14 alpha-methyl sterols correlates with the subsequent loss of ergosterol in the fungal cell membrane and may be responsible for the antifungal activity of voriconazole. Voriconazole has been shown to be more selective for fungal cytochrome P-450 enzymes than for various mammalian cytochrome P-450 enzyme systems.

A comprehensive description of the indications and posology is given in the SPC.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Vfend 50 mg and 200 mg film-coated tablets (EMEA/H/C/000387) which have been registered in the EEA by Pfizer Ltd since 19 March 2002 through a centralised procedure.

The marketing authorisation is granted based on article 10(1) of Directive 2001/83/EC.

This type of application refers to information that is contained in the pharmacological-toxicological and clinical part of the dossier of the authorisation of the reference product. A reference product is a medicinal product authorised and marketed on the basis of a full dossier, i.e. including chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data. This information is not fully available in the public domain. Authorisations for generic products are therefore linked to the 'original' authorised medicinal product, which is legally allowed once the data protection time of the dossier of the reference product has expired. For this kind of application, it has to be demonstrated that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of the reference product. To this end the MAH has submitted a bioequivalence study in which the pharmacokinetic profile of the product is compared with the pharmacokinetic profile of the reference product Vfend 200 mg film-coated tablets, registered in the EEA. A bioequivalence study is the widely accepted means of demonstrating that difference of use of different excipients and different methods of manufacture have no influence on efficacy and safety. This generic product can be used instead of its reference product.

No new pre-clinical and clinical studies were conducted, which is acceptable for this abridged application.

No scientific advice has been given to the MAH with respect to these products and no paediatric development programme has been submitted, as this is not required for a generic application.

II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice
The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for this product type at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

Active substance
The active substance is voriconazole, an established 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. Voriconazole exhibits polymorphism; the polymorphic form used is Form B. Voriconazole exhibits optical isomerism with a possibility of two pairs of optical isomers i.e., 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 (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
A description of the manufacturing process have been given. The synthesis of involves four stages. The starting materials are considered to be acceptable in view of the synthesis.

Quality control of drug substance
The specification limits are set according to the European Pharmacopeia and ICH guidelines. Batch analysis results for four batches have been submitted, showing compliance to the specification.

Stability of drug substance
The re-test period of the drug substance is 48 months, which is acceptable based on provided stability data for storage at 25°±2°C/60±5%RH and 40°±2°C/75±5 %RH.

** Ph.Eur. is an official handbook (pharmacopoeia) in which methods of analysis with specifications for substances are laid down by the authorities of the EU.*

Medicinal Product

Composition
Voriconazol Sandoz 50 mg is a white to off-white, round, biconvex, film-coated tablet with '50' debossed on one side and plain on other side.
Voriconazol Sandoz 200 mg is a white to off-white, biconvex, capsule shaped film coated tablets with '200' debossed on one side and plain on other side.

The film-coated tablets are packed in PVC/PVDC/Al blisters and HDPE bottles with a child-resistant screw cap.

The excipients are:
Tablet core - lactose monohydrate, pregelatinised maize starch, croscarmellose sodium, povidone, magnesium stearate.
Film coating - HPMC2910/Hypromellulose (E464), lactose monohydrate, titanium dioxide (E171), triacetin.

The two tablet strengths are fully dose proportional.

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. During development, composition and process parameters were optimised until the final formulation was obtained. The biobatch was manufactured according to the finalized composition and manufacturing process. The applicant demonstrated 85% dissolution in 15 minutes in three media for both strengths. Hence, a biowaiver for the 50 mg can be granted from a chemical-pharmaceutical point of view. The pharmaceutical development of the product has been adequately performed.

Manufacturing process
The manufacturing process involves the following steps: dispensing of raw materials, sifting, mixing, binder solution preparation, granulation and drying, sifting and milling, blending, sifting and lubrication, compression, coating suspension preparation, film-coating of tablets and drying, and finally packaging.
The manufacturing process is adequately validated on three commercial-size batches per strength. All parameters tested complied with the pre-set limits and no unexpected results were observed.

Control of excipients
The excipient used and their quantities, are common for film-coated tablets. Analytical procedures for all the excipients except the Opadry II White, are performed as per requirement specified in the Ph.Eur. (for some of the excipients, additional parameters are tested with in-house methods, such as microbiological contamination and particle size). The qualitative and quantitative composition of Opadry II White is provided, and references to the Ph.Eur. as quality standard for the individual components are given.

Quality control of drug product
The product specification includes tests for appearance, identification (voriconazole and titanium dioxide), uniformity of dosage unit-mass variation, dissolution, related substances, assay, water content and microbiological contamination. The release and end-of shelf-life specifications differ for related substances and water content, the other tests and limits are identical. The proposed limits are acceptable.
The analytical methods have been adequately described and validated. Batch analytical data from three batches per strength have been provided. All batches comply with the proposed specification.

Stability of drug product
The following stability data on the product has been provided: at long term storage two batches up to 18 months, and one batch up to 12 months for the 50 mg were submitted. For the 200 mg, long term stability data for two batches up to 18 months and one batch up to 12 months were provided. At accelerated storage data up to 6 months is available for both strengths. The conditions used in the stability studies are according to the ICH stability guideline.
A photostability testing study was performed according to ICH, showing that the product remains stable when directly exposed, hence no particular storage conditions is necessary in this respect. From the data it is observed that the product remains stable throughout the testing period. The proposed shelf life of 24 months packed in a PVC/PVDC/Al blister or a HDPE bottle was therefore granted. The product does not require any special storage conditions. Six months worst case in-use testing with the HDPE bottle demonstrated that the tablets still complied with the specification; therefore a shelf life after opening is not required and is not included in the SPC.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Only lactose monohydrate is of animal origin. The lactose supplier has provided a statement confirming that the lactose is sourced from healthy animals under the same conditions as milk collected for human consumption, and that the lactose has been prepared without the use of other ruminant material than milk and calf rennet. TSE risk for the lactose used can be considered negligible.

II.2 Non-clinical aspects

This product is a generic formulation of Vfend, which is available on the European market. 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.

Environmental risk assessment
The product is intended as a substitute for other identical products on the market. The approval of this product will not result in an increase in the total quantity of voriconazole released into the environment. It does not contain any component, which results in an additional hazard to the environment during storage, distribution, use and disposal.

II.3 Clinical aspects

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 in which the pharmacokinetic profile of the test product Voriconazol Sandoz 200 mg (Sandoz B.V., the Netherlands) is compared with the pharmacokinetic profile of the reference product Vfend 200 mg film-coated tablets (Pfizer, UK).

The choice of the reference product
The choice of the reference product in the bioequivalence study is accepted, as the product 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, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 42 healthy male subjects, aged 18-34 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 10 days.

Blood samples were collected pre-dose and at 0.167, 0.333, 0.5, 0.667, 0.833, 1.0, 1.25, 1.5, 1.75, 2.0, 2.25, 2.5, 3.0, 3.5, 4.0, 5.0, 6.0, 8.0, 12.0, 16.0, 24.0, 30.0, 36.0 and 48.0 hours after administration of the products.
This single dose, crossover study under fasting conditions to assess bioequivalence for voriconazole is considered adequate.

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 in period I due to an adverse event (AE). Another subject was withdrawn before check-in for period II (protocol noncompliance). One person was withdrawn before check in of period II due to an AE and 3 subjects did not check in for period II. Thirty-six subjects completed the study and were included in the analysis.

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

Treatment N=36	AUC_{0-t} ng.h/ml	$AUC_{0-\infty}$ ng.h/ml	C_{max} ng/ml	t_{max} h	$t_{1/2}$ h
Test	11438 ± 8636	12244 ± 10322	1568 ± 470	1.73 ± 0.88	8.6 ± 3.9
Reference	10892 ± 8791	11595 ± 10359	1566 ± 527	1.66 ± 0.68	8.0 ± 3.5
***Ratio (90% CI)**	1.07 (1.01 - 1.13)	1.07 (1.01 - 1.13)	1.01 (0.92 - 1.11)	--	--
CV (%)	13.6	14.2	23.2	--	--

$AUC_{0-\infty}$ 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*

The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are in agreement with those calculated by the MAH and are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the pharmacokinetic parameters of voriconazole under fasted conditions, it can be concluded that Voriconazol Sandoz 200 mg and Vfend 200 mg tablets are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

Fasting conditions has been applied, which is in accordance with the SPC: Voriconazole are to be taken at least one hour before, or one hour following a meal. When multiple doses of voriconazole are administered with high fat meals, C_{max} and AUC_{τ} are reduced by 34 % and 24 %, respectively. The absorption of voriconazole is not affected by changes in gastric pH.

Biowaiver

- In the bioequivalence study, the 200 mg tablet strength is used. Considering the non-linear pharmacokinetics, i.e. a more than dose proportional increase in AUC and C_{max}, the 200 mg strength is considered the more sensitive strength and as such the use of this strength is acceptable.
- The 50 and 200 mg strengths are dose proportional.
- The 50 and 200 mg strengths are manufactured by the same manufacturing process.
- Dissolution data at three pH values were submitted, showing comparable dissolution (i.e. >85% within 15 min) for the 50 and 200 mg strength.

All criteria for waiving are fulfilled and the 50 mg strength is acceptable.

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).

Risk management plan

Voriconazole was first approved in 2002, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of voriconazole can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or post authorisation which are not adequately covered by the current SPC. Additional risk minimisation activities have not been identified for the reference medicinal product. The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation. Routine pharmacovigilance activities are sufficient to identify actual or potential risks and a detailed European Risk Management Plan is not necessary for this product.

Product information

SPC

The content of the SPC approved during the decentralised procedure is in line with the SPC of the reference product Vfend.

Readability test

The package leaflet has not been evaluated via a user consultation study. A bridging report has been submitted. The content of the package leaflet strictly follows the originator and is thus acceptable. Separate user testing is not required.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Voriconazol Sandoz 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 MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The SPC is consistent with that of the reference product. The SPC, package leaflet and labelling are in the agreed templates.

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 50 mg and 200 mg with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 2 May 2013. Voriconazol Sandoz 50 mg and 200 mg film-coated tablets were authorised in the Netherlands on 13 June 2013.

The date for the first renewal will be: 2 May 2018.

The following post-approval commitment has been made during the procedure:

Quality - medicinal product

- The MAH committed to include one batch of each strength in the long-term stability program on a yearly basis.

List of abbreviations

ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BP	British Pharmacopoeia
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C_{max}	Maximum plasma concentration
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CV	Coefficient of Variation
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EU	European Union
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
OTC	Over The Counter (to be supplied without prescription)
PAR	Public Assessment Report
Ph.Eur.	European Pharmacopoeia
PIL	Package Leaflet
PSUR	Periodic Safety Update Report
SD	Standard Deviation
SPC	Summary of Product Characteristics
$t_{½}$	Half-life
t_{max}	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
USP	Pharmacopoeia in the United States

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