CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Voriconazol Pfizer 50 and 200 mg, film-coated tablets
Voriconazol Pfizer 40 mg/ml, powder for oral suspension
Voriconazol Pfizer 200 mg, powder for solution for infusion
Pfizer 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/2627/001-004/DC
Registration number in the Netherlands: RVG 111883- 111886

18 July 2013

Pharmacotherapeutic group:	antimycotics for systemic use, triazole derivatives
ATC code:	J02AC03
Route of administration:	oral; intravenous
Therapeutic indication:	see next page
Prescription status:	prescription only
Date of authorisation in NL:	10 June 2013
Concerned Member States:	Decentralised procedure with AT, BE, DE, DK, EL, ES, FI, FR, IE, IT, LU, PT, SE, 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 Pfizer 50 and 200 mg, film-coated tablets, Voriconazol Pfizer 40 mg/ml, powder for oral suspension and Voriconazol Pfizer 200 mg, powder for solution for infusion from Pfizer B.V. The date of authorisation was on 10 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*).
- 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 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.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Vfend 50 mg and 200 mg film-coated tablets, 200 mg powder for solution for infusion and 40 mg/ml powder for oral suspension (EMEA/H/C/000387) which have been registered in the EEA by Pfizer Ltd since 19 March 2002 through a centralised procedure. Pfizer is also the MAH in this generic application. For further information on the assessment of the Vfend dossier, refer to the EPAR available on the EMA website (http://www.ema.europa.eu).

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

The MAH claims similarity to the originator/reference product Vfend (voriconazole) film-coated tablets (50 mg or 200 mg), powder for solution for infusion (200 mg voriconazole, equivalent to a 10 mg/mL solution following reconstitution), and powder for oral suspension (45 g of powder for oral suspension providing 40 mg/mL voriconazole when constituted with water), which are also products from Pfizer.

To bridge the current applications to the reference products, a biowaiver has been submitted, indicating that the products at issue and the reference products are identical in qualitative and quantitative composition. The active pharmaceutical ingredient used, the manufacturing process and manufacturing site for the finished dosage form are the same. A bioavailability study is therefore not required to demonstrate bioequivalence, and none is provided in this application. These generic products can be used instead of the reference products.

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 drug substance is voriconazole, an established active substance described in the European Pharmacopoeia (Ph.Eur.*). Voriconazole is a white to light coloured powder. It is a weak base and is classified as a low solubility, high permeability compound. It has a high trans-membrane absorptive flux value and is rapidly absorbed following oral administration (T_{max} is 2 hours), with oral bioavailability estimated to be 96% in man from population pharmacokinetics. Voriconazole drug substance is chemically and physically stable under all ICH stability conditions.

The active substance section for Voriconazol Pfizer has not been assessed any further. Reference is made to the Vfend dossier.

** 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
Tablets
Voriconazol Pfizer 50 mg is a white to off-white, round tablet, debossed “Pfizer” on one side and “VOR50” on the reverse.
Voriconazol Pfizer 200 mg is a white to off-white, round tablet, debossed “Pfizer” on one side and “VOR200” on the reverse.

The tablets are packed in HDPE tablet containers or PVC/Aluminium blisters.

The excipients are:
Tablet core - lactose monohydrate, pregelatinised starch, croscarmellose sodium, povidone, magnesium stearate
Coating – hypromellose, titanium dioxide (E171), lactose monohydrate, glycerol triacetate.

Powder for oral suspension
Voriconazol Pfizer 40 mg/ml is white to off-white powder for oral suspension. Each ml of oral suspension contains 40 mg of voriconazole when reconstituted with water.
One 100 ml high-density polyethylene (HDPE) bottle (with a polypropylene child resistant closure) contains 45 g of powder for oral suspension. A measuring cup (graduated to indicate 23 ml), 5 ml oral syringe and a press-in bottle adaptor are also provided. Each bottle contains 3 g of voriconazole.

The excipients are: sucrose, silica colloidal anhydrous, titanium dioxide (E171), xanthan gum, sodium citrate, citric acid anhydrous, sodium benzoate (E211), natural orange flavor.

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

A 30 ml clear type I glass vial with rubber stopper (composed of chlorobutyl-isoprene) and aluminium cap with plastic seal is provided in one pack.

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

Voriconazol tablets, powder for oral suspension and powder for solution for infusion are identical to Vfend and have an identical quality dossier; the drug substance used, the manufacturing process and manufacturing site for the finished dosage forms are the same. Refer to the EPAR of Vfend for further information on the quality assessment.

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.

To bridge the current applications to the reference products Vfend, a biowaiver has been submitted, indicating the products at issue and the reference products to be identical in qualitative and quantitative composition. A bioavailability study is therefore not required to demonstrate bioequivalence, and none is provided in this application. This is agreed by the member states.

The indication sought for and the posology of the different pharmaceutical forms and strenghts are identical to the indications and posology as approved for the originator Vfend as presented in the proposed SPC.

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. The MAH submitted a copy of the approved Risk management plan for Vfend. This is considered acceptable.

Product information

SPC
The content of the SPC approved during the decentralised procedure is in accordance with that accepted for the reference product Vfend.

Readability test
The package leaflet has not been evaluated via a user consultation study. The PILs are identical to the innovator PIL in both content and lay out. Separate user testing is not required.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Voriconazol Pfizer 50 and 200 mg, film-coated tablets, Voriconazol Pfizer 40 mg/ml, powder for oral suspension and Voriconazol Pfizer 200 mg, powder for solution for infusion have a proven chemical-pharmaceutical quality and are generic forms of Vfend 50 mg and 200 mg film-coated tablets, 200 mg powder for solution for infusion and 40 mg/ml powder for oral suspension. Vfend is a well-known medicinal product with an established favourable efficacy and safety profile.

A bioequivalence study was not deemed necessary, as the products at issue and the reference products are identical in qualitative and quantitative composition.

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 Pfizer 50 and 200 mg, film-coated tablets, Voriconazol Pfizer 40 mg/ml, powder for oral suspension and Voriconazol Pfizer 200 mg, powder for solution for infusion with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 18 April 2013. Voriconazol Pfizer 50 and 200 mg, film-coated tablets, Voriconazol Pfizer 40 mg/ml, powder for oral suspension and Voriconazol Pfizer 200 mg, powder for solution for infusion were authorised in the Netherlands on 10 June 2013.

PSURs will be submitted with a yearly cycle, in accordance with the innovator product Vfend. The first data lock point is 28 February 2014.

The date for the first renewal will be: 18 April 2018.

There were no post-approval commitments made during the procedure.

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