CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Voriconazol AET 50 mg and 200 mg film-coated tablets Alfred Tiefenbacher (GmbH & Co. KG), Germany

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/2647/001-002/DC
Registration number in the Netherlands: RVG 111731-111732

1 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:	11 April 2013
Concerned Member States:	Decentralised procedure with DE
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 AET 50 mg and 200 mg film-coated tablets from Alfred Tiefenbacher (GmbH & Co. KG). The date of authorisation was on 11 April 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.

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.). It is a white or almost white powder, which is freely soluble in acetonitrile, acetone, methanol, dichloromethane and chloroform, soluble in ethanol and practically insoluble in hexane and water. Chirality and polymorphic form have been adequately discussed and demonstrated.

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 manufacturing of the drug substance consist of three steps. The manufacturing process has been described in sufficient detail. The starting materials are considered to be acceptable in view of the synthesis steps that follow.

Quality control of drug substance
The specification of voriconazole is based on the Ph.Eur. monograph with additional tests and limits for residual solvents and metal catalysts. The MAH based its specification also on the Ph.Eur. monograph and the additional tests an limits as mentioned by the DMF-holder.
Batch analytical data demonstrating compliance with the specification have been provided.

Stability of drug substance
Stability data on the drug substance have been provided for three batches stored at 25°C/60% RH and 40°C/75% RH. At long term and accelerated conditions no trends or out of specification results were observed. A retest period of 24 months without special storage conditions was granted.

** 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 AET 50 mg is a white to off-white, round, film-coated tablet.
Voriconazol AET 200 mg is a white to off-white, capsule-shaped, film-coated tablet.

The tablets are packed in PVC/Aluminium blisters.

The excipients are:
Tablet core - lactose monohydrate, pregelatinised starch (maize starch), croscarmellose sodium, povidone (K30), magnesium stearate.
Film-coating - Opadry® II white – 31K58875, consisting of lactose monohydrate, hypromellose (E464), titanium dioxide (E171), triacetin.

The tablets are 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 composition of the batch used in the bioequivalence study is identical to the proposed final composition. Comparative dissolution data have been provided in three pHs. In all media similarity has been demonstrated, more than 85% was dissolved within 15 minutes. Comparative dissolution data at three pH values between the 50 mg and 200 mg bioequivalence batch also demonstrated similarity. The pharmaceutical development of the product has been adequately performed..

Manufacturing process
The manufacturing process involves the following steps: wet granulation, tableting and packaging. The process is adequately validated on three commercial-scale batches. All parameters tested complied with the pre-set limits and no unexpected results were observed.

Control of excipients
All excipients are in accordance with the Ph.Eur. requirements. These specifications are acceptable.

Quality control of drug product
The product specification includes tests for description, identification, assay, average mass, uniformity of dosage units by mass variation, dissolution, related substances and microbiological quality. The release and end-of-shelf-life specifications are identical. The analytical methods have been adequately described and validated. Batch analytical data from three full-scale batches per strength, have been provided. All batches complied with the proposed specification.

Stability of drug product
Stability data of the drug product have been provided for three commercial-scale batches per strength stored at 25°C/60% RH (18 months) and 40°C/75% RH (6 months) packed in the proposed PVC/Al blister packaging. A small trend in total impurities was observed at accelerated conditions. Furthermore an increase in water content during long term stability studies was observed at the first three months of storage. A photostability study demonstrated that the product is not sensitive to light. Based on the submitted data the proposed shelf life of 30 months was granted, when stored in PVC/Al blister with the storage condition “Store in the original container in order to protect from moisture”.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
The drug product contains lactose monohydrate which complies with the Note for Guidance *on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products* (EMEA/410/01 rev 2). Lactose monohydrate is produced from milk obtained from healthy animals in the same conditions as those used to collect milk for human consumption. The lactose used in the manufacture of the product has been prepared without the use of ruminant material other than calf rennet. Magnesium stearate is produced using raw materials of vegetable origin.

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 AET 200 mg (Alfred Tiefenbacher (GmbH & Co. KG), Germany) is compared with the pharmacokinetic profile of the reference product Vfend 200 mg tablets (Pfizer, Germany).

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-stage, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 24 healthy male subjects, aged 20-46 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 6 hours after dosing. There were 2 dosing periods, separated by a washout period of 7 days.

Blood samples were collected pre-dose and at 0.25, 0.5, 0.75, 1, 1.33, 1.67, 2, 2.33, 2.67, 3, 3.5, 4, 5, 6, 8, 10, 12, 16, 24, 36, and 48 hours after administration of the products.

This single-dose, crossover study to assess bioequivalence is considered adequate.

Analytical/statistical methods
The analytical methods have been adequately validated and are 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 were included in the analysis.

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

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	4386 ± 2362	4754 ± 2586	1504 ± 488	0.75 (0.5 – 2.67)	5.6 ± 1.9
Reference	4261 ± 2410	4595 ± 2571	1576 ± 625	0.75 (0.5 – 3.0)	5.7 ± 2.1
***Ratio (90% CI)**	1.05 (0.94-1.16)	--	0.98 (0.84-1.14)	--	--
CV (%)	21.3	--	30.9	--	--

$AUC_{0-\infty}$	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

**ln-transformed values*

The 90% confidence intervals calculated for AUC_{0-t} 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 AET 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.

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. The originator Vfend has undergone successful user testing. The layout of the package leaflet follows an established corporate PL layout, which has been tested in several Readability User Tests on other products of the MAH. All tests have proven the patient friendliness of the layout, which supports patients in finding key safety messages in PLs. The bridging report is considered acceptable. Separate user testing is not required.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Voriconazol AET 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 AET 50 mg and 200 mg with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 20 March 2013. Voriconazol AET 50 mg and 200 mg film-coated tablets were authorised in the Netherlands on 11 April 2013.

The date for the first renewal will be: 20 March 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