CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Voriconazol Teva 50 mg and 200 mg, film-coated tablets Teva Nederland 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/2585/001-002/DC
Registration number in the Netherlands: RVG 111707-111708

18 September 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:	27 June 2013
Concerned Member States:	Decentralised procedure with 50 mg - BE DE, DK, EL, ES, FI, FR, HU, IS, IT, LU, NO, PL, PT, RO, SE, UK. 200 mg - AT, BE, CZ, DE, DK, EE, EL, ES, FI, FR, HU, IE, IS, IT, LT, LU, LV, MT, NO, PL, PT, RO, 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 Teva 50 mg and 200 mg, film-coated tablets from Teva Nederland B.V. The date of authorisation was on 27 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.

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 produced 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.

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 limits are set according to the European Pharmacopeia and ICH guidelines. Batch analysis results by the drug product manufacturer for four batches have been submitted, showing compliance to the specification.

Stability of drug substance
Stability information from accelerated and long-term testing has been provided on three batches of production scale. The available results of long-term and accelerated data indicates that there are no significant changes in physical characteristics and impurity profile, under the storage conditions tested. The claimed re-test period of 48 months is acceptable, based on available completed stability studies.

** 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 Teva 50 mg is a white, round, biconvex film-coated tablet with imprint "V" on one and "50" on the other side.
Voriconazol Teva 200 mg is a white, oblong film-coated tablet with imprint "V" on one and "200" on the other side.

The film-coated tablets are packed in PVC/Alu-blisters and white HDPE bottle with PP screw cap.

The excipients are:
Tablet core - lactose monohydrate, croscarmellose sodium, povidone K25, pregelatinised maize starch magnesium stearate
Film-coat - hypropmellose 5 mPa·s, glycerol 85 %, titanium dioxide (E171).

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 dissolution method has been developed in line with the recommended dissolution method of the FDA. The discriminating nature of the dissolution method has been adequately demonstrated. Comparative *in-vitro* dissolution data demonstrate similarity between the test and reference products with the fast dissolution (>85% in 15 minutes) at pH 1.2, 4.5 and 6.8. The biowaiver for the 50 mg tablet 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 concerns a standard fluid bed granulation process which involves the following steps: mixing, binder solution preparation, granulation and drying, mixing with pregelatinised starch, lubrication, compression, film-coating of tablets and drying, and finally packaging.
The manufacturing process on commercial scale has not been validated, but development data on the pilot-scale batches (three batches of 50 mg and two batches of 200 mg) are considered sufficient. Production-scale batches will be validated post-approval on three commercial size batches per strength.

Control of excipients
The excipients used and their quantities applied are common for film-coated tablets. All excipients are in line with their Ph.Eur. monograph, and a discussion on functionality-related characteristics has been provided. These specifications are acceptable.

Quality control of drug product
The product specification includes tests for appearance, average mass, resistance to crushing, loss on drying, identification (of voriconazole and titanium dioxide), assay, uniformity of dosage unit-mass variation, dissolution, related substances and microbiological purity. The release and end-of shelf-life specifications are identical with the exception of the limit for loss on drying.
The proposed limits for the other parameters are acceptable. The analytical methods have been adequately described and validated or reference is made to the Ph.Eur.
Batch analytical data has been presented for two batches per strength, including the bio-batch. All batches comply with the proposed specification.

Stability of drug product
Stability data on the drug product has been provided on four pilot-scale batches, stored at 25°C/60% RH (24 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 PVC-Al blisters or HDPE bottles with PP cap. Bottles of 50 and 100 mL are described, but only the 50 mL bottles were placed on stability. Since it has been justified that 30 tablet in a 50 ml bottle represents the worst case packaging to be marketed, this was considered to be acceptable. From the data it is observed that the product remains stable throughout the testing period.
The MAH has performed a photostability study in line with ICH Q1B to test the photostability of the drug product. It was demonstrated that the drug product was photostable. Hence the product does not need to be protected from light. A shelf life of 36 months without special storage conditions packed in PVC-Al blister or HDPE bottle is acceptable.
Eight weeks of in-use stability data for the HDPE bottles has been provided. The study is performed on both strengths packed in 50 mL HDPE bottles and stored closed with in-use simulation or open at 25ºC/60%RH. No trends could be observed, justifying the claimed shelf-life after first opening of 12 weeks.

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.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 Teva 200 mg (Teva Nederland B.V., the Netherlands) 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-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 48 healthy subjects (29 males, 19 females), aged 20-55 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. There were 2 dosing periods, separated by a washout period of 8 days.

Blood samples were collected pre-dose and at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 3.5, 4, 6, 8, 12, 16 and 24 after administration of the products.
A single dose, crossover study under fasting conditions to assess bioequivalence for voriconazol is considered adequate. The sampling scheme is adequate to estimate pharmacokinetic parameters.

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 II due to an adverse event; 47 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=47	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	5110 ± 3201	5922 ± 5656	1354 ± 593	1.27 ± 0.79	6.9 ± 3.7
Reference	4963 ± 3234	5686 ± 5196	1263 ± 556	1.41 ± 0.68	6.8 ± 3.0
***Ratio (90% CI)**	1.05 (1.01 - 1.09)	1.05 (1.01 - 1.09)	1.08 (0.99 - 1.19)	--	--
CV (%)	11.9	11.7	26.9	--	--

$AUC_{0-\infty}$ 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}, $AUC_{0-\infty}$ 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 Teva 200 mg and Vfend 200 mg tablets are bioequivalent with respect to rate and extent of absorption, and fulfill the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

Fasting conditions has been applied, which is in accordance with the SPC: Voriconazole is 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
This application concerns 2 strengths (50 and 200 mg). Bioequivalence is proven for the 200 mg strength. The following criteria for extrapolation have been fulfilled:
- the formulations are dose-proportional
- the formulations are manufactured by the same manufacturer and manufacturing process
- voriconazol shows a more than dose proportional increase in pharmacokinetics and as such the highest strength has been used in the bioequivalence study
- dissolution data have been submitted showing comparable dissolution at a pH of 1.0, 4.5 and 6.8.

The biowaiver for the 50 mg tablet 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 been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The test consisted of two rounds with 10 participants each.
Twenty questions were drafted using hypothetical questions, with additional questions as “what would you do” to verify that the participant comprehended the information as to make the correct decision. Key safety issues were properly covered in the test.
The participants were all considered to be potential users of Voriconazole tablets (above 18 years).
Inclusion, exclusion criteria and the demographics (gender, age- and educational distribution) were acceptable.
Three additional questions were posed to solicit positive or negative feedback about the users friendliness of the PIL. The quantitative and quantitative results of the first round showed the correct section was traced to answer the question, on average, 99% of the time. Revision was not considered necessary.
The data on the second round show the correct section was traced to answer the question, on average, 98.5% of the time. The same result was achieved where, on average, each question was answered correctly 98.5% of the time. No revisions were done.
Although the PIL passed the test, the feedback comments received were taken into account and therefore two minor changes were introduced to further improve tracing/readability.
The results of this test indicate that the PIL is well structured and organized, easy to understand and written in a comprehensible manner.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Voriconazol Teva 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 Teva 50 mg and 200 mg with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 29 May 2013. Voriconazol Teva 50 mg and 200 mg, film-coated tablets were authorised in the Netherlands on 27 June 2013.

The date for the first renewal will be: 29 May 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