

Public Assessment Report

Scientific discussion

**Voriconazol Genthon 50 mg and 200 mg,
film-coated tablets**

**Voriconazol Genthon 200 mg powder for
solution for infusion**

(voriconazole)

NL/H/3364/001-003/MR

Date: 25 May 2016

This module reflects the scientific discussion for the approval of Voriconazol Genthon. The procedure was finalised on 18 May 2015. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Voriconazol Genthon 50 mg and 200 mg, film-coated tablets, and 200 mg powder for solution for infusion, from Genthon B.V.

The product is indicated for

Voriconazol Genthon, 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 candidaemia 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.

Voriconazol Genthon should be administered primarily to patients with progressive, possibly life-threatening infections.

Prophylaxis of invasive fungal infections in high risk allogeneic hematopoietic stem cell transplant (HSCT) recipients.

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

This mutual recognition procedure concerns a generic application claiming essential similarity with the innovator product Vfend 50 mg and 200 mg film-coated tablets, and 200 mg powder for solution for infusion (EMA/H/C/000387), which have been registered by Pfizer since 21 March 2002 by a centralised procedure.

The concerned member states (CMS) involved in this procedure were the Germany, Greece, Spain, France and Poland.

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

II. QUALITY ASPECTS

II.1 Introduction

Voriconazol Genthon 50 mg is a white to off-white, round, biconvex film-coated tablet debossed with "V9CN" on one side and "50" on the reverse. Each tablet contains 50 mg voriconazole.

Voriconazol Genthon 200 mg is a white to off-white, oval, biconvex film-coated tablet debossed with "V9CN" on one side and "200" on the reverse. Each tablet contains 200 mg voriconazole.

The film-coated tablets are packed in transparent PVC/Al blisters. The two tablet strengths are dose proportional.

The excipients are:

Tablet core - lactose monohydrate, pregelatinised maize starch, croscarmellose sodium, povidone K 29-32, magnesium stearate

Film-coating – hypromellose, titanium dioxide (E171), lactose monohydrate, triacetin

Voriconazol Genthon 200 mg powder for solution for infusion is white to off-white lyophilized powder. One vial is used for each infusion. After reconstitution each ml contains 10 mg of voriconazole. Once reconstituted further dilution is required before administration.

The powder for solution for infusion is packed in a clear type I glass vial that is closed with a type I rubber bromobutyl stopper and aluminium flip-off cap. One vial is used for each infusion. Each vial contains 200 mg of voriconazole.

The excipients are hydroxypropylbetadex and lactose monohydrate.

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 or almost white non-hygroscopic powder, which is freely soluble in acetone and in methylene chloride, and insoluble in water. Further, voriconazole exhibits polymorphism. The two active substance manufacturers produce the same polymorphic form. The substance consists of two asymmetric carbons with a configuration of (2R,3S). Isomerism has been sufficiently specified.

The Active Substance Master File (ASMF) procedure is used for both manufacturers of 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

For both manufacturers a description of the process have been given, in sufficient detail and from acceptable starting materials.

Quality control of drug substance

The MAH laid down a drug substance specification which complies with the Ph.Eur. monograph of voriconazole. In addition, a test for particle size is included. Sufficient batch analysis data have been provided, demonstrating compliance with the specification.

Stability of drug substance

A re-test period of the drug substance of 48 months is applicable for the first manufacturer. Data have been provided during storage at $25^{\circ}\pm 2^{\circ}\text{C}/60\pm 5\% \text{RH}$ (44 months) and $40^{\circ}\pm 2^{\circ}\text{C}/75\pm 5\% \text{RH}$ (6 months). For the second manufacturer a re-test period of 12 months has been granted based on stability data obtained at $25^{\circ}\pm 2^{\circ}\text{C}/60\pm 5\% \text{RH}$ (6 months) and $40^{\circ}\pm 2^{\circ}\text{C}/75\pm 5\% \text{RH}$ (6 months). No specific storage conditions apply.

II.3 Medicinal Product

Voriconazol Genthon 50 mg and 200 mg film-coated tablets

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. A limit for particle size has been included in the drug substance specification based on the bioequivalence batch.

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 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 wet granulation process which involves the following steps: mixing, granulation, sieving and drying, mixing, lubrication, compression, film-coating of tablets and drying, and finally packaging.

The manufacturing process has been validated on two and three full-scale batches for 50 mg and 200 mg strength respectively. Process validation was adequately performed. Holding times have been laid down.

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. These specifications are acceptable.

Quality control of drug product

The product specification includes tests for appearance, identification, uniformity of dosage unit-mass variation, water content, dissolution, related substances, assay and microbiological purity. The release and end-of shelf-life specifications are identical with the exception of the limit for assay and total impurities.

The analytical methods have been adequately described and validated. For microbiological quality, the method has been verified. The stability indicating nature of the assay and impurity methods has been demonstrated. Batch analytical data has been presented for two batches (50 mg strength) and three batches (200 mg strength), including the bio-batch.

Stability of drug product

Stability data on the drug product has been provided on five full-scale batches stored at 25°C/60% RH (four up to 36 months and one up to 30 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.

The MAH performed a photostability study in line with ICH Q1B demonstrating the photostability of the drug product. From the available stability data no clear trends could be observed for any of the parameters, which indicates the stability of the drug product. A shelf-life of 36 months can be granted. The product does not require any special storage conditions.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

Only lactose monohydrate is of animal origin. TSE statements from representative manufacturer regarding the safety and compliance of lactose monohydrate, have been provided. TSE risk for the lactose used can be considered negligible.

Voriconazol Genthon 200 mg, powder for solution for infusion

Pharmaceutical development

The development of the product has been described, the choice of excipients is justified and the difference in solubiliser with the respect to the reference product has been explained. The use of hydroxypropylbetadex instead of sulfobutylether beta-cyclodextrin is acceptable. The selection of the different solubiliser is further supported by the bioequivalence study performed.

During development, composition and process parameters were optimised until the final formulation was obtained. The stability of the formulation was demonstrated to be similar to the reference product Vfend. The choice of sterilization by aseptic processing and filtration is justified as dry heat sterilization and radiation sterilization lead to significant degradation of the drug product.

The choice of container closures system, discussion on microbiological attributes and compatibility with the list of diluents mentioned in the SmPC are acceptable.

The pharmaceutical development of the product has been adequately performed. The applied overfill of 10% is required. The overfill of 10% leads to a vial containing 220 mg of voriconazole, which needs to be reconstituted with 19 ml prior to use, thus obtaining a volume of 22 ml and a concentration of 10 mg/ml. This is the same reconstitution volume and final concentration as the reference product.

Manufacturing process

The manufacturing process concerns a non-standard lyophilisation process which involves the following steps: preparation of the bulk solution, filtration of the bulk solution, filling of the vials, lyophilisation, closing and capping of the vials. The manufacturing process has been validated on three full-scale batches.

Control of excipients

All the excipients, used in the manufacturing of the powder for solution for infusion are of pharmacopoeial grade (Ph.Eur.) and tested as per their Ph.Eur. monograph. These specifications are adequate.

Quality control of drug product

The product specification includes tests for appearance, reconstitution time, pH, uniformity of dosage units, water content, particulate contamination, identification, assay, impurities, sterility and bacterial endotoxins. The release and end-of shelf-life specifications are identical with the exception of the limits for assay and impurities. The analytical methods have been adequately described. The validation of the methods is adequately performed. Batch analytical data has been presented for three batches, including the bio-batch. All batches comply with the specification.

Stability of drug product

Stability data on the drug product has been provided on three batches stored at 25°C/60% RH (36 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 glass vial with rubber stopper as proposed for marketing. The MAH performed a photostability study in line with ICH Q1B demonstrating the photostability of the drug product. Based on the stability data provided, a shelf-life of 36 months was granted. Supported by the complying results under accelerated storage conditions, no special storage conditions are considered necessary.

Stability data after reconstitution with water for injections or 0.9% NaCl and further dilution with the list of diluents mentioned in the SPC have been presented. The product is stable up to 24 hours at 2-8 °C.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

Only lactose monohydrate is of animal origin. TSE statements from representative manufacturer regarding the safety and compliance of lactose monohydrate, have been provided. TSE risk for the lactose used can be considered negligible.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Voriconazol Genthon 50 mg and 200 mg film-coated tablets, and 200 mg powder for solution for infusion has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Voriconazol Genthon 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.

For this generic application, the MAH has submitted two bioequivalence studies, which are discussed below.

IV.2 Pharmacokinetics

The MAH submitted the following bioequivalence studies:

- To support the application for the 50 and 200 mg film-coated tablets, a single-dose bioequivalence study was conducted with Voriconazol Genthon 200 mg, film-coated tablets (Genthon B.V., The Netherlands) versus Vfend 200 mg tablets (Pfizer, Austria).
- To support the application for Voriconazol Genthon 200 mg powder for solution for infusion, the MAH submitted a single-dose bioequivalence study versus Vfend 200 mg powder for solution for infusion (Pfizer, Poland).

The choice of the reference products in the bioequivalence studies is accepted, as Vfend has been registered through a centralised procedure.

The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Biowaiver

The results from the study with the 200 mg tablets can be extrapolated to the 50 mg strength, as the following conditions have been fulfilled:

- the formulations are dose-proportional
- the formulations are manufactured by the same manufacturer and manufacturing process
- voriconazole shows a more than dose proportional increase in pharmacokinetics and as such the highest, most sensitive strength has been used in the bioequivalence study
- The *in vitro* dissolution results show similar profiles for the 50 and 200 mg strengths in three different media.

Bioequivalence studies

Study I – 200 mg film-coated tablets

Design

A single-dose, 4-period, 2-sequence, replicate cross-over bioequivalence study was carried out under fasted conditions in 24 healthy male subjects, aged 23-56 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 4 dosing periods, separated by a washout period of 7 days.

Blood samples were collected pre-dose and at 0.25, 0.5, 0.67, 0.83, 1, 1.17, 1.33, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 16, 24 and 30 hours after administration of the products.

This single-dose, crossover design to assess bioequivalence for voriconazole is considered adequate. Fasted conditions are appropriate, as voriconazole should be taken without food, according to the SmPC.

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

Of the 24 subjects who were included in the study, 23 subjects completed all four study periods and 24 subjects completed at least two clinical study periods with a crossover (Test vs. Reference). One subject did not show-up for period 2 and received one single oral dose of the test (Voriconazol Genthon 200 mg) in periods 1 and 3 and one single oral dose of the Reference (Vfend 200 mg) in period 4. Twenty-four (24) subjects were analysed and included in the pharmacokinetic and statistical analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of a 200 mg voriconazole film-coated tablet under fasted conditions.

Treatment N=24	AUC _{0-t} ng.h/ml	AUC _{0-∞} ng.h/ml	C _{max} ng/ml	t _{max} h	t _{1/2} h
Test	5165 ± 2345	5465 ± 2648	1253 ± 510	1.0 (0.5 – 4.0)	7.4 ± 2.1
Reference	5219 ± 2401	5517 ± 2698	1265 ± 513	1.17 (0.5 – 4.0)	7.2 ± 1.9
*Ratio (90% CI)	1.00 (0.94-1.06)	--	1.00 (0.90-1.11)	--	--
CV (%)	18.1	--	30.3	--	--
AUC_{0-∞} 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					

**In-transformed values*

Study II – 200 mg powder for solution for infusion

Design

A single-dose, 2-period, 2-sequence, cross-over bioequivalence study was carried out in 24 healthy male subjects, aged 25-77 years. Each subject received a single dose (200 mg infusion over about 1.5 h) of one of the 2 voriconazole formulations. There were 2 dosing periods, separated by a washout period of 7 days.

Blood samples were collected pre-dose and at 0.33, 0.67, 1, 1.25, 1.5, 1.58, 1.67, 1.83, 2, 2.5, 3, 4, 6, 8, 10, 12, 16, 24 and 30 hours after administration of the products.

A single dose, crossover study to assess bioequivalence for voriconazole is considered adequate. The study was conducted to evaluate bioequivalence between the test formulation with hydroxypropylbetadex and the reference with sulfobutylether beta-cyclodextrin. Overall, the use of hydroxypropylbetadex instead of sulfobutylether beta-cyclodextrin is acceptable. The complex is considered rapidly ‘dissolved’ after the blood stream.

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

All subjects completed the study and data from 24 subjects were included in the pharmacokinetic and statistical analysis.

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean \pm SD, t_{max} (median, range)) of 200 mg voriconazole powder for solution for infusion.

Treatment N=24	AUC _{0-t} ng.h/ml	AUC _{0-∞} ng.h/ml	C _{max} ng/ml	t _{max} h	t _{1/2} h
Test	7139 \pm 2299	7327 \pm 2352	1987 \pm 475	1.5 (1.25 – 6.0)	6.3 \pm 1.1
Reference	6660 \pm 1712	6879 \pm 1850	1927 \pm 433	1.5 (1.25 – 1.58)	6.3 \pm 1.4
*Ratio (90% CI)	1.06 (1.00-1.12)	--	1.03 (0.97-1.10)	--	--
CV (%)	11.6	--	12.3	--	--
AUC_{0-∞} 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					

**In-transformed values*

A t_{max} of 6 h was observed in 1 subject; this was a second peak. The observed t_{max} values in the other subjects ranged from 1.25–1.58 h. The second peak may be likely explained by withdrawing blood from the administration catheter causing unusual high voriconazole plasma concentrations due to possible ‘left over’.

Conclusion on bioequivalence studies:

The 90% confidence intervals calculated for AUC_{0-t} and C_{max} are within the bioequivalence acceptance range of 0.80–1.25. Based on the submitted bioequivalence studies Voriconazol Genthon 200 mg, film-coated tablets and Voriconazol Genthon 200 mg powder for solution for infusion are considered bioequivalent with Vfend.

The MEB has been assured that the bioequivalence studies have 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).

IV.1 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 Genthon film-coated tablets and powder for solution for infusion.

Summary table of safety concerns as approved in RMP

Important identified risks	<ul style="list-style-type: none"> • Hepatotoxicity • Neuropathy peripheral • Phototoxicity • QTc prolongation and torsades de pointes • Squamous cell carcinomas • Visual effects (including optic neuritis, papilloedema and other visual concerns)
Important potential risks	<ul style="list-style-type: none"> • Long-term treatment • Other skin cancer (non-SCC) • Suicide-related events
Important missing information	<ul style="list-style-type: none"> • Resistance • Use in children below two years of age • Use in patients with severe chronic hepatic cirrhosis (Child-Pugh C)

	• Use in pregnant and lactating women
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Additional risk minimisation measures are required relating to hepatotoxicity and squamous cell carcinoma. These have been laid down in line with the reference product. It concerns the following additional risk minimisation measures for these two safety concerns:

- Health Care Professional Checklist for phototoxicity, Squamous Cell Carcinoma and hepatic toxicity
- Health Care Professional Question and Answer Brochure for phototoxicity, Squamous Cell Carcinoma and hepatic toxicity
- Patient Alert Card for Squamous Cell Carcinoma

The implementation of the additional measures will be agreed at a national level in each of the member states.

IV.2 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. The MAH demonstrated through a bioequivalence study that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. 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 making reference to the innovator product Vfend, which is registered through a centralised procedure. Minor changes have been made to the PL in line with company house style, which has been subject to successful user tests for other products. These tests confirm that the MAH's house style does not affect readability of the leaflet.

The bridging report submitted has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Voriconazol Genthon 50 mg and 200 mg, film-coated tablets, and Voriconazol Genthon 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, and 200 mg powder for solution for infusion. 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 Board followed the advice of the assessors. The date of authorisation in the Netherlands was 16 December 2014.

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 Genthon with the reference product, and have therefore granted a marketing authorisation. The mutual recognition procedure was finalised with a positive outcome on 18 May 2015.

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
Introduction of a summary of pharmacovigilance system, changes in QPPV (including contact details) and/or changes in the Pharmacovigilance System Master File (PSMF) location.	NL/H/3364/I B/001/G	IB	7-12-2015	6-1-2016	Approval	No
A new batch release site is added	NL/H/3364/1-3/IA/002	IA	2-12-2015	22-12-2015	Approval	No
Change in the name in Germany to "riconazol STADA 200 mg Pulver zur Herstellung einer Infusionslösung" and a new PSMF for Germany.	NL/H/3364/I B/IB/004/G	IB	21-4-2016	24-5-2016	Approval	No