COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Voriconazol CF 10 mg/ml, concentrate for solution for infusion

(voriconazole)

NL/H/5773/001/DC

Date: 12 August 2024

This module reflects the scientific discussion for the approval of Voriconazol CF 10 mg/ml, concentrate for solution for infusion. The procedure was finalised on 8 February 2024. 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
EMA	European Medicines Agency
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
RMS	Reference Member State
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 CF 10 mg/ml, concentrate for solution for infusion, from Centrafarm B.V.

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 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.

Voriconazole 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 up-to-date indications and posology is given in the SmPC.

The marketing authorisation has been granted pursuant to Article 10(3) of Directive 2001/83/EC, which concerns a hybrid application, as the pharmaceutical form of Voriconazol CF (concentrate for solution for infusion) differs from the pharmaceutical form of the reference product (powder for solution for infusion).

In this decentralised procedure, essential similarity is proven between the new product and the innovator product Vfend 200 mg powder for solution for infusion (EMEA/H/C/000387) which has been registered in the EEA by Pfizer Ltd since 21 March 2002 through a centralised procedure.

The concerned member states (CMS) involved in this procedure were Belgium, Denmark, Finland, Iceland, Luxembourg, Norway and Sweden.

Similarity assessment

According to Article 8(1) of Regulation (EC) No 141/2000, no marketing authorisation can be granted for a product similar to an orphan medicinal product for a period of ten years, when this concerns a similar medicinal product with the same therapeutic indication. A similarity assessment has been performed between Voriconazol CF and Isavuconazonium sulfate (Cresemba). The similarity assessment report concluded that the two products were not similar. Therefore, the existence of any market exclusivity for Isavuconazonium sulfate (Cresemba) in the treatment of invasive aspergillosis, does not prevent the granting of the marketing authorisation of Voriconazol CF 10 mg/ml, concentrate for solution for infusion. This finding is without prejudice to the outcome of the scientific assessment of the marketing authorisation application.

II. QUALITY ASPECTS

II.1 Introduction

Voriconazol CF is a clear and colourless concentrate for solution for infusion with a pH of 5.5-7.0 and an osmolarity of 513-518 mOsmol/kg. Each ml of concentrate contains 10 mg of voriconazole and each vial contains 200 mg of voriconazole. Further dilution is required before administration.

The excipients are sulfobutyl ether beta cyclodextrin sodium (SBECD) and water for injections.

The concentrate for solution for infusion is packed in a clear glass vial with rubber stopper and aluminium cap with plastic seal. The concentrate is a clear and colourless solution. Each vial of 30 ml contains 20 ml concentrate.

II.2 Drug Substance

The active substance is voriconazole, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is a white or almost white powder and is practically insoluble in water. Voriconazole contains two chiral centres, and has the 2R,3S-configuration. Different polymorphs of voriconazole are known. Because the drug substance is completely dissolved during the manufacturing of the drug product polymorphism is not relevant.

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the Ph.Eur.

Manufacturing process

A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance

The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. and CEP with additional requirements for acetic acid and microbial limit. The specification is acceptable. Batch analytical data demonstrating compliance with this specification have been provided for three batches.

Stability of drug substance

Stability data on the active substance have been provided for three pilot scaled batches stored at 25°C/60% RH (60 months) and 40°C/75% RH (6 months), and one full scale batch stored at 25°C/60% RH for 6 months. No significant changes or obvious trends were seen during storage. The proposed retest period of 60 months is justified.

II.3 Medicinal Product

Pharmaceutical development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The choice of excipients is justified and their functions explained. The proposed drug product, a concentrate for solution for infusion, was formulated according to the reference product, a powder for solution for infusion. The active ingredient, the excipient types and the drug concentration of the active ingredient are equivalent to the reference product.

The packaging and the manufacturing process, including the sterilisation process, have been justified. A bioequivalence study has not been performed and is not required since it concerns a concentrate for solution for infusion. The pharmaceutical development of the product has been adequately performed.

Manufacturing process

The manufacturing process consists of treatment of inner packaging materials (washing and sterilisation of vials, stoppers and over-seals), weighing of drug substance and excipients, compounding, filtration, filling, capping and products collection, visual inspection, and packaging. The process has been validated according to relevant European guidelines. Process validation data on the product have been presented for three commercial scaled batches in accordance with the relevant European guidelines.

Control of excipients

The excipients comply with Ph.Eur. requirements. The specifications are acceptable.

Microbiological attributes

Microbiological testing is part of the drug product specification. The container closure system sufficiently isolates the drug product form the outer environment. This medicinal product is for single use only and any unused solution should be discarded. Only clear solutions without particles should be used.

Quality control of drug product

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for appearance, identification, appearance of solution, pH, fill volume, visible particles, particulate matter, bacterial endotoxins, sterility, related substances, and assay. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. An adequate nitrosamines risk evaluation report has been provided. No risk for presence of nitrosamines in the drug product was identified. Satisfactory validation data for the analytical methods have

been provided. Batch analytical data from three full scaled batches from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product have been provided for three commercial scaled batches stored at 25°C/60% RH (6 months) and 2~8°C (12 months). The stability was tested in accordance with applicable European guidelines. Photostability studies were performed in accordance with ICH recommendations and showed that the product is not stable when exposed to light. On basis of the data submitted, a shelf life was granted of 2 years. The labelled storage conditions are: "*Protect from light. Store in a refrigerator (2°C – 8°C)*". Chemical and physical in-use stability has been demonstrated for 24 hours at 2-8°C. From a microbiological point of view, once diluted, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to the use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

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

There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Voriconazol CF 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 CF is intended for hybrid substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment was therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a hybrid formulation of Vfend which is available on the European market. Reference was made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which was 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

Voriconazol CF 10 mg/ml, concentrate for solution for infusion is a parenteral formulation and therefore fulfils the exemption mentioned in the Note for Guidance on bioequivalence "5.1.6 parenteral solutions", which states that a bioequivalence study is not required if the product is administered as an aqueous intravenous solution containing the same active substance in the same concentration as the currently authorised reference medicinal product (NfG CPMP/EWP/QWP 1401/98). The MAH has stated the formulation proposed for Voriconazole CF is similar to that of the reference product Vfend except it differs in pharmaceutical form (i.e., the reference product is a powder for solution for infusion) and contains the same quantity of active substance before administration as reference product. The excipients in the reference medicinal product and in the proposed medicinal product are the same and their composition have no impact on the bioavailability of the active substance.
Therefore, Voriconazol CF may be considered as therapeutic equivalent, with the same efficacy/safety profile as known for the active substance of the reference medicinal product. The current product can be used instead of its reference product.

IV.2 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 CF.

Table 1. Summary table of safety concerns as approved in RMP

Important identified risks	• Phototoxicity • Squamous cell carcinoma • Hepatic toxcity
Important potential risks	None
Missing information	None

The MAH agreed to provide educational material that should contain the following key elements:

- Health Care Professional (HCP) Question and Answer Brochure for Phototoxicity, SCC and Hepatic toxicity:
  - Advises HCPs on the risks of Phototoxicity, SCC and Hepatic toxicity associated with voriconazole use.
  - Provides HCPs with the current recommendations to monitor and manage these risks.

  - Reminds HCPs of use of the HCP Checklist and the Patient Alert Card and how to obtain additional copies.
- Health Care Professional (HCP) Checklist for Phototoxicity, SCC and Hepatic toxicity:
  - Reminds HCPs of the risks of phototoxicity, skin SCC and hepatotoxicity reported with voriconazole use.
  - Provides HCPs with the current recommendations to monitor and manage these risks.
  - Reminds HCPs to discuss with the patient/care giver the risks of phototoxicity/skin SCC and hepatotoxicity, what to look for, how and when to seek immediate attention.
  - Reminds HCPs to provide a Patient Alert Card to the patient.
- Patient Alert Card for Phototoxicity and SCC:
  - Reminds patients of the risk of phototoxicity and skin SCC.
  - Reminds patients when and how to report relevant signs and symptoms of phototoxicity and skin cancer.
  - Reminds patients to take steps to minimise the risk of skin reactions and skin SCC (by avoiding exposure to direct sunlight, use of a sunscreen and protective clothing) and inform HCPs if they experience relevant skin abnormalities.

IV.3 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. A biowaiver has been granted. Risk management is adequately addressed. This hybrid medicinal product can be used instead of the reference product.

V. USER CONSULTATION

The package leaflet (PL) 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: a pilot test followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The results show that the PL meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Voriconazol CF 10 mg/ml, concentrate for solution for infusion has a proven chemical-pharmaceutical quality and is a hybrid form of Vfend 200 mg powder for solution for infusion. Vfend is a well-known medicinal product with an established favourable efficacy and safety profile.

Since both the reference and current product are intended for parenteral use, no bioequivalence study is deemed necessary. A biowaiver has been granted.

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 CF with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 8 February 2024.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
-	-	-	-	-	-