COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Voriconazol hameln 200 mg powder for solution for infusion (voriconazole)

NL/H/5539/001/DC

Date: 12 November 2024

This module reflects the scientific discussion for the approval of Voriconazol hameln 200 mg, powder for solution for infusion. The procedure was finalised on 16 August 2023. 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 Voriconazole hameln 200 mg, powder for solution for infusion from hameln pharma gmbH.

The product is indicated for:

- 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.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

The powder is reconstituted with either 19 mL of water for injections or 19 mL of sodium chloride 9 mg/mL (0.9 %) solution for injection to obtain an extractable volume of 20 mL of clear concentrate containing 10 mg/mL of voriconazole. Discard the vial if vacuum does not pull the diluent into the vial. It is recommended that a standard 20 mL (non-automated) syringe be used to ensure that the exact amount (19.0 mL) of water for injections or sodium chloride 9 mg/mL (0.9 %) solution for injection is dispensed. This medicinal product is for single use only and any unused solution should be discarded. Only clear solutions without particles should be used.

For administration, the required volume of the reconstituted concentrate is added to a recommended compatible infusion solution to obtain a final voriconazole solution containing 0.5-5 mg/mL.

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(1) of Directive 2001/83/EC, which concerns a generic application.

In this decentralised procedure, essential similarity is proven between the new product and the innovator product Vfend 200 mg, powder for solution for infusion, which has been registered in the EEA via a centralised procedure (EU/1/02/212) by Pfizer Europe MA EEIG on 19 March 2002.

The concerned member states (CMS) involved in this procedure were Austria, Belgium, Bulgaria, Czechia, Denmark, Finland, Germany, Ireland, Italy, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, 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 Voriconazole hameln and Cresemba, which obtained orphan market exclusivity on 19 October 2015, based on designation EU/3/14/1284. The similarity assessment report was completed in August 2022, concluding the two products were not similar and that the existence of any market exclusivity for Cresemba in the treatment of invasive aspergillosis, does not prevent the granting of the marketing authorisation of Voriconazole hameln.

II. QUALITY ASPECTS

II.1 Introduction

Voriconazole hameln is a white to off-white lyophilised powder, free of visible evidence of contamination. Once reconstituted with either water for injections or sodium chloride 9 mg/mL (0.9%) solution for injection, the pH range is between 5.0 - 7.0 with an osmolality of 530 mOsmol/kg ± 10%.

Each vial contains 200 mg of voriconazole. After reconstitution (total volume of 20 mL) each mL contains 10 mg of voriconazole. Once reconstituted, further dilution is required before administration.

The excipients are: hydroxypropylbetadex, sodium chloride and concentrated hydrochloric acid (for pH adjustment).

The powder for solution for infusion is packed in a 25 mL clear type I glass vial with a grey, type I chlorobutyl rubber stopper and aluminium cap with plastic red flip-off seal. The vials are packedin a carton.

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, very slightly soluble in water, freely soluble in acetone and in methylene chloride.

Site 1: 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.

Site 2: 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

Site 1: The manufacturing process consists of three stages. Two starting materials are used. Adequate specifications have been adopted for starting materials, solvents and reagents. The active substance has been adequately characterised and the manufacturing process is described in sufficient detail.

Site 2: A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance

The active substance specifications of both sites are considered adequate to control the quality and meet the requirements of the monograph in the Ph.Eur. Batch analytical data demonstrating compliance with this specification have been provided for four batches from each site (eight total).

Stability of drug substance

The active substance is stable for 60 months when stored under the stated conditions (no special storage conditions). Assessment thereof was part of granting the ASMF and CEP (and has been granted by the EDQM).

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 target of the development of the product Voriconazole hameln 200 mg powder for solution for infusion was to achieve a generic equivalent, stable formulation to the innovator product Vfend. The development of the product has been presented in detail. The formulation development can be considered to be in line with the requirements of the guideline EMEA/CHMP/167068/2004-ICH Q8 (R2) "Pharmaceutical development". The qualitative and quantitative composition of the drug product obtained as a result of pharmaceutical

development ensures the physico-chemical properties and stability during storage of the drug product, although the generic drug product contains different excipients.
Pharmaceutical equivalence has been investigated on three batches of the generic product and three batches of the reference product. Results are considered comparable.
With response documentation further information on manufacturing process development is provided, selection of the sterilisation method is addressed and control strategy is established.

Manufacturing process
The manufacturing process consists of a preparation of a bulk solution, followed by filtration, filling and a lyophilisation step and thus is considered a non-standard process. The process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for six commercial scale batches in accordance with the relevant European guidelines.

Control of excipients
All excipients comply with the respective monographs in the Ph.Eur. These specifications are acceptable.

Microbiological attributes
For sterile products, the integrity of the container closure system to prevent microbial contamination should be addressed. The drug product conforms to the microbial limits according to the Ph.Eur. No antioxidants or preservatives are contained in the solution. A microbial challenge test has been performed on three batches. No evidence of microbial growth was found.

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 of active substance, colour and clarity of solution, osmolality, pH of solution, assay, related substances, uniformity of dosage units, particulate contamination, tightness of vials, sterility and bacterial endotoxins. The limits for specified impurities are above the ICH Q3B qualification threshold. The higher limits for these impurities were justified by the MAH by toxicological risk assessment, furthermore, replying to raised issue release limit for both impurities has been tightened. 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 six commercial scale 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 batches with active substance from site 1 stored at 25°C/ 60% RH (36 months), 30°C/ 65% RH (12 months) and 40°C/75% RH (6 months). Stability data on the product with active substance from site 2 are on-going. However, available data has been provided from three batches stored at 25°C/ 60% RH (36

months), 30°C/ 65% RH (12 months) and 40°C/75% RH (6 months) conditions. The stability was tested in accordance with applicable European guidelines. On basis of the data submitted, a shelf life was granted of 36 months. Photostability study demonstrated that the product t is photostable. No specific storage conditions needed to be included in the SmPC or on the label.

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 hameln 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 hameln is intended for generic 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 generic 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 is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The member states

agreed that no further clinical studies are required, besides the one bioequivalence study, which is discussed below.

IV.2 Pharmacokinetics

Because of the use of a separate complexing agent, a bioequivalence study is provided, in line with the Guideline on Investigation of Bioequivalence. The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Voriconazol hameln 200 mg, powder for solution for infusion (hameln pharma gmbh, Germany) was compared with the pharmacokinetic profile of the reference product Vfend 200 mg powder for solution for infusion (Europe MA EEIG, Belgium).

Bioequivalence studies

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover open-label comparative bioequivalence study was carried out under fasted conditions in 26 healthy male subjects, aged 23-61 years. Each subject received a single dose (200 mg) of one of the two voriconazol formulations. The infusion was to be administered by slow intravenous injection via an indwelling catheter over an approximate 1.5-hour period after an overnight fast of at least 10 hours. There were two 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 36 hours after administration of the products.

The design of the study is acceptable.

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

26 subjects enrolled and were eligible for pharmacokinetic analysis.

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

Treatment N=26	**AUC_{0-t} (ng.h/mL)**	**$AUC_{0-\infty}$ (ng.h/mL)**	**C_{max} (ng/mL)**	**t_{max} (h)**
Test	6375 ± 2080	6574 ± 2118	1686 ± 271	1.50 (1.25 – 1.67)
Reference	6850 ± 2323	7054 ± 2407	1767 ± 309	1.50 (1.25 – 1.58)
***Ratio (90% CI)**	0.93 (0.91 – 0.96)	-	0.96 (0.91 – 1.00)	-

$AUC_{0-\infty}$	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 = 24 hours
C_{max}	Maximum plasma concentration
t_{max}	Time after administration when maximum plasma concentration occurs
CI	Confidence interval

**ln-transformed values*

Conclusion on bioequivalence study:
The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Voriconazol hameln is considered bioequivalent with Vfend.

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).

IV.3 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 hameln.

Table 2. Summary table of safety concerns as approved in RMP

Important identified risks	• Phototoxicity • Squamous cell carcinoma (SCC) • Hepatic toxicity • QTc prolongation • Visual events
Important potential risks	• Skin cancer (non-SCC) • Suicide-related events
Missing information	• Effects in pregnancy • Effects in paediatrics • Off-label use

The member states agreed that routine pharmacovigilance activities are sufficient for the risks and areas of missing information. Additional risk minimisation measures were proposed in line with the risk minimisation measures for the reference product Vfend.

The MAH proposes educational material to Health Care Professionals (HCPs) and patients.

The educational material for HCPs includes the following:

- Health Care Professional (HCP) Question and Answer Brochure for Phototoxicity, SCC

and Hepatic toxicity

- Health Care Professional (HCP) Checklist for Phototoxicity, SCC and Hepatic toxicity

The educational material for patients includes the following:

- Patient Alert Card for Phototoxicity and SCC.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Vfend. 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

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.

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of two bridging reports making reference to Vfend 200 mg powder for solution for infusion (EU/1/02/212) for content and Clarithromycin 500 mg powder for concentrate for solution for infusion (DE/H/6290/001/DC) for layout. The bridging report submitted by the MAH has been found acceptable; bridging is justified for both content and layout of the leaflet.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Voriconazol hameln 200 mg, powder for solution for injection has a proven chemical-pharmaceutical quality and is a generic 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.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

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 hameln 200 mg,

powder for solution for infusion with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 16 August 2023.

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
NL/H/5539/IB /001/G	**Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet of a generic/hybrid/biosimilar medicinal products following assessment of the same change for the reference product** • *Implementation of change(s) for which no new additional data are submitted by the MAH* **Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the risk management plan** • *Other variation*	Yes No	01-03-2024	Approved	N/A