COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Vedida 200 mg
powder for solution for infusion
(voriconazole)

NL/H/5075/001/DC

Date: 6 February 2025

This module reflects the scientific discussion for the approval of Vedida 200 mg, powder for solution for infusion. The procedure was finalised on 10 March 2021. 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 Vedida 200 mg, powder for solution for infusion, from Medochemie Limited.

The product, 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(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 from Pfizer Europe MA EEIG that was first authorised in the EEA via a centralised procedure (EU/I/02/212/025) on 19 March 2002.

The concerned member states (CMS) involved in this procedure were Bulgaria, Cyprus, Czechia, Estonia, Croatia, Lithuania, Romania and Slovakia.

Similarity assessment in view of the orphan drug legislation
The MAH provided a similarity assessment between Vedida (voriconazole) and Cresemba (isavuconazole). The MAH addressed the three criteria that have been defined by the Regulation on Orphan medicinal products: therapeutic indication, mechanism of action and principal molecular structural features. The MAH indicates that the therapeutic indication, the mechanism of action and the principal molecular structural features are similar. However, the RMS considers the principal molecular structures of voriconazole and isavuconazole to be non-similar based on the New Active Substance status dedicated to Cresemba. Due to the fact that only two of the three criteria listed in the guideline are met, the two molecules are considered non-similar. Therefore, with reference to Article 8 of Regulation (EC) No. 141/2000, the existence of any market exclusivity for Cresemba in the treatment of invasive aspergillosis, does not prevent the granting of the marketing authorisation of Vedida.

II. QUALITY ASPECTS

II.1 Introduction

Vedida is a white to off-white freeze-dried powder or cake. Each vial contains as active substance 200 mg of voriconazole. After reconstitution each ml contains 10 mg of voriconazole. Once reconstituted further dilution is required before administration. The pH of the reconstituted product is 4.0 – 6.8 and the osmolality of the solution upon reconstitution is 400 - 550 mOsmol/kg.

The only excipient is betadex sulfobutyl ether sodium.

The powder is packed in 50 ml type I clear glass vials with bromobutyl rubber stopper and aluminium seal with blue plastic flip-off cap.

II.2 Drug Substance

The active substance is voriconazole, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The drug substance is a white or almost white powder and is very slightly soluble in water. Voriconazole contains two asymmetric carbons, and has the 2R,3S-confirguration. Different polymorphs of voriconazole are known and Form-B is used.

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 of the CEP with additional requirements for microbial limit and bacterial endotoxins. The specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with this specification have been provided for three batches.

Stability of drug substance

The active substance is stable for 5 years when stored under the stated conditions. Assessment thereof was part of granting the 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 choice of excipients is justified and their functions explained. The proposed drug product was formulated according to the reference medicinal product. The active ingredient, the excipient types and the drug concentration of active ingredient are the same as the reference medicinal product. Therefore, formal experimental designs to identify and optimise critical components were not performed, only the ratio of the excipient betadex sulfobutyl ether sodium to the drug substance was optimised. The MAH has added an overfill to the product. The amended process with the overfill has been sufficiently validated. A bioequivalence study has not been performed and is not required since it concerns a powder for solution for injection/infusion.

Manufacturing process

The product is manufactured using conventional manufacturing techniques. The manufacturing process includes: treatment of primary packaging materials (vials, stoppers), weighing of drug substance and excipients, compounding and filtration, filling, lyophilisation, capping and products collection, visual inspection and packaging. The manufacturing process has been validated, process validation on the amended process, including an overfill, are accepted.

Control of excipients

The excipient betadex sulfobutyl ether sodium complies with the Ph. Eur. requirements. These specifications are acceptable.

Microbiological attributes

After final sealing, the tightness of the vials is tested by the methylene blue method. Package integrity with microbial challenge was carried out in order to assure the maintenance of an effective barrier against ingress of microorganisms. Furthermore, sterility and bacterial endotoxins are checked throughout the stability storage in order to ensure the integrity of the container to prevent microbial contamination.

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, water content, assay, uniformity of dosage units, related substances, sterility, bacterial endotoxins for the powder and description, clarity and degree of coloration, pH, assay and particulate contamination for the reconstituted solution. The release and shelf-life requirements/limits are identical except for the limit for a certain impurity and each unspecified impurity. 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 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 in accordance with applicable European guidelines demonstrating the stability of the product at 25°C/60% RH (36 months), 30°C/65% RH (36 months), and 40°C/75% RH (6 months). On basis of the data submitted, a shelf life was granted of 36 months. No specific storage conditions need to be included in the SmPC or on the label.

From a microbiological point of view, once reconstituted, the product must be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C to 8°C (in a refrigerator), unless reconstitution has taken place in controlled and validated aseptic conditions. Chemical and physical in-use stability has been demonstrated for 24 hours at 2°C to 8°C.

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 Vedida 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 Vedida 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

Voriconazole is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. Therefore, the member states agreed that no further clinical studies are required.

IV.2 Pharmacokinetics

Biowaiver

Vedida 200 mg powder 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 quantitative composition of Verole is entirely the same as the originator. Therefore, it 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.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 Vedida.

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

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

The risk minimisation measures consist of:

- Health Care Professional (HCP) Question and Answer Brochure for Phototoxicity, SCC and Hepatic toxicity:
  - Advises HCPs on the risks of phototoxicity, skin SCC and liver 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 minimize 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.4 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. 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 Vfend 200 mg powder for solution for infusion (EMEA/H/C/000387), for content, and Zofiren 750 mg and 1500 mg powder for solution for injection/infusion (PT/H/2097/001-002), 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

Vedida 200 mg powder for solution for infusion 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.

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 Vedida with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 10 March 2021.

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/5075/1/IB /001	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	Yes	3 November 2021	Approved	N/A
NL/H/5075/1/IB /002	Update the SmPC and PIL of the product according to the SmPC and PIL of the reference product Vfend that is centrally authorised in EU with procedure number EMEA/H/C/000387.	Yes	24 March 2022	Approved	N/A
NL/H/5075/1/IA /003	Change(s) in the Summary of Product Characteristics, labelling or package leaflet of human medicinal products intended to implement the outcome of a procedure concerning PSUR or PASS, or the outcome of the assessment done by the competent authority under Articles 45 or 46 of Regulation 1901/2006SmPCSmPC. Implementation of PRAC recommendation EMEA/H/C/PSUSA/00003127/202102 for Voriconazole, published on 20 Dec. 2021.	Yes	11 May 2022	Approved	N/A

NL/H/5075/1/IA /004	Changes (Safety/Efficacy) to Human and Veterinary Medicinal Products. Other variation.	Yes	5 December 2024	Approved	N/A
NL/H/5075/1/IB /005	Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the risk management plan. Other variation. New version of Risk Management Plan	No	18 September 2024	Approved	N/A
NL/H/5075/1/IB /006	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	Yes	31 October 2024	Approved	N/A