EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

26 March 2015
EMA/CHMP/151531/2015
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Voriconazole Hospira

International non-proprietary name: voriconazole

Procedure No. EMEA/H/C/003737/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Administrative information

Name of the medicinal product:	Voriconazole Hospira
Applicant:	Hospira UK Limited Queensway Royal Leamington Spa Warwickshire CV31 3RW UNITED KINGDOM
Active substance:	Voriconazole
International Nonproprietary Name:	voriconazole
Pharmaco-therapeutic group (ATC Code):	Voriconazole (J02AC03)
Therapeutic indication(s):	• 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.
Pharmaceutical form(s):	Powder for solution for infusion
Strength(s):	200 mg
Route(s) of administration:	Intravenous use
Packaging:	vial (glass)
Package size(s):	1 vial and 5 vials

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List of abbreviations

ALT	alanine aminotransferase
ATC	anatomical therapeutic chemical
AUC	area under the curve
AUC/MIC	area under the curve in relation to the minimum inhibitory concentration
AUC_T	area under the curve from time zero to the time with detectable measurement
AST	aspartate aminotransferase
C_{max}	maximum concentration
CSF	cerebrospinal fluid
EU	European Union
IA	invasive aspergillosis
IP	intraperitoneal
IV	intravenous
MAA	marketing authorisation application
MIC	minimum inhibitory concentration
MIC_{50}	minimum inhibitory concentration required to inhibit the growth of 50% of organisms
MIC_{90}	minimum inhibitory concentration required to inhibit the growth of 90% of organisms
mins	minutes
MLC	minimal lethal concentration
PAFE	postantifungal effect
PD	Pharmacodynamics
PK	Pharmacokinetics
RMD	recommended maintenance dose
SBE-ß-CD	sufobutyl ether beta cyclodextrin sodium
$t_{1/2}$	elimination half-life
TD_{Lo}	lowest toxic dose
t_{max}	time to reach maximum concentration

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Hospira UK Limited submitted on 27 February 2014 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Voriconazole Hospira, through the centralised procedure under Article 3(3) of Regulation (EC) No. 726/2004– 'Generic of a Centrally authorised product'. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 21 March 2013.

The application concerns a generic medicinal product as defined in Article 10(2)(b) of Directive 2001/83/EC and refers to a reference product for which a Marketing Authorisation is or has been granted in the Union on the basis of a complete dossier in accordance with Article 8(3) of Directive 2001/83/EC.

The applicant applied for the following indication:

- 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.

The legal basis for this application refers to:

Generic application (Article 10(1) of Directive No 2001/83/EC).

The application submitted is composed of administrative information, complete quality data and a bioequivalence study with the reference medicinal product Vfend instead of non-clinical and clinical unless justified otherwise.

The chosen reference product is a:

- Medicinal product which is or has been authorised in accordance with Community provisions in accordance with Community provisions in force for not less than 6/10 years in the EEA:
  - Product name, strength, pharmaceutical form: Vfend, 200 mg, Powder for solution for infusion
  - Marketing authorisation holder: Pfizer Limited
  - Date of authorisation: 21/03/2002
  - Marketing authorisation granted by:
    - Community
      - Marketing authorisation number: EU/1/02/212/025

- Medicinal product authorised in the Community/Members State where the application is made or European reference medicinal product:
  - Product name, strength, pharmaceutical form: Vfend, 200 mg, Powder for solution for infusion
  - Marketing authorisation holder: Pfizer Limited
  - Date of authorisation: 21/03/2002
  - Marketing authorisation granted by:
    - Community
      - Marketing authorisation number: EU/1/02/212/025

Licensing status

At the time of submission of this, an application was filed in the following countries: USA.

The product was not licensed in any country at the time of submission of the application.

Information on paediatric requirements

Not applicable

1.2. Manufacturers

Manufacturers responsible for batch release

Hospira UK Limited
Queensway
Royal Leamington Spa
Warwickshire
CV31 3RW
UNITED KINGDOM

Hospira Enterprises B.V.
Randstad 22-11
NL-1316 BN Almere
The Netherlands

1.3. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP:

Rapporteur: Juris Pokrotnieks

- The application was received by the EMA on 27 February 2014.
- The procedure started on 26 March 2014.
- The Rapporteur's first Assessment Report was circulated to CHMP members on 25 June 2014.
- PRAC RMP Advice and assessment overview, adopted by PRAC on 10 July 2014.
- During the meeting on 24 July 2014, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final List of Questions was sent to the applicant on 24 July 2014.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 19 September 2014.
- The summary report of the GMP inspection carried out at the following sites site: GLAND PHARMA LIMITED Survey No: 143 - 148, 150&151, Dommara Pochampally, Near Gandi Maisamma Cross Roads Qutbullapur Mandal, Ranga Reddy District Hyderabad Andhra Pradesh 500 043 India between 10 and 14 November 2014 was issued on 10 February 2015.

- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 27 October 2014.
- During the CHMP meeting on 20 November 2014, the CHMP agreed on a list of outstanding issues to be addressed by the applicant.
- The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on 20 February 2015.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 3 March 2015.
- PRAC RMP Advice and assessment overview, adopted by PRAC on 12 March 2015.
- During their March 2015 meeting, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Voriconazole Hospira.

2. Scientific discussion

2.1. Introduction

Voriconazole is a broad spectrum, second generation triazole antifungal agent with close structural similarity to fluconazole. Like other azole antifungals, voriconazole acts by inhibiting the cytochrome P450-dependent enzyme, 14-α-sterol demethylase that is required for ergosterol biosynthesis. Exposure of fungi to voriconazole results in depletion of ergosterol and accumulation of 14- α-methylated sterols which are thought to contribute to the disruption of membrane structure and function thereby inhibiting fungal growth.

In vitro, voriconazole displays broad-spectrum antifungal activity against *Candida* species (including fluconazole resistant *C. krusei* and resistant strains of *C. glabrata* and *C. albicans*) and fungicidal activity against all *Aspergillus* species tested. In addition voriconazole shows in vitro fungicidal activity against emerging fungal pathogens, including those such as *Scedosporium* or *Fusarium* which have limited susceptibility to existing antifungal agents. Its mode of action is inhibition of fungal cytochrome P450-mediated 14α-sterol demethylation, an essential step in ergosterol biosynthesis.

Voriconazole has shown various levels of clinical efficacy against *Aspergillus* spp (including *A. flavus*, *A. fumigatus*, *A. terreus*, *A. niger*, *A. nidulans)*, *Candida* spp. (including *C. albicans*, *C. glabrata*, *C. krusei*, *C. parapsilosis*, *C. tropicalis*, *C. dubliniensis*, *C. inconspicua*, *C. guilliermondii)*, *Scedosporium spp*.(including *S. apiospermum*, *S. prolificans)* and *Fusarium spp*.

The reference medicinal product for this application, Vfend 200 mg powder for solution for infusion 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.

VFEND 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.

The applicant for this generic medicinal product chose to apply for the above indications, except the prophylaxis one. It is therefore proposed that Voriconazole Hospira 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. The applicant proposed an additional pack size containing 5 vials, in addition to the one containing 1 vial, as is the case for the reference medicinal product.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as a powder for solution for infusion containing 200 mg of voriconazole as active substance.

Other ingredients are: sulphobutylether beta cyclodextrin sodium (SBECD).

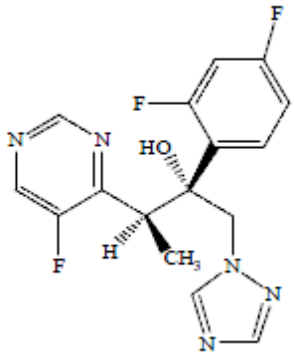
The product is available in 30 ml clear type I glass vial closed with a chlorobutyl rubber stopper and sealed with an aluminium flip off seal with a red plastic matte top button.

After reconstitution each ml contains 10 mg of voriconazole. Once reconstituted, further dilution is required before administration.

2.2.2. Active substance

General information

The chemical name of voriconazole is (2R,3S) -2- (2,4-difluorophenyl) -3- (5-flouro-4-pyrimidinyl) -1(1H-1,2,4-triazol-1-yl) 2-butanol and has the following structure:



The active substance is a non-hygroscopic white or almost white powder that is very slightly soluble in water, freely soluble in acetone and methylene chloride.

The information on the active substance is provided according to the Active Substance Master File (ASMF) procedure.

The structure of voriconazole has been confirmed by CHN analysis, UV, IR, ^{1}H NMR, MS, DSC and XRD studies.

Voriconazole exhibits stereoisomerism due to the presence of 2 chiral centres. Enantiomeric purity is controlled routinely by chiral HPLC. Polymorphism has been observed for voriconazole. Based on DSC and X-Ray diffraction studies, it is concluded that the manufacturing process followed by ASMF holder consistently produces the same polymorphic form.

Manufacture, characterisation and process controls

Voriconazole is synthesized in 4 main steps using commercially available well defined starting materials with acceptable specifications. Two manufacturing sites are involved in the voriconazole manufacture.

The active substance manufacturer has developed a high yielding diasterioselective process to form voriconazole.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities were well discussed with regards to their origin and characterised.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.

Detailed information on the manufacturing of the active substance has been provided in the restricted part of the ASMF and it was considered satisfactory.

Specification

The active substance specification includes tests for: appearance, solubility, identity (IR, HPLC), appearance of solution (Ph. Eur.), assay (HPLC), impurities including eniantomeric purity (HPLC), residual solvents (GC), water content (Ph. Eur.), heavy metals (Ph. Eur.), sulphated ash (Ph. Eur.), polymorphic identity (XRD), nickel (ICP-OES), bacterial endotoxin test (Ph. Eur.), TAMC/TYMC and test for specified microorganisms (Ph. Eur.).

Voriconazole is described in the Ph. Eur. and limits are in line (or tighter) with current Ph. Eur. limits.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines.

Batch analysis data (7 batches including 3 production scale batches) of the active substance are provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data on 6 batches including 3 production scale batches of active substance from the proposed manufacturers stored in a container closure system representative of that intended for the market for up to 60 months (18 months for the 3 production scale batches) under long term conditions at 25 ºC / 60% RH and for up to 6 months under accelerated conditions at 40 ºC / 75% RH according to the ICH guidelines were provided.

The parameters tested were the same as for release. The analytical methods used were the same as for release and were stability indicating.

As part of analytical method validation, photostability testing following the ICH guideline Q1B was performed on two batches. Results showed that the active substance is light sensitive but adequately protected in the proposed packaging. Results also showed that voriconazole is very sensitive to base, slightly degraded due to acid and peroxide, and very slightly degraded due to water at 60˚C. Voriconazole is not degraded due to thermal or humidity stress conditions.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period in the proposed container.

2.2.3. Finished medicinal product

Description of the product and pharmaceutical development

The aim was to develop a powder for solution for infusion that contains 200 mg of voriconazole in a concentration of 10 mg/ml once reconstituted, that has a safety and stability profile similar to the centrally authorised reference product Vfend (EMEA/H/C/000387). The applicant has developed the formulation based on the information from the product information available for reference product, the analytical results obtained from analysis of the reference product and CHMP EPAR-scientific discussion report for Vfend published. The studies performed by applicant on the reference product as part of the development work are qualitative and quantitative composition, container closure characterization, head space analysis and physicochemical properties of reference product.

The excipient types and grades were selected to be the same as those in the reference product. The excipient is a well-known pharmaceutical ingredient and its quality is compliant with pharmacopoeial standards (USP). There is no novel excipient used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC.

Comparative data between the proposed finished product and the reference product regarding substitution pattern and average degree of the SBECD molecule as well data on formation of the complex active substance /excipient were provided.

No bioequivalence study was performed as the generic finished product is applied by parenteral administration route.

The proposed manufacturing process consists of a sterile filtration /aseptic process followed by a lyophilisation step.

The applicant has performed extensive development and optimization studies of the proposed manufacturing process.

No overage is used. However, an overfill is included to allow an extractable volume of 20ml.

Compatibility studies were performed to assure that the finished product is compatible with reconstituents and diluents listed in the package leaflet. Results demonstrate that voriconazole is physically compatible and chemically stable when reconstituted with: water for injection or Sodium chloride (0.9%) solution for injection, and further diluted with 5% Dextrose and Lactated Ringers USP, 5% Dextrose and 0.45% Sodium Chloride USP, 5% Dextrose and 20 mEq Potassium Chloride USP, 5% Dextrose and 0.9% Sodium Chloride USP.

The primary packaging is 30 ml clear type I glass vial closed with a chlorobutyl rubber stopper and sealed with an aluminium flip off seal with a red plastic matte. The material complies with Ph. Eur. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process consists of 5 main steps: solution preparation/compounding, pre- and sterile filtration, filling and stoppering, lyophilisation, capping and labelling. The process is considered to be a non-standard manufacturing process.

The critical steps are compounding, filtration, filling and lyophilisation.

The in-process controls are adequate for this type of manufacturing process.

Major steps of the manufacturing process have been validated on 3 production scale batches. In addition the following validation data were also provided: filter validation, media fill study, holding time validation data, validation of sterilization and depyrogenation of containers and closures. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form: appearance, identification of the active substance (UV, HPLC), assay (HPLC), related substances (HPLC), water content (KF), pH (Ph. Eur.), appearance and clarity of reconstituted solution (visual and Ph.Eur.), colour of solution (Ph. Eur.), reconstitution time, uniformity of dosage units (Ph. Eur.), osmolality (Ph.Eur.), sterility (Ph. Eur.), bacterial endotoxins level (Ph. Eur.), particulate contamination (Ph. Eur.).

The finished product is released on the market based on the above release specifications, through traditional final product release testing.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines.

Batch analysis results are provided on three production scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data on 3 production scale batches of finished product stored under long term conditions for 12 months at 25 ºC / 60% RH and 30 ºC / 65% RH and for up to 6 months under accelerated conditions at 40 ºC / 75% RH according to the ICH guidelines were provided. Samples were stored in the inverted and upright position. The batches are representative to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested according to the methods used for release testing with the exception of the identification of the active substance test, the uniformity of dosage units test and osmolality test that were not performed. The analytical procedures used are stability indicating.

Stress studies on the finished product were performed by subjecting the samples to temperature cycling. The study was performed by storing samples at –20°C ± 5°C for 48 hours followed by 40°C ± 2°C/75% RH ± 5% RH for 48 hours for a total of 3 temperature cycles. The results demonstrate that the thermal cycling conditions had no impact on the stability of the finished product.

In addition, samples from one batch of finished product stored in primary packaging, primary and secondary packaging and primary packaging with foil wrapping were exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. The results showed that there was a substantial increase in the impurity level observed in the directly exposed product and that the degradation can be prevented by storing the finished product in the outer carton. The following storage precaution "Store in the original package in order to protect from light" is included in the SmPC.

Stability data regarding the finished product admixture with intravenous solutions were provided. The storage conditions studied were storage for up to 36 hours at refrigerated conditions (2°C-8°C) for the primary reconstituted vial, followed by dilution and further storage up to 36 hours at refrigerated conditions (2°C-8°C) and 3 hours at room temperature.

Based on available stability data, the shelf-life and storage conditions as stated in the SmPC are acceptable.

Adventitious agents

No excipients derived from animal or human origin have been used.

2.2.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendation(s) for future quality development

None.

2.3. Non-clinical aspects

2.3.1. Introduction

A non-clinical overview has been provided, and was based on up-to-date and adequate scientific literature (referring 42 publications up to year 2013). The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. The non-clinical aspects of the SmPC are brought in line with the SmPC of the reference product. The impurity profile has been discussed and was considered acceptable.

Therefore, the CHMP agreed that no further non-clinical studies are required.

2.3.2. Pharmacology

The pharmacology of voriconazole is well characterised and established. Additional pharmacology studies have not been conducted by the applicant, as they are not required for this generic MAA. The submitted non-clinical overview provides detailed information on the *in vitro* and *in vivo* activity-efficacy studies in animal models from the published literature.

2.3.3. Pharmacokinetics

The pharmacokinetics of voriconazole is well known. Formal non-clinical pharmacokinetic studies have not been conducted and CHMP considered this acceptable for this generic application.

The submitted non-clinical overview provided a comprehensive overview of the published information on the pharmacokinetics of voriconazole, including the PK parameters in different animal species.

2.3.4. Toxicology

Published toxicity data for voriconazole, including acute, subacute and chronic toxicity data, genotoxicity, reproductive toxicity, carcinogenicity were provided and assessed by the CHMP. The information included in the product information was deemed acceptable by the CHMP.

The impurity profile of Voriconazole Hospira 200 mg powder for solution for infusion is considered comparable to that of the reference product. CHMP agreed that comprehensive toxicology studies were therefore not required.

The non-clinical aspects included in sections 4.6 and 5.3 of the product SmPC are in line with the information of the reference product and with the published scientific literature and were considered acceptable by the CHMP.

2.3.5. Ecotoxicity/environmental risk assessment

No environmental risk assessment (ERA) was submitted. According to Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447/00) the absence of ERA can be acceptable for marketing authorisation applications for generic medicinal products, if adequately justified.

The absence of an ERA with this application was justified by the applicant by the fact that the introduction of Voriconazole Hospira is considered unlikely to result in any significant increase in the combined sales volumes for all voriconazole containing products and the exposure of the environment to the active substance. Thus, the ERA is expected to be similar and not increased.

The applicant also confirmed that there are no materials of animal origin used in the manufacture of the proposed product. Therefore, there are no concerns with regard to the compliance with the Note for Guidance on Minimizing the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products (EMEA/410/01 Rev. 3).

The CHMP considered the applicant's justification for omitting a further environmental risk assessment as acceptable.

2.3.6. Discussion on non-clinical aspects

The preclinical safety (toxicology) of voriconazole has been extensively investigated in a series of studies, which included *in vitro* and *in vivo* genotoxicity studies, general toxicology studies, carcinogenicity and reproductive studies. Results from these studies indicate that the toxicity profile of voriconazole is well characterised and is acceptable. Additional toxicity studies for generic voriconazole are not warranted. CHMP agreed that the PK of voriconazole is sufficiently characterised and no additional studies are deemed necessary.

2.3.7. Conclusion on the non-clinical aspects

The provided non-clinical literature and the non-clinical review pertaining to the pharmacology and the toxicology of voriconazole was considered acceptable by the CHMP.

2.4. Clinical aspects

2.4.1. Introduction

This is an application for a powder for solution for infusion containing voriconazole 200 mg. The applicant provided a clinical overview outlining the clinical pharmacokinetics and pharmacodynamics of voriconazole, and provided efficacy and safety data for voriconazole based on published literature (the overview refers to 101 publications up to year 2013). The product information of this generic is brought in line with the product information of the reference product, for the indications applied for.

No CHMP scientific advice pertinent to the clinical development was given for this medicinal product.

As already mentioned, for the clinical assessment the Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98) is of particular relevance.

Exemption

According to the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **) an *in-vivo* bioequivalence study was not requested for this application, as "*the product is to be administered as an aqueous intravenous solution containing the same active substance in the same concentration as the currently approved product*".

Bioequivalence studies are generally not required if the generic medicinal product is to be administered as an aqueous intravenous solution containing the same active substance as the currently approved product. However, if any excipients interact with the active substance (e.g. complex formation), or otherwise affect the disposition of the active substance, a bioequivalence study is required unless both products contain the same excipients in very similar quantity and it can be adequately justified that any difference in quantity does not affect the pharmacokinetics of the active substance.

The excipient sulphobutylether beta cyclodextrin sodium forms a complex with the active substance voriconazole. According to the applicant the applied product contains the same amount of sulphobutylether beta cyclodextrin sodium as the reference product. The CHMP therefore agreed that a biowaiver is acceptable.

2.4.2. Pharmacokinetics

Voriconazole is rapidly and almost completely absorbed following oral administration, with maximum plasma concentrations (Cmax) achieved 1-2 hours after dosing. The absolute bioavailability of voriconazole after oral administration is estimated to be 96 %.

The volume of distribution at steady state for voriconazole is estimated to be 4.6 l/kg, suggesting extensive distribution into tissues. Plasma protein binding is estimated to be 58 %. Less than 5% of the drug is excreted unchanged in the urine. The inter-individual variability of voriconazole pharmacokinetics is high.

In vitro studies showed that voriconazole is metabolised by the hepatic cytochrome P450 isoenzymes, CYP2C19, CYP2C9 and CYP3A4.

In vivo studies indicated that CYP2C19 is significantly involved in the metabolism of voriconazole. This enzyme exhibits genetic polymorphism. For example, 15-20 % of Asian populations may be expected to be poor metabolisers. For Caucasians and Blacks the prevalence of poor metabolisers is 3-5 %. Studies conducted in Caucasian and Japanese healthy subjects have shown that poor metabolisers have, on average, 4-fold higher voriconazole exposure (AUC_T) than their homozygous extensive metaboliser counterparts. Subjects who are heterozygous extensive metabolisers have on average 2-fold higher voriconazole exposure than their homozygous extensive metaboliser counterparts.

The major metabolite of voriconazole is the N-oxide, which accounts for 72 % of the circulating radiolabelled metabolites in plasma. This metabolite has minimal antifungal activity and does not contribute to the overall efficacy of voriconazole. Voriconazole is eliminated via hepatic metabolism with less than 2 % of the dose excreted unchanged in the urine.

After administration of a radiolabelled dose of voriconazole, approximately 80 % of the radioactivity is recovered in the urine after multiple intravenous dosing and 83 % in the urine after multiple oral dosing. The majority (>94 %) of the total radioactivity is excreted in the first 96 hours after both oral and intravenous dosing.

The terminal half-life of voriconazole depends on dose and is approximately 6 hours at 200 mg (orally). Because of non-linear pharmacokinetics, the terminal half-life is not useful in the prediction of the accumulation or elimination of voriconazole.

The applicant has submitted no additional PK study and CHMP agreed that no such studies are required for this application.

Bioequivalence studies are generally not required if the generic medicinal product is to be administered as an aqueous intravenous solution containing the same active substance as the currently approved product. However, if any excipients interact with the active substance (e.g. complex formation), or otherwise affect the disposition of the active substance, a bioequivalence study is required unless both products contain the same

excipients in very similar quantity and it can be adequately justified that any difference in quantity does not affect the pharmacokinetics of the active substance.

The excipient sulphobutylether beta cyclodextrin sodium forms a complex with the active substance voriconazole. According to the applicant the applied product contains the same amount of sulphobutylether beta cyclodextrin sodium as the reference product. Thus, a biowaiver was considered acceptable by CHMP.

2.4.3. Pharmacodynamics

No new pharmacodynamic studies were presented and CHMP agreed that no such studies are required for this application.

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.

2.4.4. Post marketing experience

No post-marketing data are available. The medicinal product has not been marketed in any country.

2.4.5. Discussion on clinical aspects

As already mentioned, all requirements described in the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **, Appendix III) are fulfilled, and CHMP agreed that a biowaiver is acceptable.

Voriconazole has been in medicinal use in the EU for more than 10 years, and its efficacy and safety profile are well known.

The applicant has not conducted any clinical trials for efficacy and safety with Voriconazole Hospira, since it is essentially similar to the reference product.

The applicant provided in the submitted clinical overview the necessary supportive information explaining the information given in the proposed Voriconazole Hospira product information. CHMP agreed that the product information of Voriconazole Hospira included in this application reflects the approved PI of the reference product for the indications applied for by Voriconazole Hospira.

The efficacy of voriconazole has been shown in a number of randomized clinical trials. A discussion on the safety and tolerability of voriconazole has been also provided, and has adequately addressed the known issues on renal safety, hepatic safety, visual disturbances and dermatological reactions.

In accordance to the risk minimisation measures requested by the CHMP for the reference product, additional risk minimisation measures will be also introduced for the important identified risks of hepatic toxicity and squamous cell carcinoma (SCC) for Voriconazole Hospira. Hospira will develop a Patient Alert Card, a HCP check list and Q&A document, similar to the requests made by the CHMP for the reference medicinal product.

The CHMP considered the provided clinical overview on clinical pharmacology, efficacy and safety as adequate.

The CHMP also noted that the applicant has aligned the product information of Voriconazole Hospira with the updated product information of the reference medicinal product for the indications claimed for by Voriconazole Hospira.

2.4.6. Conclusions on clinical aspects

The CHMP considers that in view of the provided information, the application is approvable from the clinical point of view.

2.5. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

2.6. Risk management plan

The CHMP received the following PRAC Assessment report on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 3 is acceptable. The PRAC endorsed the PRAC Rapporteur assessment report is attached. The CHMP endorsed the PRAC AR without changes.

The CHMP endorsed the Risk Management Plan version 3 with the following content:

Safety concerns

Summary of safety concerns	
Important identified risks	Hepatic toxicity QTc prolongation Visual events (including optic neuritis, papiloedema and other visual concerns) Phototoxicity Peripheral neuropathy Squamous cell carcinoma (SCC)
Important potential risks	Skin cancers (non-SCC) Suicide-related events

Missing information	Effects in pregnancy Effects in paediatrics Off-label use Resistance

Pharmacovigilance plan

No additional pharmacovigilance studies or activities are proposed.

Risk minimisation measures

Safety concern	**Routine risk minimisation measures**	**Additional risk minimisation measures**
Hepatic toxicity	**SmPC:** **Special warnings and precaution for use text in Section 4.4 of the SmPC** **Undesirable effects text in Section 4.8** **PIL: Section 4. Possible side effects**	Hospira will develop a Patient Alert Card, HCP check list and Q&A document similar to the content of the innovator product VFEND and as agreed by the
QTc prolongation	**SmPC:** **Contraindications text in Section 4.3 of the SmPC** **Special warnings and precaution for use text in Section 4.4 of the SmPC** **Interaction with other medicinal products and other forms of interaction text in Section 4.5 of the SmPC** **Undesirable effects text in Section 4.8 of the SmPC** **PIL:** **Section 2 What you need to know before you take Voriconazole Hospira** **Section 4 Possible side effects**	None

Visual events (including optic neuritis, papiloedema and other visual concerns)	**SmPC:** **Special warning and precaution for use text in Section 4.4 of the SmPC** **Effects on ability to drive and use machines text in Section 4.7 of the SmPC** **Undesirable effects text in Section 4.8 of the SmPC** **PIL:** **Section 4. Possible side Effects**	None
Phototoxicity	**SmPC:** **Special warning and**	Hospira will develop a Patient Alert Card, HCP check list and
	precaution for use text in Section 4.4 of the SmPC **Undesirable effects text in Section 4.8 of the SmPC** **PIL:** **Section 2. What you need to know before you take Voriconazole Hospira** **Section 4. Possible side effects**	Q&A document similar to the content of the innovator product VFEND and as agreed by the CHMP.
Peripheral neuropathy	**SmPC:** **Undesirable effects text in Section 4.8 of the SmPC** **PIL:** **Section 4. Possible side Effects**	None

Squamous cell carcinoma (SCC)	**SmPC:** **Special warning and precaution for use text in Section 4.4 of the SmPC** **Undesirable effects text in Section 4.8 of the SmPC** **PIL:** **Section 2. What you need to know before you take Voriconazole Hospira** **Section 4 : Possible side effects**	Hospira will develop a Patient Alert Card, HCP check list and Q&A document similar to the content of the innovator product VFEND and as agreed by the CHMP.
Skin cancers (non-SCC)	**PIL:** **Section 2. What you need to know before you take Voriconazole Hospira** **Section 4 : Possible side effects**	None
Suicide-related events	None	None
Effects in pregnancy	**SmPC:** **Fertility, pregnancy and lactation text in Section 4.4 of the SmPC** **PIL:** **Section 2. What you need to know before you take Voriconazole Hospira**	None

Effects in paediatrics	**SmPC:** **Special warning and precaution for use text in Section 4.4 of the SmPC** **Undesirable effects text in Section 4.8 of the SmPC** **Overdose text in Section 4.9 of the SmPC** **Section 5.2 Pharmacokinetic properties** **PIL:** **Section 2. What you need to know before you take Voriconazole Hospira**	None
Off-label use	None	None
Resistance	None	None

2.7. PSUR submission

At the time of granting the marketing authorisation, the submission of periodic safety update reports is not required for this medicinal product. However, the marketing authorisation holder shall submit periodic safety update reports for this medicinal product if the product is included in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83 and published on the European medicines web-portal.

2.8. Product information

2.8.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet 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.

3. Benefit-risk balance

This application concerns a generic version of voriconazole 200 mg powder for solution for infusion. The reference product Vfend is indicated for the treatment of invasive aspergillosis, treatment of candidaemia in non-neutropenic patients, treatment of fluconazole-resistant serious invasive *Candida* infections (including *C. krusei*) and treatment of serious fungal infections caused by *Scedosporium* spp. and *Fusarium* spp. Vfend should be administered primarily to patients with progressive, possibly life-threatening infections. In addition, Vfend is

also indicated for the prophylaxis of invasive fungal infections in high risk allogeneic hematopoietic stem cell transplant (HSCT) recipients, indication which was not applied for by this applicant.

No non-clinical studies have been provided for this application, but an adequate summary of the available nonclinical information for the active substance was presented and considered sufficient by the CHMP. From a clinical perspective, this application does not contain new data on the pharmacokinetics and pharmacodynamics as well as the efficacy and safety of the active substance; the applicant's clinical overview on these clinical aspects based on information from published literature was considered sufficient by the CHMP.

According to the Guideline on the Investigation of Bioequivalence (London, 20 January 2010, Doc. Ref.: CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **) an *in-vivo* bioequivalence study was not requested for this application, as "*the product is to be administered as an aqueous intravenous solution containing the same active substance in the same concentration as the currently approved product*" and a biowaiver was accepted by the CHMP.

The applicant has made the appropriate amendments to the Voriconazole Hospira product information, which was brought in line with the updated latest information for the reference product. This was considered acceptable by the CHMP. As mentioned above, the prophylaxis indication which was approved for Vfend was not claimed for by Voriconazole Hospira and is therefore not reflected in the approved PI of Voriconazole Hospira.

The CHMP agreed that the overall benefit/risk ratio for Voriconazole Hospira 200 mg powder for solution for infusion is positive.

The CHMP, having considered the data submitted in the application and available on the chosen reference medicinal product, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

4. Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Voriconazole Hospira in the treatment of invasive aspergillosis, treatment of candidaemia in non-neutropenic patients, treatment of fluconazole-resistant serious invasive *Candida* infections (including *C. krusei*) and treatment of serious fungal infections caused by *Scedosporium* spp. and *Fusarium* spp is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription

Conditions and requirements of the Marketing Authorisation

Periodic Safety Update Reports

At the time of granting the marketing authorisation, the submission of periodic safety update reports is not required for this medicinal product. However, the marketing authorisation holder shall submit periodic safety update reports for this medicinal product if the product is included in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83 and published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

Additional risk minimisation measures

- 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.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.