London, 21 March 2013
EMA/CHMP/151290/2013
Committee for Medicinal Products for Human Use (CHMP)

Voriconazole Accord

International non-proprietary name: voriconazole

Procedure No.: EMEA/H/C/002669

Marketing authorisation holder: Accord Healthcare Limited

Assessment report for initial marketing authorisation application

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

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List of abbreviations

AE : Adverse Event
ANOVA : Analysis of Variance
AUC : Area Under Curve
$AUC_{0-\infty\_Pred}$: The Area Under the Plasma Concentration Versus Time Curve From Time Zero to Infinity.
AUC0-t: The Area Under the Plasma Concentration Versus Time Curve From Time Zero to the last Measurable Plasma Concentration
Residual Area_Pred: % of the Area Under the Curve That has been Derived After Extrapolation Or % Residual Area
BA: Bioavailability
BE : Bioequivalence
BMI : Body Mass Index
BP : Blood Pressure
CL : Confidence Limit
Cmax : Maximum Measured plasma Concentration
e-CRF : Electronic Case Record Form
CRO : Contract Research Organization
CV : Curriculum Vitae
DCGI : Drug Controller General (India)
ECG/EKG : Electrocardiogram
GCP : Good Clinical Practice
GLP : Good Laboratory Practice
HbsAg : Hepatitis B surface antigen
HCV : Hepatitis C Virus
HPLC : High Performance Liquid Chromatography
Hr/Hrs : Hours
ICMR : Indian Council of Medical Research
ICF : Informed Consent Form
ICH : International Conference on Harmonization
IEC : Independent Ethics Committee
IMP : Investigational Medicinal Product
K2EDTA : Dipotassium Ethylenediaminetetraacetate
LC-MS/MS : Liquid Chromatography/ Tandem Mass Spectrometry
ng / mL : Nanogram per Milliliter
MS : Method SOP
MV : Method Validation
N : Number
ng / mL : Nanogram per Milliliter
rcf : Relative Centrifugal Force
PPCP Polypropylene Copolymer.
SAE : Serious Adverse Event
SCF : Subject Consent Form
SIS : Subject Information Sheet
SOP : Standard Operating Procedure
t1/2 : The elimination OR terminal half-life
Tmax : Time of the maximum measured plasma concentration
λ_z : First order rate constant associated with the terminal (loglinear) portion of the curve

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Accord Healthcare Limited submitted on 29 May 2012 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Voriconazole Accord, 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 December 2011.

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 candidemia 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 50 mg and 200 mg film-coated tablets instead of non-clinical and clinical unless justified otherwise.

Information on paediatric requirements

Not applicable

The chosen reference product is:

■ 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, 50 mg and 200 mg film-coated tablets
- Marketing authorisation holder: Pfizer Limited
- Date of authorisation: 21/03/2002
- Marketing authorisation granted by:
  - Community

Marketing authorisation number: EU/1/02/212/001-024

■ Medicinal product authorised in the Community/Members State where the application is made or European reference medicinal product:

- Product name, strength, pharmaceutical form: VFEND, 50 mg, 200 mg film-coated tablets
- Marketing authorisation holder: Pfizer Limited
- Date of authorisation: 21/03/2002
- Marketing authorisation granted by:

- Community
- Marketing authorisation number: EU/1/02/212/001-024
-

■ Medicinal product which is or has been authorised in accordance with Community provisions in force and to which bioequivalence has been demonstrated by appropriate bioavailability studies:

- Product name, strength, pharmaceutical form: 200 mg film-coated tablets
- Marketing authorisation holder: Pfizer Limited
- Date of authorisation:21/03/2002
- Marketing authorisation granted by:
  - Community
  - Member State (EEA) : Hungary
  - Marketing authorisation number(s): EU/1/02/212/013-024
- Bioavailability study number(s): 009-11

Scientific advice

The applicant did not seek scientific advice at the CHMP.

Licensing status

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

1.2. Manufacturers

Manufacturer(s) responsible for batch release

Accord Healthcare Limited

Sage House

319 Pinner Road North Harrow, Middlesex,

HA1 4HF

UNITED KINGDOM

1.3. Steps taken for the assessment of the product

The Rapporteur and appointed by the CHMP and the evaluation team was:

Rapporteur: John Joseph Borg

- The application was received by the EMA on 29 May 2012.
- The procedure started on 20 June 2012.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 7 September 2012.
- During the meeting on 18 October 2012, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 18 October 2012.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 18 January

2013.

- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 18 February 2013.
- Upon request of the CHMP, the PRAC provided an opinion on the Risk Management Plan 07 March 2013.
- The Rapporteur circulated a final Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 12 March 2013.
- During the meeting on 21 March 2013, 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 Accord.

2. Scientific discussion

2.1. Introduction

Voriconazole, is a broad spectrum, triazole antifungal agent and is indicated in adults and children aged 2 years and above. Voriconazole is active against all *Candida* species, including *Candida krusei*, strains of *Candida glabrata* that are inherently fluconazole-resistant and strains of *Candida* albicans that have acquired resistance to fluconazole. 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.

Voriconazole was first introduced into the market in Europe at least eight years ago as Voriconazole 50 mg and 200 mg film-coated tablets. This Marketing Authorization application (MAA) is submitted in accordance with Article 10.1 of Directive 2001/83/EC as amended as a so called generic application. The medicinal product is a generic of the reference medicinal product, which has been authorized within the community, in accordance with community provisions in force, for not less than ten years in a member state or in the community.

This MAA is made on the basis that the Voriconazole tablet a generic of Vfend® 50 mg and 200 mg film-coated tablets marketed by Pfizer Limited. The indications sought for Voriconazole film-coated tablets are the same as those for Vfend® film-coated tablets. [Treatment of invasive aspergillosis; Treatment of candidemia 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].

As this is an abridged license, this is a generic application of a currently marketed product, no clinical studies have been undertaken to support the application. However, one clinical study was undertaken, which is considered as pivotal, and is a bioequivalence study comparing Voriconazole 200 mg film-coated tablets against Vfend® 200 mg film-coated tablets.

2.2. Quality aspects

2.2.1. Introduction

Voriconazole Accord tablets are presented as immediate release film-coated tablets of two different strengths (50 mg and 200 mg) of voriconazole as active substance. The 50 mg strength tablets are white to off white, round, film-coated tablets, debossed with 'V50' on one side and plain on the other side while the 200 mg tablets are white to off white, oval, film-coated tablets, debossed with 'V200' on one side and plain on the other side. Other ingredients are defined in the SmPC section 6.1.

Voriconazole Film-coated Tablets are packed in PVC-Alu blister. Clear PVC/ Aluminium blister pack comprises clear transparent PVC film as forming foil and hard tampered aluminium foil with HSL coating on bright side as lidding foil. PPCP container comprises, tablets packed in LDPE bag closed with twist tie, this LDPE bag is placed another LDPE bag containing silica gel and twist tied and placed in PPCP container.

2.2.2. Active substance

The Chemical name of the active substance, voriconazole, is: (2R,3S) -2- (2,4-difluorophenyl) -3-(5-flouro-4-pyrimidinyl) -1(1H-1,2,4-triazol-1-yl) 2-butanol. Voriconazole is freely soluble in Acetone and in Methylene chloride and insoluble in water. Voriconazole drug substance is non–hygroscopic and it exhibits polymorphism; however based on DSC and X-Ray diffraction studies, the manufacturing process followed by the ASMF holder consistently produces Form-B.

Voriconazole consists of two asymmetric carbons; hence it exhibits optical isomerism with a possibility of two pairs of optical isomers i.e., four isomers. However the active substance manufacturer has developed a high yielding diasterioselective process to form (2R,3S) -2- (2,4-difluorophenyl) -3-(5-flouro-4-pyrimidinyl) -1(1H-1,2,4-triazol-1-yl) 2-butanol.

Manufacture

An ASMF is used for information on the drug substance. The synthesis of voriconazole is well described. The structure of voriconazole has been adequately proven and its physico-chemical properties sufficiently described.

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 drug substance specification includes tests for appearance (Ph. Eur), solubility (Ph. Eur), identification (IR, HPLC), enantiomeric purity (HPLC), appearance of solution (Ph. Eur), related substances (HPLC), heavy metals (Ph. Eur), water (Ph. Eur), sulphated ash (Ph. Eur), residual solvents (GC), polymorphic identity (XRD) and assay (HPLC)

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

Batch analysis data of the active substance has been provided. The results are within the specifications and consistent from batch to batch.

Stability

The stability of Voriconazole is being assessed at ICH long term stability conditions i.e. 25 ± 2°C/60 ± 5% RH, and at ICH accelerated stability conditions i.e. 40 ± 2°C/75 ± 5% RH. The batches have completed 44 months of testing at both long term and intermediate conditions and 6 months testing at accelerated conditions.

The parameters tested up to 36 months were*:* appearance (Ph. Eur), identification (IR), loss on drying, impurities, assay and polymorphic identity (HPLC). The parameters tested at 44 months were*:* appearance (Ph. Eur), identification (IR) and identification by enantiomeric purity (HPLC), impurities, water (Ph. Eur), assay (HPLC), polymorphic identity (XRD)

Forced degradation study reports have been provided. Stress conditions included temperature, light, acid/base hydrolysis, water hydrolysis and oxidation. The methods can be considered as stability indicating from the data presented.

The active substance is packaged in double low density PE bags and then placed in a triple laminated bag and kept inside an HDPE container. The packaging materials have been described in sufficient detail and are in compliance with the Ph. Eur. and Directive 2002/72/EC.

The stability results indicate that the drug substance is sufficiently stable and justify the proposed retest period with no special conditions for storage if packed in the container closure system intended for marketing as described above.

2.2.3. Finished medicinal product

Pharmaceutical development

The aim of product development was to formulate a robust, essentially similar, stable and bioequivalent generic formulation of Voriconazole film-coated tablets to the reference product (Vfend®). The choice of excipients used in the Voriconazole 50 mg and 200 mg film-coated tablets was based on qualitative composition of reference product i.e. Vfend® 50mg and 200mg film-coated tablets. The development of the finished product has been described in sufficient detail, the choice of excipients is justified and their functions explained. During development, the finished product composition and the manufacturing process parameters were optimised until the final formulation was obtained. The composition of the 50mg and 200mg strengths are proportional.

The development and discriminating nature of the chosen dissolution method has been adequately described. Comparative in-vitro dissolution data demonstrate similarity between the 200 mg strengths of test and reference products with fast dissolution (>85% in 15 minutes) at pH 1.2, 4.5 and 6.8. The applicant has also provided comparative dissolution data between the 50mg strength of the test and reference products in 3 pH's. Again, in all 3 dissolution media, all batches of test and reference product exhibited rapid dissolution and the dissolution profiles can be considered as being similar without further mathematical calculations since more than 85% of the labeled amount of drug substance is released within 15 minutes. A BE study was carried out on Voriconazole Accord 200mg tablets against the reference product Vfend 200 mg tablets of Pfizer Limited, UK (Sourced from Hungary). The bioequivalence data showed that the 90% confidence intervals of the test/reference (T/R) ratio for voriconazole lie within the prospectively defined acceptance criteria of 80% to 125% for AUCt , AUC ∞ and C_{max}. A bio-waiver for the additional strength (50 mg) was accepted taking into account that all the conditions set out in the Note for Guidance on the Investigation of Bioavailability and Bioequivalence CPMP/EWP/QWP/1401/98 have been fulfilled as described in section 2.4.

Adventitious agents

None of the excipients (except lactose monohydrate) used in the manufacture of the finished product is of human or animal origin. According to the applicant, it is confirmed by the manufacturer that lactose is prepared without the use of other ruminant material than milk and calf rennet. Milk is sourced from healthy animals in the same conditions as milk collected for human consumption in accordance with the EU food hygiene regulations. TSE/BSE free declarations have been provided for all excipients from their respective suppliers.

Manufacture of the product

The manufacturing process concerns a standard wet granulation process which involves the following steps: mixing, binder solution preparation, granulation and drying, mixing , lubrication, compression, film-coating and finally packaging. The in-process controls have been described. Manufacturing process validation has been initiated and results from two batches of each strength of the finish product have been provided. The overall results of the validation studies conducted show that the manufacturing process is capable of consistently producing common granule blend and film-coated tablets of the desired quality.

Product specification

The product specification includes appropriate parameters for the dosage and pharmaceutical form. Validation results of the analytical procedures have been presented (or the analytical procedures have been adequately validated). The results of the batch analysis presented show that the finished product meets the proposed specification.

The release specifications of the finished product contains tests with suitable limits for an immediate release film-coated tablet. These include: description, average weight of tablet, identification (HPLC, UV, titanium dioxide), resistance to crushing (Ph. Eur), water (Ph. Eur), dissolution, Uniformity of dosage units (Ph. Eur), related substances (HPLC), assay (HPLC), microbial examination (Ph. Eur).

The shelf-life specification contains similar tests with the exception of average weight of tablet, identification and uniformity of dosage units.

All excipients used in the manufacture of the finished product are controlled according to the respective current Ph. Eur. monographs.

Stability of the product

The applicant conducted the following stability studies to support this marketing authorisation application: a) Formal stability studies (i.e. long-term accelerated and intermediate conditions in accordance to ICH guidelines), b) Thermal cycling study (to study the effect of transportation on the stability of the finish product in PPCP containers), c) Photostability study
Stability data has been provided for three production scale batches for the 50mg and 200mg strength of the finished product. For the finished product packed in the container and closure system intended for marketing, updated stability data covering 12 moths of testing at long term conditions 25 ± 2°C/60 ± 5% RH has been provided for the two batches of each strength of the finished product presented at submission. Additionally, data covering 6 months testing at accelerated conditions 40 ± 2°C/75 ± 5% RH and 9 months testing at long term conditions has been presented for an additional batch of each strength.

Photo stability study was conducted as per ICH guideline. Both irradiated and not-irradiated samples were analyzed for description, assay and related substances as per shelf life specifications. The results of the photostability study confirm that the finished product is not sensitive to light and the immediate packaging adequately protects the finished product

For the finished product packed in the bulk transportation pack, updated stability data covering 12 moths of testing at long term conditions has been provided for the two batches of each strength of the finished product presented at submission. Additionally, data covering 6 months testing at long term conditions has been presented for an additional batch of each strength.

In both container closure systems no out of specification results were noted. All results are well within the specification limits and no specific trends were noted. For the finished product packed in the container and closure system intended for marketing, based on the long term and accelerated data provided, the proposed shelf-life with no special precautions for storage was granted.

2.2.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of this pharmaceutical form 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 the clinic.

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

Not applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. The non-clinical aspects of the SmPC are in line with the SmPC of the reference product.

The products have been formulated utilising conventional pharmacopoeial excipients the safety profile of which has been established. The product impurity profile has been discussed and percentage impurity content restriction as proposed by the applicant is considered acceptable.

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

2.3.2. Ecotoxicity/environmental risk assessment

No Environmental Risk Assessment was submitted. This was justified by the applicant as the

introduction of for Voriconazole Accord 50mg and 200mg Film-Coated Tablets manufactured by Accord Healthcare Limited 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 CHMP considers this justification acceptable.

2.3.3. Conclusion on the non-clinical aspects

The CHMP agreed that there are no objections to the approval of Voriconazole Accord 50mg and 200mg Film-Coated Tablets from a non-clinical point of view.

2.4. Clinical aspects

2.4.1. Introduction

This is an application for immediate release film-coated tablets of two different strengths (50 mg and 200 mg) of voriconazole as active substance. To support the marketing authorisation application the applicant conducted one bioequivalence study with cross-over design under fasting conditions. This study was the pivotal study for the assessment.

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

For the clinical assessment the Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98) as well as the Guideline on Bioanalytical method validation (EMEA/CHMP/EWP/192217/09) are of particular relevance.

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement, as requested by Article 8 (ib) of Directive 2001/83/EC, to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Exemption

The bioequivalence study was carried out on Voriconazole 200 mg film-coated tablets. Based on the acceptable bioequivalence study for Voriconazole 200 mg film-coated tablets, a request for waiver of biostudy on the lower strength 50mg was requested based on the five general requirements (Ref: Guideline on the Investigation of Bioequivalence, Doc. Ref.:CPMP/EWP/QWP/1401/98 Rev. 1).

The dissolution studies show that more than 85% of Active Pharmaceutical Ingredient (API) is released in 15 minutes. All the five criteria for bio waiver as stated in the guideline are fulfilled. There are no quality issues in the comparative dissolution testing hence the CHMP agreed that the bio waiver is acceptable.

Clinical study

To support the application, the applicant has submitted one bioequivalence study.

2.4.2. Pharmacokinetics

Study Project No 009-11 : An open-label, balanced, randomized, two-treatment, two-period, two-sequence, single dose, cross over, comparative oral bioequivalence study of two formulations of voriconzole 200 mg tablets in normal, healthy, adult human subjects under fasting conditions.

Methods

Study design

The study was a single centre, open label, randomised, single dose, two-period, two-treatment, two-sequence, crossover study, performed under fasting conditions in healthy adult volunteers. Each subject received a single dose of respective formulation in each period with 240 ml of water after an overnight fast. Each treatment was administered once according to a randomisation list. Standardised meals were served during each study phase. The investigational products were administered orally on 12.2.2012 for period 1 and on 18.2.2012 for period 2. The wash-out period was 6 days which is more than 5 times the half-life.

Test and reference products

The following Voriconazole Tablets 200 mg manufactured by Intas Pharmaceuticals Limited, India has been compared to reference product Vfend 200 mg film-coated tablets manufactured by Pfizer Manufacturing Deutschland GmbH.

Reference Product-R

Formulation:	VFEND® 200 mg film-coated tablets
Manufacturer:	Pfizer Manufacturing Deutschland GmbH
	Heinrich –Mack-Str.35 D-89257 Illertissen, Germany
Batch No:	910406431 H
Expiry Date:	08/2012
Measured content:	102.0%

Test Product-T

Formulation:	Voriconazole Tablets 200 mg
Manufactured by:	Intas Pharmaceuticals Limited, India
Batch No:	M12185
Manufacturing Date:	November 2011
Expiry Date:	October 2013
Storage Condition:	Store below 30°C
Measured content:	101.1%

Population(s) studied

Thirty-six (36) healthy, non-smoker/ex-smokers, male subjects were randomized into the study.

Mean age (± SD) of the thirty six subjects (men) was 28.1 ± 6.46 years; mean height 168.14 ± 5.839 cm; mean weight 63.68 ± 6.721 kg; and mean BMI 22.491 ± 1.7102 kg/m^2.
Two subjects dropped out from the study. Subject No.1015 withdrew from the trial on their own accord and subject no. 1010 was withdrawn from the trial on medical grounds on the check-in day of Period-II (pyrexia); in both cases after administration of the reference product. Thus, thirty-four (34) subjects completed both study periods entirely.

Analytical methods

A validation report for the method MV-436-11 with Addendum I are provided and dated on August 3, 2011 and on October 18, 2011, respectively. The validation is declared to be performed between June 24, 2011 and July 3, 2011 at the same site. Voriconazole-d3 was used as internal standard (IS).
Linearity was demonstrated within the calibration range 5.029 to 3004.759 ng/ml on a set of 8 standards. The range of precision and accuracy of the back-calculated concentrations of the standard curve points for voriconazole was from 0.7 % to 1.8 % and from 98.1 % to 101.6 %o respectively and correlation coefficient 0.9994 to 0.9998.
The bio analytical report 009-11 is provided and dated on March 16, 2012. A statement of compliance with GLP, protocol and SOP is presented. The bio analytical part of the study was conducted between February 22 and February 29, 2012. A total of nineteen (19) successful calibration curves were generated during study sample analysis (including 1 for repeats). The calibration range was from 5.043 ng/ml to 3004.460 ng/ml of voriconazole. The correlation coefficients were ≥0.9958.
Repeat sample analysis was performed on 0.7% of the total samples. The original value, repeat values and accepted value are listed for each individual repeat sample. No sample was repeated because of pharmacokinetic reason. Incurred sample analysis was performed and the results confirmed reproducibility.
The long term stability covering interval of storage of plasma sample has been demonstrated.
The relevant SOPs on sampling, validation of the analytical method, repeat analysis, and preparation of the calibration curve have been appended are in accordance with the Guideline on bio analytical method validation EMEA/CHMP/EWP/192217/2009.

Pharmacokinetic variables

The following pharmacokinetic parameters were observed or calculated for voriconazole:
AUC0-t, AUCinf, Cmax, AUC0-t /inf, Tmax, Kel, and T½.
As declared in the protocol, for claiming bioequivalence, the 90% geometric confidence intervals of the ratio (T/R) of least-squares means from the ANOVA of ln-transformed AUC0-t and Cmax should be within 80% to 125%.

Statistical methods

Based on the literature data, the intra-subject coefficients of variation of about 18% were considered. Thus, with these expected coefficients of variation and an expected ratio of AUC and Cmax within 90% and 110%, the study should have a power of at least 80% to show bioequivalence with 30 subjects. In order to account for possible dropouts, 36 subjects were included in the study.
ANOVA was carried out on ln-transformed $AUC_{0\text{-last}}$, $AUC_{0\text{-}\infty}$, C_{max} values. The sequence, treatment, subject effect (nested in sequence) and period were included in the model as fixed effect. Non parametric test was performed on T_{max}.

Results

Table 1. Pharmacokinetic parameters for Voriconazole (non-transformed values)

Pharmacokinetic parameter	Test		Reference	
	arithmetic mean	SD	arithmetic mean	SD
AUC(0-t)	12267.662	6359.4532	12524.128	5858.8368
AUC(0-∞)	13820.558	9050.6412	14049.517	8150.4825
Cmax	1889.858	655.4067	2050.223	621.1319
Tmax*	1.5	(0.5 - 4.0)	1.375	(0.5 - 4.0)

AUC0-t area under the plasma concentration-time curve from time zero to t hours
AUC0-72h area under the plasma concentration-time curve from time zero to 72 hours
AUC0-∞ area under the plasma concentration-time curve from time zero to infinity
Cmax maximum plasma concentration
Tmax time for maximum concentration (* median, range)

Table 2. Statistical analysis for Voriconazole (ln-transformed values)

Pharmacokinetic Parameter	Geometric Mean Ration test/reference	Confidence Intervals	CV%*
$AUC_{(0-t)}$	95.9	91.72-100.17	10.7
C_{max}	90.7	82.32 – 99.89	23.8

* estimated from the Residual Mean Squares

It is noted that the ANOVA analysis was independently applied by the assessor on AUCt, AUCinf and Cmax and the results were found identical.
The ratios and 90% CI of AUC0-t, AUCinf, Cmax ln-transformed values are within the limits of 80-125% as predefined.

Safety data

Two mild adverse events were reported, one with the test (pyrexia during washout phase) and the other with the reference product (white blood cell count increased).

Overall the two treatments are well tolerated. There are no new concerns arising from this study as the two products have similar safety profiles.

Conclusions

Based on the presented bioequivalence study Voriconazole Accord 200 mg film-coated tablets is considered bioequivalent with the reference VFEND® 200 mg film-coated tablet.

The bio waiver for the 50mg strength is approvable and the results of study Project No 009-11 with the 200 mg film-coated tablet formulation can be extrapolated to the other 50 mg strength , according to conditions in the Guidelines.

2.4.3. Pharmacodynamics

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

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. Conclusions on clinical aspects

Based on the presented bioequivalence study, the CHMP agrees that Voriconazole Accord 200 mg film-coated tablets is considered bioequivalent to the reference medicinal product VFEND® 200 mg film-coated tablets. In addition, the bio waiver for the 50mg strength is approvable and the results of the study can be extrapolated to the 50 mg strength.

The CHMP is therefore of the opinion that bioequivalence has been demonstrated and that the clinical aspects of Voriconazole Accord are satisfactory.

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.

Risk management plan

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

PRAC Advice

Based on the PRAC review of the Risk Management Plan version 2.0, the PRAC considers by consensus that the risk management system for voriconazole (Voriconazole Accord in the treatment, in adults and children aged 2 years and above, of invasive aspergillosis, candidemia in non-neutropenic patients, fluconazole-resistant serious invasive *Candida* infections (including C. krusei), serious fungal infections caused by Scedosporium spp. and Fusarium spp, is acceptable.

This advice is based on the following content of the Risk Management Plan:

Safety concerns

The applicant identified the following safety concerns in the RMP:

Summary of safety concerns	
Important identified risks	Hepatoxicity
	QTc prolongation
	Visual effects (including optic neuritis, papilloedema and other visual concerns)
	Phototoxicity
	Peripheral neuropathy
Important potential risks	Skin cancer (including squamous cell carcinoma)
	Suicide-related events

Summary of safety concerns	
	Effects in paediatrics
	Off-label use
	Drug Resistance
	Effects in pregnancy
Important missing information	none proposed

The PRAC agreed with the identified safety concerns by the applicant.

Pharmacovigilance plans

The PRAC, having considered the data submitted, was of the opinion that routine pharmacovigilance is sufficient to identify and characterise the risks of the product.

The PRAC also considered that routine PhV is sufficient to monitor the effectiveness of the risk minimisation measures.

Risk minimisation measures

No addition risk minimisation beyond SmPC labelling is proposed.

The PRAC, having considered the data submitted, was of the opinion that the proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication(s).

The CHMP endorsed the PRAC advice without changes.

PSUR submission

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list)) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines webportal.

User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the applicant and has been found acceptable for the following reasons: comparative tables are showing that the content, layout, design of the Patient Leaflet (PL) of Voriconazole Accord is in line with the reference product (Vfend) PL. The CHMP considers that it is acceptable.

3. Benefit-risk balance

This application concerns a generic version of Voriconazole Accord film-coated tablets. The reference product Vfend is indicated for “Treatment of invasive aspergillosis; Treatment of candidemia 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.

No non-clinical studies have been provided for this application but an adequate summary of the available non-clinical information for the active substance was presented and considered sufficient.

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.

The bioequivalence study forms the pivotal basis with a cross over design and performed under fasting conditions in healthy adults. The study design was considered adequate to evaluate the bioequivalence of this formulation and was in line with the respective European requirements. Choice of dose, sampling points, overall sampling time as well as wash-out period were adequate. The analytical method was validated. Pharmacokinetic and statistical methods applied were adequate.

The test formulation of Voriconazole tablets 200 mg met the protocol-defined criteria for bioequivalence when compared with the VFEND® 200 mg film-coated tablets. The point estimates and their 90% confidence intervals for the parameters AUC_{0-t},, $AUC_{0-\infty}$, and C_{max} were all contained within the protocol-defined acceptance range of 80 to 125%. Bioequivalence of the two formulations was demonstrated.

A benefit/risk ratio comparable to the reference medicinal product can therefore be concluded.

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 Accord in the treatment of invasive aspergillosis; treatment of candidemia 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 is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal products 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.