Decentralised Procedure

Public Assessment Report

Voriconazol Zentiva 50 mg / 200 mg Filmtabletten

Voriconazole

DE/H/3920/001-002/DC

Applicant: Zentiva k.s.
U Kabelovny 130
Dolni Mecholupy
10237 Prague

Reference Member State	DE

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ADMINISTRATIVE INFORMATION

Proposed name of the medicinal product in the RMS	Voriconazol Zentiva 50 mg Filmtabletten Voriconazol Zentiva 200 mg Filmtabletten
Name of the drug substance (INN name):	Voriconazole
Pharmaco-therapeutic group (ATC Code):	Antimycotics for systemic use, triazole derivatives (J02AC03)
Pharmaceutical form(s) and strength(s):	Film-coated tablet; 50 mg and 200 mg
Reference Number(s) for the Decentralised Procedure	DE/H/3920/001-002/DC
Reference Member State:	DE
Concerned Member States:	CZ, ES, FR, PL, PT, RO, UK
Applicant (name and address)	Zentiva k.s. U Kabelovny 130 Dolni Mecholupy 10237 Prague

I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the application for *Voriconazol Zentiva 50 mg / 200 mg Filmtabletten*, indicated in adults and children aged 2 years and above for the treatment of invasive aspergillosis, candidemia in non-neutropenic patients, fluconazole-resistant serious invasive *Candida* infections (including *C. krusei*) and serious fungal infections caused by *Scedosporium* spp. and *Fusarium* spp., is approved.

II. EXECUTIVE SUMMARY

II.1 Problem statement

For generic application this section is not applicable.

II.2 About the product

Voriconazole is a broad spectrum, triazole antifungal agent and is indicated in adults and children aged 2 years and above in the following indications:

- 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

Voriconazole should be administered primarily to patients with progressive, possibly life-threatening infections.

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. Voriconazole is active against a wide range of yeasts and filmentous fungi, including *Aspergillus, Candida, Fusarium and Scedosporium.*

The pharmacokinetics of voriconazole are non-linear due to saturation of its metabolism and have been characterised in healthy subjects, special populations and patients.

II.3 General comments on the submitted dossier

These are article 10(1) generic marketing authorisation applications for Voriconazole Zentiva 50 and 200 mg film-coated tablets. As reference medicinal products which have been authorised for not less than 6/10 years in the EEA, Vfend 50 and 200 mg film-coated tablets, Pfizer Limited, UK are declared. The marketing authorisations of these reference products were granted in 2002 as centralised procedure.

The applicant Zentiva k.s., Czech Republic claims similarity to the originator/reference product Vfend (voriconazole) film-coated tablets (50 mg or 200 mg).

To support the application, the applicant has submitted as report a single dose bioequivalence study with Voriconazole Zentiva 200 mg film-coated tablets against the German innovator Vfend® 200 mg film-coated tablets.

No Scientific Advice was sought and no paediatric development programme is available, which is acceptable and not required for a generic application.

A biowaiver was requested by the applicant for the lower strength of 50 mg Zentiva tablets based on the requirements as laid down in the *Guideline on the Investigation of Bioequivalence, Doc. Ref.:CPMP/EWP/QWP/ 1401/98 Rev.*

II.4 General comments on compliance with GMP, GLP, GCP and agreed ethical principles

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the Community, the RMS has accepted copies of current GMP Certificates of satisfactory inspection summary reports, 'close-out letters' or 'exchange of information' issued by the inspection services of the competent authorities (or those countries with

which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.
Regarding the clinical studies, the applicant stated that the studies have been conducted according to the guidelines on GCP and to the principles of GLP as well as to the ethical principles of the Declaration of Helsinki and the U.S. Code of Federal Regulations (Title 21, Part 56), the Directive 2001/20/EC (Europe) and the Tri-Council Policy Statement (Canada).
Quality assurance documents were provided.

III. SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 Quality aspects

Drug substance

The drug substance is a compendial substance. The documentation of the drug substance manufacturer is provided as CEP. The manufacturing process of the drug substance (including synthesis, purification, amounts of raw materials and yields) is adequately described. The structure of the substance is sufficiently characterised. Potential impurities (related substances, residual solvents, etc.) arising from the manufacturing process are identified. The drug substance specification provided complies with the Ph. Eur. monograph "Voriconazole". Additional requirements for residual solvents are set. Batch analysis results showing the compliance with the drug substance specification are given. Based on the provided stability results over 6 months at accelerated and 24 months under normal conditions the proposed re-test period of 2 years is justified.

Drug Product

The drug products are film-coated tablets containing 50mg and 200 mg voriconazole. The drug product is packaged in PVC/Al blisters. The pharmaceutical development is described. Comparative dissolution profiles between the 200 mg biobatches of the Voriconazole Zentiva 200 mg tablets and of the reference product Vfend are presented at three pH values 1.2, 4.5, and 6.8. In addition, the similarity of dissolution profiles between 50 mg drug product batches against the 200 mg biobatch of the drug product used in the bioequivalence study has been shown at three pH values 1.2, 4.5, and 6.8. The manufacturing process including flow chart is adequately documented. Process validation schemes of all batch sizes have been provided. Each of the excipients except the dye complies with respective Ph. Eur. monographs. Information given for the dye is sufficient. The release and shelf life specifications contain all parameters appropriate for this pharmaceutical form. All analytical control methods are adequately described. Validation studies for analytical methods are provided. Batch analysis data are given showing compliance with set specifications. Quality of packaging materials has been sufficiently proven. Based on the provided stability data for each of the strengths a shelf life of 18 months is accepted.

III.2 Non-clinical aspects

Pharmacodynamic, pharmacokinetic and toxicological properties of voriconazole are well known. As voriconazole is a widely used, well-known active substance, the applicant has not provided additional studies and further studies are not required. Overview based on literature review is, thus, appropriate.
The non-clinical overview refers 38 publications up to the year 2013.

Environmental Risk Assessment (ERA)

Since the product is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.3 Clinical aspects

The clinical overview refers to 59 articles from the year 1997 to 2013.
The applicant has conducted a single dose bioequivalence study with voriconazole 200 mg tablets.

Study code: VRL-P2-621

The study was a single center, randomized, single dose, laboratory-blinded, 4-period, 2-sequence, replicate, crossover design in healthy male subjects. The study was conducted under fasting conditions on thirty (30) healthy male subjects. The rate and extent of absorption of voriconazole were measured and compared following a single dose (1 x 200 mg) of either the Test or the Reference formulations on day 1, day 8, day 15 and day 22.

Thirty healthy, male subjects, aged 25 - 75 years, were randomized and dosed in the trial.
29 subjects completed the crossover design and received a single oral dose of the assigned formulation on day 1, day 8, day 15 and day 22.
A validated analytical method was used for the determination of voriconazole in human plasma.

Results:
Based on the pharmacokinetic parameters of voriconazole, the test product voriconazole 200 mg tablets and the reference product (voriconazole 200 mg manufactured by Pfizer Ltd., Germany) is considered bioequivalent. The 90% confidence intervals derived from the analyses of the pharmacokinetic parameters for voriconazole in plasma are within the 80-125% acceptance range for AUC_{0-t} and C_{max} (see table 1 below).

Table 1: Bioequivalence comparison of test and reference products

PARAMETER	INTRA-SUBJECT C.V. (%)	GEOMETRIC LSMEANS *		RATIO (%)	90% CONFIDENCE LIMITS (%)	
		TEST	REFERENCE		LOWER	UPPER
C_{max}	29.9	1321.6	1301.9	101.52	92.82	111.03
AUC_T	16.2	4809.7	4757.9	101.09	96.21	106.21

* units are ng/ml for C_{max} and ng·h/ml for AUC_T

The request for a biowaiver for the lower strength of the 50 mg voriconazole formulation is acceptable. All the five criteria for biowaiver as stated in the guideline are fulfilled. There are no quality issues in the comparative dissolution testing.

Safety evaluation
The severity of adverse events ranged from mild to severe. One (1) severe adverse event (Reference: accidental injury) was observed during the study. Of all adverse events, none were unexpected and reasonably possibly related to the administration of the (Test or Reference) products.

The required dissolution profiles for justifying the biowaiver for the lower strength were presented. Similarity of the dissolution profiles could be demonstrated at different pH according to the requirements as laid down in the 'Note for the guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98)'.

Pharmacokinetics
The pharmacokinetic properties of voriconazole are well-known. They are adequately described in the relevant section of the SmPC regarding healthy subjects as well as specific target population.

Pharmacodynamics
There are no new data. The pharmacodynamic profile of voriconazole is well characterized in literature and adequately presented in the relevant section of the SmPC.

User Testing
The submitted Readability Test complies with Article 59(3) of Directive 2001/83/EC which requires the package leaflet 'to reflect the results of consultations with target patient groups to ensure that it is legible, clear and easy to use'. The results meet the success criteria where in each round of testing at least 8 out of 10 subjects are able to answer each questions correctly.
The results indicate that the final version of the submitted Pl can be considered as user friendly.

Summary Pharmacovigilance system
The Applicant/Proposed Future MAH has submitted a signed Summary of the Applicant's/Proposed Future MAH's Pharmacovigilance System. Provided that the Pharmacovigilance System Master File

fully complies with the new legal requirements as set out in the Commission Implementing Regulation and as detailed in the GVP module, the RMS considers the Summary acceptable.

Risk Management Plan

Summary of safety concerns	
Important identified risks	• Hepatic toxicity • QTc prolongation • Visual events (including optic neuritis, papilloedema and other visual concerns) • Phototoxicity • Peripheral Neuropathy • Squamous cell carcinoma (SCC)
Important potential risks	• Skin cancer (non-SCC) • Suicide-related events • Off-label use • Drug resistance
Important missing information	• Safety in pregnancy • Safety in paediatrics

The applicant has provided an RMP within the new format of GVP module V. The applicant has generated a list of important safety concerns (i.e. important identified risks, potential risk and missing information) based on information provided in sections 4.3-4.6 of the SmPC. The RMP is approved.

Periodic Safety Update Report (PSUR)
With regard to PSUR submission, the MAH should take the following into account:

- For medicinal products authorized under the legal basis of Article 10(1) or Article 10a of Directive 2001/83/EC, no routine PSURs need to be submitted, unless otherwise specified in the EURD list.

IV. BENEFIT RISK ASSESSMENT

The applications contain an adequate review of published non-clinical and clinical data. Bioequivalence could be demonstrated for the 200 mg formulations as applied for. The requested biowaiver for the 50 mg formulation as applied for is justified and can be accepted.
The pharmacology, pharmacokinetics and toxicology of the active substance are sufficiently known. The sought indications are similar to those approved in Germany for the market leader. Thus the benefit/risk balance of these generic voriconazole formulations can be considered similar to that of the reference product.
The benefit/risk assessment is considered positive.
The application is approved.
For intermediate amendments see current product information.