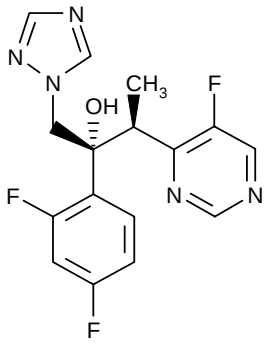
SCIENTIFIC DISCUSSION

This module reflects the initial scientific discussion for the approval of Vfend. For information on changes after approval please refer to module 8B.

1. Introduction

This centralised procedure concerns Vfend film-coated tablets and powder for solution for infusion (10 mg/ml after reconstitution) with the new active antimycotic substance voriconazole. This new systemic antimycotic agent is a triazole derivative.



voriconazole

A new excipient sulphobutylether beta-cyclodextrin sodium (SBECD) is used in the parenteral formulation to enhance the solubility of voriconazole. Voriconazole is complexed with SBECD and the concentration of SBECD in the reconstituted voriconazole solution for injection is 160 mg/ml

The approved indications include:

- 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.

Posology:

	Intravenous	**Oral**	
		Patients 40 kg and above	Patients less than 40 kg
Loading Dose Regimen (first 24 hours)	6 mg/kg every 12 hours (for the first 24 hours)	400 mg every 12 hours (for the first 24 hours)	200 mg every 12 hours (for the first 24 hours)
Maintenance Dose (after first 24 hours)	4 mg/kg twice daily	200 mg twice daily	100 mg twice daily

Voriconazole is a novel triazole antifungal agent shown to have *in vitro* activity against *Aspergillus* and *Candida* species. Voriconazole represents a therapeutic alternative especially with regard to amphotericin B characterised by a nephrotoxicity of concern in clinical practice.

2. Part II: Chemical, pharmaceutical and biological aspects

Composition

Film-coated tablets:

Voriconazole is presented as immediate release - white film-coated tablets (debossed "Pfizer" on one side and "VOR50" or "VOR200" as appropriate on the reverse) available in two strengths, 50 mg and 200 mg. The tablet core contains lactose monohydrate, pregelatinised starch, croscarmellose sodium, povidone and magnesium stearate. The tablet core is coated with an Opadry aqueous film coat which consists of hypromellose, titanium dioxide (E171), lactose monohydrate and glycerol triacetate. Tablets are packaged in either PVC blisters with aluminium lidding foil or HDPE bottles.

Powder for solution for infusion:

Voriconazole is also presented as a lyophilised sterile powder for solution for infusion to be reconstituted and diluted prior to administration. There is only one parenteral presentation, a vial containing 200mg voriconazole, equivalent to a 10mg/ml solution when reconstituted. The powder for solution for infusion consists of voriconazole and SBECD.

Each vial has an overfill of 1.13 ml to allow an extractable volume of 20 ml, corresponding to 200 mg voriconazole, when reconstituted. After reconstitution with 19 ml water for injections, the resultant solution contains 10 mg voriconazole per ml.

This parenteral product is presented as a powder in clear colourless Type I glass vials (30 ml capacity) closed with siliconised chlorobutyl-isoprene stoppers and sealed with polypropylene/aluminium overseals.

Active substance

The active substance, voriconazole, is (2R,3S)-2-(2,4-difluorophenyl)-3-(5-fluoro-4-pyrimidinyl)-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol (laboratory code UK-109,496). The structure of voriconazole has been confirmed by combustion analysis, MS, IR, ^{1}H NMR, ^{13}C NMR and ^{19}F NMR, single crystal X-ray crystallography. It is a weak base, is not hygroscopic and is classified as a low solubility, high permeability compound. Voriconazole is a crystalline powder. Investigations into its solid-state properties revealed no evidence of either polymorphism or solvates.

Voriconazole is produced by organic synthesis.

Satisfactory control specifications are provided for the active substance, starting materials, key intermediates, reagents and solvents.

All analytical methods have been submitted as well as validation data, in accordance with the relevant Note for Guidance.

Based upon the qualification limits for the specified impurities the specification is acceptable, although specification requirements may be tightened or justified once full-scale batches of drug product have been produced.

Batch analysis results of more than twenty commercial scale batches produced at the three proposed production sites confirm satisfactory uniformity and compliance with the specification.

The stability of voriconazole has been examined under a variety of stress testing conditions. Degradation occurs in aqueous solution, particularly under basic conditions. Photodegradation takes place under severe light stress conditions. Oxidative degradation also takes place. The degradation products have been identified.

Real-time and accelerated stability studies have been performed on voriconazole. No significant changes in any parameter were observed. The proposed retest period of 3 years is justified.

Other ingredients

Film-coated tablets:

The excipients are conventional and all comply with the appropriate monographs and specification requirements of the current PhEur except for the proprietary film-coating (Opadry). However, all the components of the Opadry powder comply with their respective current PhEur Monographs.

Lactose monohydrate is classified as a Category IV excipient in the CPMP Note for Guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via medicinal products CPMP/BWP/1230/98. The applicant states that all other ingredients including the magnesium stearate are of vegetable or of synthetic origin and do not contain any material of bovine ovine or caprine derivation.

Satisfactory control specifications are provided for the primary packaging materials for both the blisters and bottles.

Powder for solution for infusion:

The other ingredients used in the manufacture of the parenteral product are water for injections and nitrogen that is used prior to stoppering. The water for injections and the nitrogen comply with the current relevant PhEur monographs.

SBECD is a new excipient and data have been submitted in accordance with the Note for Guidance 'Excipients in the dossier for application for Marketing Authorization of a Medical Product'. SBECD is a derivative of beta-cyclodextrin and is a chiral molecule composed of seven α-D-glucopyranose units. The stereochemistry is maintained during derivatization of the starting material beta-cyclodextrin.

The synthesis of SBECD, from beta-cyclodextrin and 1,4-butane sultone is described. All the specifications, in-process controls and analytical methods (with their associated validation) are satisfactory. Several techniques were used to determine the structure of SBECD.

The limits proposed for the impurities are justified by reference to batch and toxicological data.

The applicant has committed to attempt to find an alternative route of synthesis for SBECD, in order to avoid the presence of 1,4 butane sultone in SBECD. Meanwhile, the limit for 1,4-butane sultone will be reduced to less than 1 ppm. Should an alternative route of synthesis not be possible, alternative formulations will be considered after discussion with CPMP. Additionally, batch analyses data for the first three production batches of SBECD, and associated stability data, will be provided when these data become available.

A 3-year retest period has been proposed and justified for SBECD in the specified packaging.

The primary packaging for Vfend powder for solution for infusion consists of 30 ml clear, colourless, Type I glass vials with grey siliconised chlorobutyl-isoprene rubber stoppers and overseals consisting of flip-off polypropylene caps and aluminium lacquered seals. Satisfactory control specifications are provided.

<u>Product development and finished product</u>

Film-coated tablets:

Several formulations were produced during the development, which led to the tablet composition. The manufacturing process has been well described and the critical process parameters identified. In-process controls are described and justified. The manufacturing process is typical for a wet granulated film-coated formulation. Both tablet strengths are manufactured from the same granulate (common blend). A typical batch size is 150 kg. Validation data from the first three production batches will be provided.

All specifications are acceptable. All the methods of analysis are satisfactorily described and validated, in accordance with the relevant Notes for Guidance.

Batch analyses data have been provided for batches ranging from laboratory to pilot production scale. These data demonstrate both compliance with the proposed specifications and consistency of manufacture. After granting a Marketing Authorisation the batch analysis data of the first three full production scale batches for each strength should be submitted.

Powder for solution for infusion:

Voriconazole is a weak base and only slightly soluble in water over the acceptable pH range. By forming inclusion complexes with derivatised cyclodextrins (SBECD) the target solubility was reached that had not been possible with conventional pharmaceutical approaches.

SBECD was used at a minimum concentration to achieve a balance between maintaining the target voriconazole solubility of 10 mg/ml at 4°C, required to underwrite refrigerated storage after reconstitution, ease of reconstitution and resultant solution viscosity. The compatibility of the chosen formulation with SBECD and voriconazole has been demonstrated by stability studies in accordance with the ICH guidelines. Because of stability limitations a ready to use aqueous solution of voriconazole is not feasible and therefore a lyophilised powder for infusion has been developed that is manufactured using an aseptic manufacturing process employing a microbial retentive filter. To ensure the label claim an overfill of 1.13 ml is provided.

Manufacturing process development has taken place. The process is typical for products of this type. The lyophilisation cycle has been studied extensively. Four batches at approximately 65% of the intended scale have been successfully manufactured at the proposed production site. As the batch sizes examined were not at the proposed full production scale, further validation data on the first three production batches will be required.

After reconstitution with 19 ml water for injections, the product contains 10 mg/ml voriconazole and 160 mg/ml SBECD. The chemical stability after reconstitution has been studied: the solution is physically and chemically stable for 48 hours at 25ºC. The product should be further diluted in a suitable diluent prior to infusion. Compatibility studies have been presented for a range of diluents. The studies revealed an incompatibility with parenteral nutrition (e.g. Aminofusin 10% Plus) and 4.2% Sodium Bicarbonate. In the SPC the use of these diluents is not recommended. The compatibility of the diluents mentioned in the SPC has been proven.

In-process controls have been justified.

The acceptance criteria for the impurities are based upon the criteria for impurities in the drug substance and the degradation during the manufacturing process and are consistent with the qualification threshold stipulated in the ICH Guideline Q3B "Impurities in New Drug Products". The limit for bacterial endotoxins has been calculated for the maximum infusion rate 3 mg/kg/hour. With the threshold value 5 endotoxins/kg/hour the endotoxin limit concentration 1.67 IU/mg is acceptable. All specifications are justified and acceptable. The methods of analysis are submitted and have been validated in accordance with the relevant Notes for Guidance. Data from the manufacture of thirteen batches at Madaus, Germany and from the manufacture of four batches at Catalytica, USA have been submitted. All batches fulfilled the specification requirements. After granting a Marketing Authorization the batch analysis data of the first three batches on full production scale should be submitted.

Stability of the Product

Film-coated tablets:

The claimed shelf-life of 24 months without any special storage conditions is justified. The applicant has committed to monitor the stability of the first three production scale batches.

Powder for solution for infusion:

The end-of shelf-life specification is identical to the release specification except for the limits for degradation products. This is justified.

Apart from a small increase of some degradation products, no changes in any parameter at any condition were observed. The claimed shelf-life of 24 months without special storage conditions is justified. The applicant has committed to monitor the stability of the first three production-scale batches.

The stability of the reconstituted solution has been studied at 5ºC and at ambient conditions, in both the dark and in ambient light for 48 hours in an inverted position. Physical and chemical stability parameters were tested. No significant changes (including any racemisation) were observed. The drug product solution has also been analysed for extractables from the closures and no significant changes were found. The reconstituted product is demonstrated to be stable for up to 24 hours at 5ºC and at ambient conditions, as defined in the SPC.

3. Part III: Toxico-pharmacological aspects

With the exception of some exploratory and pilot studies, the investigations reported in Part III of the dossier conformed to GLP standards.

Pharmacodynamics

Voriconazole is a broad-spectrum antifungal agent with potent *in vitro* activity against the primary opportunistic pathogens: *Aspergillus spp.*, *Candida spp.* and *Cryptococcus spp.*, fluconazole-resistant strains of *C. albicans*, as well as other *Candida spp.* which are inherently less sensitive to fluconazole *(e.g. C. krusei and C. glabrata*). Voriconazole is also active against a wide range of less common pathogens, including organisms that are resistant to fluconazole, itraconazole and amphotericin B *(e.g. Fusarium spp., Scedosporium inflatum, Acremonium kilensii, Trichosporon spp).* Furthermore, it is fungicidal for *Aspergillus spp.* The activity of the circulating N-oxide metabolite of voriconazole against a range of fungal pathogens was 100-fold less than that of voriconazole.

Consistent with its potency *in vitro*, voriconazole is highly effective *in vivo* against systemic and pulmonary aspergillosis, systemic candidosis and pulmonary and intracranial cryptococcosis, in both immune normal and immunocompromised guinea pigs.

SBECD is devoid of antifungal activity against a wide range of fungal pathogens *in vitro* and in animal models of systemic candidosis. When combined with voriconazole, it had no effect on the antigungal activity of the latter either *in vitro* or *in vivo*.

In anaesthetised dogs, voriconazole caused cardiac arrhythmia in one dog at plasma levels 7 times the maximal therapeutical levels and slight, probably irrelevant, dose-related prolongations in QT interval at plasma levels partly within the therapeutical range. Voriconazole had no effect on *in vitro* assays which may be predictive of effects on cardiac repolarisation. Voriconazole did not affect the respiratory system. Voriconazole had no effect on renal function following oral doses up to 10 mg/kg. A small reduction in the excretion of potassium ions was observed following 30 mg/kg i.v., but this was not associated with any other changes in renal function. Voriconazole induced reversible visual disturbances (blurred vision) in patients. Studies in dogs indicated that the primary site of action was the retina and that these effects were observed at therapeutically relevant plasma levels. No histopathological effects were observed.

Pharmacokinetics

Pharmacokinetics of voriconazole were characterised by gender dependence in rat with higher plasma concentrations and AUC values in female compared with male rats. No sex difference was observed in the dog. In rabbits, the elimination profile was log-linear with an elimination half-life of 1.7h.

The increase in plasma exposure was more than dose proportional in guinea pig (dog to lesser extent) and rat following single exposure, but not in rat after multiple dosing. Consequently, plasma clearance and volume of distribution data are of limited utility, being specific to the dose level used. Apparent volume of distribution values, generally greater than total body water (approx. 0.8 l/kg), indicate that voriconazole has some tissue affinity, in keeping with its moderately lipophilic nature.

Multiple dose administration of voriconazole resulted in a decrease in plasma exposure in rat and mouse and to lesser extent in dog and guinea pig due to autoinduction of metabolism. In contrast, in rabbit and in immunocompromised guinea pig, multiple administration resulted in higher systemic exposure than would be expected from single dose data. Accumulation of voriconazole occurred in dog following multiple administration at high (and toxic) dose levels.

The plasma exposures in rat and dog at the no observed adverse effect level (NOAEL) were lower than or similar to those at the standard maintenance doses in humans and lower than those at the maximal maintenance doses in humans.

Absorption of voriconazole from the gastrointestinal tract is likely to be high in all species since the apparent oral bioavailability is >75% in all species. Voriconazole penetrates the CNS and CSF well. Studies in guinea pig indicate complete transfer of the free fraction of voriconazole in plasma across the blood-CSF barrier. Following administration of radiolabelled voriconazole to rats, there were no sites of accumulation or prolonged retention of radioactivity. Distribution was not studied in pregnant animals.

Voriconazole is eliminated predominantly by metabolism. Metabolites were found not to show any pharmacological activity. The major primary route of metabolism in human involved fluoropyrimidine N-oxidation to form metabolite UK-121,265. Biotransformation of voriconazole in toxicology species was similar. Overall, whilst there were minor species differences in the relative amounts of excreted metabolites, all of the major pathways of voriconazole metabolism in human are represented in laboratory animals. From *in vitro* studies with human microsomes it was concluded that voriconazole is metabolised by CYP2C9, CYP2C19 and CYP3A4. The metabolite UK-121,265 has been shown to have inhibitory potency against CYP2C9, CYP2C19 and CYP3A4, which is similar to or less than that of voriconazole. The potential of voriconazole to interact with concomitant medications has led to the instigation of an extensive clinical pharmacology drug interaction programme which is detailed in part IV. The predominant route of excretion in rat, rabbit and dog was the urine whereas in mouse and guinea pig the faeces contained a slightly higher proportion of the dose than the urine. Unchanged voriconazole recovered in excreta was less than 10% of total dosed radioactivity in all species. In all species, more than 92% of excreted radioactivity was recovered within 120h (majority within first 48h).

For SBECD, AUC-values following single i.v. dosing in dog and male rat increased superproportionally at the highest doses. However, dose proportional increases are expected to occur in humans since SBECD dosed to humans resulted in much lower plasma exposure. SBECD is not metabolised and the pattern of distribution of the radioactivity was consistent with its presence in the vasculature, with very little penetration in tissues. Distribution was not studied in pregnant animals. In all cases, the excretion was rapid and essentially via renal elimination.

Toxicology

Dose ranges in toxicity studies were limited due to toxicity at the high doses. Generally, systemic exposures at the high doses in repeated dose toxicity studies were comparable to systemic exposure in humans with the maximal therapeutic doses.

The clinical signs observed in rodents [mydriasis, titubation (loss of balance when moving), depressed behaviour, prostration, rigid extended limbs, partially closed eyes and dyspnoea] at intravenous doses of 50 mg/kg and above and at oral doses of 100 mg/kg and above suggest high acute doses of voriconazole mainly affect the central nervous system.

Repeat-dose oral studies in rats, mice and dogs have shown the liver to be the main target organ, with a range of adaptive and functional changes: Increases in liver weight, centrilobular hypertrophy, proliferation of smooth endoplasmic reticulum and induction of cytochrome P450 appeared in a dose-related fashion. When administered orally to dogs for up to 1 month, voriconazole had no effect on transaminase activities, except at the toxic dose of 24 mg/kg, where increases in ASAT and ALAT accompanied systemic toxicity. Longer exposure to voriconazole in the 6- and 12-month studies at 12 mg/kg produced evidence of hepatotoxicity (single cell necrosis, increases in plasma ALAT and alkaline phosphatase). Transient severe clinical signs at 10 mg/kg limited the high dose in intravenous studies in dogs to 6 mg/kg. In these studies, adaptive liver response were seen from 1 mg/kg i.v, however no hepatotoxicity was noted.

In rats and dogs the adaptive changes were reversible after withdrawing the treatment. The hepatotoxic effects of voriconazole seen in animals at systemic exposures comparable to the human therapeutic levels of exposure are a serious safety concern for the use of voriconazole in humans.

Comparison of systemic exposures of voriconazole at the NOAELs in the repeat-dose toxicity studies with systemic exposure at the maximal human therapeutic doses showed that no margin of safety could be established. It was concluded that, based on the preclinical data, toxicity notably in the liver and possibly in the kidney may be expected in humans at therapeutic doses. Furthermore, adrenal changes may occur due to changes in hormone metabolism and anaemic effects may be encountered. In the repeated dose toxicity studies no histopathological changes were noted that would indicate damage of the retina. The only finding was a slight reduction of the number of outer nuclear layers of the peripheral retina of the high dose females in the rat oncogenicity study.

For SBECD no effects in rodents were observed after a single intravenous dose of SBECD 2000 mg/kg. After repeated dosing in rats and dogs, foamy macrophages in a variety of organs but predominantly in liver and lungs were observed. In addition, vacuolation occurred in renal tubular

cells, the urinary tract and hepatocytes, the kidney being more sensitive than the liver in both species. In both rats and dogs, continued SBECD treatment for 6 months showed no progression of either renal histological findings or functional changes, indicating that SBECD contains low (if any) toxicological potential. For SBECD, safety margins calculated by means of the MTED approach were very low.

The main adverse effects of voriconazole noted in reproduction studies in rats were dystocia, difficulties during delivery leading to maternal death and decrease of litter size and survival of pups, and teratogenicity, notably cleft palate and visceral anomalies in the renal area. Voriconazole was not teratogenic in rabbits, but became embryotoxic at 100 mg/kg. As in the repeat-dose studies, the systemic exposure at the developmental NOAELs was lower than systemic exposure at the intended human therapeutic doses. Therefore no margin of safety for developmental toxicity could be established. SBECD did not impair fertility in rats of either sex. It was devoid of teratogenic potential and did not impair pre- or postnatal development of pups.

A standard battery of genotoxicity tests was carried out and it was concluded that voriconazole does not pose a genotoxic hazard. The sponsor has committed to further elucidate the genotoxic potential of the fluoropyrimidinedihydroxy metabolite.

The carcinogenic potential of voriconazole was assayed in rats and mice by administration through the diet for 24 months. In the carcinogenicity studies and the repeat dose studies it has been shown that the liver is a target organ for voriconazole toxicity. Adaptive changes occur at lower doses, consisting of enzyme induction, proliferation of smooth endoplasmic reticulum, centrilobular hypertrophy and fatty changes. At higher doses single cell necrosis and cellular alteration are found. Ultimately, this stimulation leads to the formation of neoplasms in the liver. This is a well-known mechanism occurring in rodents, following the chronic administration of enzyme-inducers. Therefore, these studies do not indicate a risk for carcinogenicity by voriconazole in humans.

There is no carcinogenicity data on the excipient SBECD. The impurity 1,4-butane sultone, which is present in SBECD, has been shown to be an alkylating mutagenic agent with evidence for carcinogenicity in rodents. The applicant has committed to attempt to find an alternative route of synthesis for SBECD, in order to avoid the presence of 1,4 butane sultone in SBECD. This issue has been addressed in section 5.3. of the SPC.

Local tolerance studies in rats and rabbits only showed slight conjunctival irritancy in eye irritancy tests in rabbits. SBECD elicited reversible transient mild conjunctival irritation in the eyes of rabbits. No antigenicity of voriconazole was found in guinea pigs.

4. Part IV: Clinical aspects

This application for marketing authorisation presents data from 48 Phase 1 studies and a total of 18 clinical trials Phase 2-3 or compassionate use programmes. In addition, data are also presented for patients from six Phase 1 studies conducted in Japan.

The intravenous formulation of voriconazole contains a novel excipient, sulphobutylether beta-cyclodextrin sodium (SBECD), used to solubilise voriconazole. Details of the safety and pharmacokinetics of SBECD are provided. This excipient does not have any intrinsic antifungal activity.

Clinical pharmacology

Pharmacodynamics

Voriconazole is a broad-spectrum anti-fungal agent that shows activity against a wide range of yeasts and filamentous fungi, including *Candida* spp., *Cryptococcus neoformans* and *Aspergillus* spp. *In vitro*, mean voriconazole MICs for the key Candida species were 0.05mcg/ml for *C. albicans*, 0.38mcg/ml for *C. glabrata* and 0.29mcg/ml for *C. krusei*. Voriconazole was more efficacious than fluconazole and itraconazole in neutropenic animals infected with fluconazole-resistant strains *of C. albicans, C. krusei* and *C. glabrata*.

In vitro it is 10 to 5000-fold more potent than fluconazole and exhibits both fungicidal (MFCs in the range 0.78-1.0mcg/ml) and fungistatic activities (with MICs in the range 0.19-0.50mcg/ml) against *Aspergillus* spp. (see Preclinical Mycological Properties).

PK/PD analysis did not detect any relationship between plasma levels of voriconazole and efficacy, in terms of successful treatment of fungal infection. The recommended dosage regimen resulted in a successful outcome in the majority of patients with invasive aspergillosis but less so in patients with *Scedosporium* or *Fusarium* infections or in patients with refractory invasive candidiasis. Comparison of MIC with clinical outcome, as well as MIC with clinical outcome plus the mean voriconazole plasma concentration for each treated patient did not reveal any obvious relationship between these parameters. For instance, the MICs of some isolates even exceeded the voriconazole mean plasma concentration (notably some patients with *C.tropicalis* infection & *Fusarium* isolates) and yet these patients had successful outcomes. Successful outcomes at end of treatment were observed at a similar rate over a range of mean plasma concentrations between 0.5mcg and 5mcg/ml. With the current analysis of pharmacokinetics and pharmacodynamics, therefore, plasma levels do not predict successful outcome.

Although a relationship between plasma levels and aspects of toxicity was seen, specific guidance for the physician is not readily apparent based on a plasma level determination of voriconazole.

Resistance: Mechanism Studies with *Saccharomyces cerevisiae, C.albicans* and *C.glabrata* have demonstrated that there are three mechanisms of azole resistance: mutations in the target enzyme, cytochrome P450-dependent 14-alpha sterol demethylase (SD); changes in 5-6 sterol desaturase which compensate for the inhibition of SD by azoles; and the expression of multi-drug resistance efflux pumps.

(Cross-)resistance. A significant number of the organisms tested by the Applicant show decreased susceptibilities to fluconazole, including *C.albicans* and *C.neoformans* strains which have acquired resistance, and various *Candida* non- *albicans* spp. and *Trichosporon* spp. which are intrinsically resistant to fluconazole (geometric MICs range from 12.5 to 71mcg/ml). These organisms also show reduced susceptibility to voriconazole and itraconazole consistent with common mechanisms of azole resistance. However, voriconazole still retains potent antifungal activity, with MICs below 1mcg/ml against these pathogens.

For those voriconazole-treated patients from the clinical studies for whom a sequence of fungal isolates was available, there was no evidence for a systematic decrease in susceptibility during therapy (as manifested by an increase in the 48 hour MIC of greater than 2 doubling dilutions) with time of exposure to voriconazole. Indeed, such a significant decrease was recorded in only 2 patients. In one patient with a *C.albicans* oropharyngeal infection this decreased susceptibility correlated with a failed clinical outcome (MIC increase from 0.006mcg/ml to 0.78mcg/ml). The other patient had a *C.glabrata* infection, which responded to therapy despite the MIC increasing from 0.049mcg/ml to 3.1mcg/ml. The mean voriconazole plasma concentration for this patient was 4.5mcg/ml.

For fluconazole-treated patients in oesophageal candidiasis protocol 150-305, correlation of the fluconazole MICs for all *Candida* isolates was analysed. A comparison with the corresponding voriconazole MICs for these same isolates indicated that voriconazole was some 30- to 200-fold more potent *in vitro* than fluconazole. In addition, there was a tendency for the voriconazole MICs to increase in parallel with the increase in fluconazole MICs of the three fluconazole breakpoint groups. However, despite these parallel increases, all isolates had MICs within the range established for the successfully treated voriconazole patients in protocol 150-305.

The applicant has committed to monitor development of acquired resistance after marketing and further to gather world-wide surveillance *in vitro* data to assist with resistance and break-point setting.

Pharmacokinetics

Forty-three studies were submitted in which human pharmacokinetics of voriconazole were evaluated:

- 6 single dose studies in healthy volunteers (150-202, -204, -207, -213, -226, VRC-JP-96-502)
- 6 repeated dose studies in healthy volunteers (150-205, -214, -227, -230, VRC-JP-96-503, VRC-JP-97-501)
- 1 study using 14C-labelled voriconazole (150-220)
- 3 food interaction studies (150-217, -222, VRC-JP-96-501)

- 15 pharmacokinetic interaction studies (150-001, -210, -228, -229, -233, -235, -236, -239, -240, -241, -243, -244, -247, A1501009, A1501013).
- 6 studies with special patient groups (150-237, -238, -249, -250, A1501012, 95CK39-0673)
- 6 bioavailability/bioequivalence studies (150-203, -224, -232, -245, -248, A1501005)

Voriconazole is a single enantiomer ((-)-voriconazole). After *in vivo* administration of (-)-voriconazole, no conversion of (-)-voriconazole into (+)-voriconazole was observed. After single oral dosing of voriconazole, AUC and Cmax increased not dose proportionally over the studied dose range of 100 to 400 mg. The coefficient of variation for AUC and Cmax is high (up to 100%). The elimination half-life at 400 mg was more than doubled compared with the 100 mg dose. Saturation of metabolism is the main responsible factor. Also after IV dosing non-linear pharmacokinetics are observed. AUC increased more than dose proportional, whereas the total body clearance decreased at higher doses. The decline in plasma concentrations was in general biphasic.

After multiple dosing (oral 200 mg bid, IV 3 mg/kg bid) steady state was achieved at day 5 – 6 (with no loading dose). The absolute bioavailability is ca. 96%. By using an oral loading dose of 400 mg bid or an iv loading dose of 6 mg/kg bid at day 1, steady state was reached on day 2. At steady state, clearance decreased compared with single dosing, indicating saturation of metabolism. Accumulation at steady state was 2 – 6 fold. Switching from an IV 3 mg/kg bid dose to an oral 200 mg bid dose resulted in similar plasma levels of voriconazole and trough levels could be maintained. AUCτ and Cmax at steady state of the main metabolite of voriconazole (N-oxide-voriconazole) were in the same range as those of voriconazole. PK/PD analyses did not show a positive association between mean, maximum or minimum plasma voriconazole concentrations from start to end of treatment and efficacy.

Concomitant intake with food affects the rate and extent of absorption of voriconazole. Therefore it is recommended to take voriconazole tablets at least 1 hour before, or 1 hour following a meal.

Protein binding of voriconazole is moderate (ca. 58%) and interactions arising from displacement are not expected to be clinically relevant.

Voriconazole is metabolised by the isoenzymes CYP2C9, CYP2C19 and CYP3A4. *In vitro* studies using human liver microsomes indicate that the affinity for CYP3A4 is 100-fold lower than that for CYP2C9 and CY2C19. CYP2C9 and CYP2C19 appear to be the most important isoenzymes at clinically relevant total voriconazole concentrations of 17 µM (6 µg/ml). Voriconazole was shown to competitively inhibit CYP2C9, CYP2C19 and CYP3A4. The major primary route of metabolism of voriconazole involved fluoropyrimidine N-oxidation to form UK-121, 265 (N-oxide-voriconazole). Fluoropyrimidine hydroxylation and dihydroxylation and methyl hydroxylation are other primary routes. Other metabolites arise from combination of these pathways to form multiple oxidised metabolites. In addition, cleavage of the N-oxide metabolite resulted in loss of the fluoropyrimidine moiety (UK-215, 364). These primary metabolites were conjugated or defluorinated.

The major metabolite N-oxide-voriconazole (UK-121, 265) is ca. 100-fold less potent than voriconazole as shown in *in vitro* susceptibility tests. Taking into account the plasma concentrations of this metabolite at steady state, which are comparable with those of the parent compound, the metabolite is not likely to contribute to the pharmacological effect. N-oxide-voriconazole has been shown to have inhibitory potency against cytochrome P450 enzymes, which is similar to or less than that of voriconazole.

The CYP2C19 isoenzyme exhibits genetic polymorphism, which in essence divides the population into poor and extensive metabolisers (PM and EM, respectively). The extensive metabolisers are further divided into homozygous and heterozygous populations. Three to five percent of the Caucasian and Black population are PMs and have essentially no CYP2C19 activity. The Asian population, including Japanese, generally has a higher proportion of PMs, constituting between 15 and 20% of the population. It has been shown *in vitro* using specific inhibitors and liver microsomes from poor metabolisers, that in the absence of CYP2C19 there is an increased role for CYP3A4 in the metabolism of voriconazole. In poor metabolisers it appeared that Cmax is ca. 3 fold higher and AUC ca. 2 – 5 fold higher compared to extensive metabolisers. Heterozygous extensive metabolisers had a ca. 1.5 fold higher AUC compared to extensive metabolisers. The AUC of N-oxide-voriconazole was

ca. 30% lower in poor metabolisers and ca. 0 – 25% lower in heterozygous metabolisers compared with extensive metabolisers.

After IV and oral administration of radioactive labelled voriconazole 80 and 84% of the dose could be recovered in urine, respectively, and in faeces, ca. 24 and 22%, respectively. Less than 2% of the dose could be detected in urine as intact drug. In faeces no intact drug could be detected.

The pharmacokinetics of voriconazole was not affected by mild to severe impaired renal function. A moderate hepatic insufficiency resulted in an increase in the systemic exposure necessitating a 50% reduction of the maintenance dose of voriconazole. Patients with severe hepatic insufficiency have not been studied. Therefore, the SPC conservatively worded the administration of voriconazole to patients with severe liver impairment.

The systemic exposure in healthy young females was approximately doubled compared with healthy young males. As the safety profile and plasma concentrations observed in male and female patients were similar, no dose adjustment is necessary. No difference in pharmacokinetics was observed between elderly males and females. For elderly, no dose adjustment is necessary. Although a higher exposure in elderly was observed compared to young, this was not associated with increased reporting of adverse events.

The interaction potential of voriconazole is extensively and sufficiently studied *in vivo*. No (clinical significant) effect of voriconazole on the pharmacokinetics of indinavir, prednisolone, and digoxin were observed, whereas the AUC of phenytoin (81%), omeprazole (280%), cyclosporin (70%), warfarin (93% increase in maximum prothrombin time) and tacrolimus (221%) increased due to concomitant intake with voriconazole. The pharmacokinetics of voriconazole were not (clinically significant) affected by cimetidine, ranitidine, indinavir, erythromycin, azithromycin and prednisolone, whereas the AUC of voriconazole was decreased due to the concomitant intake with rifampicin (96%), rifabutin (78%), and phenytoin (69%).

Overall, it is concluded that pharmacokinetics was sufficiently studied and that the SPC adequately reflects the results of the submitted studies.

Clinical efficacy

The following studies were included in the initial submission in the main indications.

Treatment of invasive aspergillosis

Study number	Study	Study Status	Design
150-304	Treatment of acute invasive aspergillosis	Complete	Non-comparative, open label
150-1003		Complete	Historical control for 150-304
150-303	Treatment of chronic aspergillosis	Complete	Non-comparative, open label
150-309, 150-604	Treatment of refractory infections	Interim analysis	Non-comparative, open label
150-303a, 150-304a	Compassionate use	Complete	Non-comparative, open label
150-301, 150-312, 150-606	Compassionate use	Interim analysis	Non-comparative, open label

Treatment of serious *Candida* infections (including *C. krusei*), including oesophageal and systemic *Candida* infections (hepatosplenic candidiasis, disseminated candidiasis, candidaemia)

Study number	Study	Study Status	Design
150-303	Treatment of chronic candidiasis	Complete	Non-comparative, open label
150-305	Oesophageal candidiasis	Complete	Randomised, controlled. double-blind
150-608	Candidemia	Interim analysis	Randomised, controlled, open label
150-309, 150-604	Treatment of refractory infections	Interim analysis	Non-comparative, open label
150-301, 150-606, 150-312	Compassionate use	Interim analysis	Non-comparative, open label

Treatment of serious fungal infections caused by *Scedosporium* spp and *Fusarium* spp

Study number	Study	Study Status	Design
150-309, 150-604	Treatment of refractory infections; Compassionate use	Interim analysis	Non-comparative, open label
150-301, 150-606, 150-303a		Interim analysis Complete	Non-comparative, open label

Empirical Treatment

Study number	Study	Study status	Design
150-603	Empirical treatment	Complete	Randomised, controlled, open label

In response to the CPMP list of questions, comparative studies (150-307/602) in invasive aspergillosis were submitted which had just been completed.

Efficacy data were pooled from the entire programme using standardised procedures referred to as the Voriconazole Efficacy Response Assessment (VERA), this enabled efficacy data from different studies to be summarised in a consistent manner for each fungal species causing an infection.

The indications for serious systemic candidiasis, fusariosis and scedosporiosis were based on pooled efficacy data across the clinical programme: 736 voriconazole and 454 control patients were included in the initial pooled efficacy analyses. Subsequently in response to CPMP questions further refractory candidiasis, fusariosis and scedosporiosis data, from the since completed studies 150-309/604, were provided.

All clinical studies were conducted after the effective date of the GCP guidelines, 1 July 1991, and were performed in accordance with GCP guidelines.

Dose-response studies and main clinical studies

Dose response studies

As mentioned above there was no dose response relationship between voriconazole plasma concentrations (or derived parameter) and efficacy in terms of successful biological response or treatment outcome as determined from available PK-PD data. Indeed successful outcomes were observed for concentrations ranging between .5mcg and 5 mcg/ml at the end of treatment. Neither Cmax nor Cmin seem to be preferentially correlated with outcome. This issue will be further explored by the Company in post marketing studies that will also compare exposure levels after doses of 4mg/kg iv and oral doses of 200mg and 300mg.

Main studies

Invasive Aspergillosis

Study 150-307/602

The primary objective of Protocols 150-307 (conducted in Europe, Israel and Australia) and 150-602 (conducted in the United States, Canada, South America and India) was to evaluate the efficacy, safety, and toleration of voriconazole compared with conventional amphotericin B as initial treatment of (definite or probable) acute invasive aspergillosis in immunocompromised patients of 12 years of age or older. Only up to four days of prior systemic anti-fungal therapy for aspergillosis was allowed. The two protocols had virtually identical inclusion and exclusion criteria, study procedures, assessments and endpoints. Therefore data from both studies were pooled and analysed together, according to a pre-defined umbrella protocol. The primary objective of the umbrella protocol was to demonstrate non-inferiority of voriconazole at Week 12 in the modified intention to treat (MITT) population. The other objectives were to demonstrate superiority of voriconazole at end of randomised therapy (EORT) in the MITT population and to assess the survival through Day 84 from the start of treatment.

A sample of 276 patients (138 per group) would provide power of at least 90% to (1) demonstrate non-inferiority in the rates of satisfactory global response between patients randomised to voriconazole and patients randomised to amphotericin B in the MITT analysis at Week 12 and (2)

detect a difference of 20% in the rates of satisfactory (complete or partial) global response between the voriconazole and amphotericin B treatment groups in the MITT analysis at the end of IRT.

The ITT population included all patients who received at least one dose of correct IRT.

Patients were, however, excluded from this population if their study therapy was not their randomised therapy.

The MITT population included all patients who:

-had received at least one dose of their IRT, and

-had confirmation of 'definite' or 'probable' primary diagnosis of invasive aspergillosis (IA) as determined by an independent Data Review Committee (DRC).

Definite or probable IA was defined by modified EORTC/MSG criteria. Satisfactory outcomes were complete response (CR) of clinical and radiological findings or partial (PR), significant clinical and >50% radiological improvement. Unsatisfactory outcomes were unchanged or worse. Definite or probable aspergillosis and efficacy were both determined by the independent DRC, which was blinded to drug therapy.

Voriconazole was given as an intravenous loading dose of 6mg/kg every 12 hours (Q12H) for the first 24 hours, followed by 4mg/kg iv Q12H. Downward adjustments for toleration of 1mg/kg Q12H were allowed to a minimum dose of 3mg/kg Q12H. At least seven days of iv dosing was recommended for all patients. The starting dose of oral voriconazole was 200mg twice daily (BID). If there was inadequate clinical response after at least three days, the dose could be escalated to 300mg BID. If this dose was not tolerated, the escalated dose could be decreased by increments of 50mg BID to a minimum dose of 200mg BID. For patients weighing less than 40kg, all doses of oral voriconazole were decreased by 50%. Therapy could be continued for a maximum total duration of 12 weeks, and an extension up to 16 weeks was possible. The total duration of treatment for each subject was based on his/her response, as determined by the investigator.

Patients who discontinued either initial randomised study treatment because of toxicity, lack of tolerability, or clinical failure could receive an other licensed antifungal treatment (OLAT). Patients were to be followed for the entire 16-week study period, regardless of any changes in treatment.

Of the 277 patients in the MITT population, 242 patients were also included in the PP population. The reasons for exclusion from the PP population were determined by the DRC and included lack of eligibility/evaluability, receipt of precluded concomitant medication and indeterminate global response at Week 12.

Results

Analysed populations are displayed in the following table. The patterns of underlying diseases and infection sites were broadly similar in each of the two treatment groups.

Summary of Numbers of Subjects within Populations used for Efficacy Analyses

Population	Voriconazole Group	Amphotericin B group	Total patients
Patients receiving study drug	196	185	381
ITT population	194	185	379
MITT population	144	133	277
PP population	131	111	242

Summary of Underlying Disease at Baseline – ITT Population

NUMBER(%) OF PATIENTS	VORICONAZOLE 194		AMPHOTERICIN B 185	
Allogeneic bone marrow transplant^	25	(12.9)	30	(16.2)
Allogeneic peripheral stem cell transplant^	19	(9.8)	8	(4.3)
Autologous bone marrow transplant-	5	(2.6)	1	(0.5)
Autologous peripheral stem cell transplant-	7	(3.6)	7	(3.8)
Other haematological condition-	106	(54.6)	112	(60.5)
HIV/AIDS+	6	(3.1)	7	(3.8)
Solid organ transplant+	11	(5.7)	8	(4.3)
Other Solid organ malignancy+	1	(0.5)	0	
High dose corticosteroid treatment+	11	(5.7)	12	(6.5)
Other+	3	(1.5)	0	

^Allogeneic bone marrow or stem cell transplant

_Autologous bone marrow or stem cell transplant or haematological condition

+Other underlying disease

As expected, virtually all of the patients entered into this study had serious medical conditions at baseline.

Of the patients in the amphotericin B group who switched to OLAT, 57 (39.6%) initially received itraconazole, 61 (42.4%) initially received liposomal amphotericin B and 26 (18%) initially received other therapies. Voriconazole was better tolerated than amphotericin B allowing for longer duration of therapy. See the following table.

Duration of Treatment

		Voriconazole group			Amphotericin B group		
		IRT (N = 196)	OLAT (N = 77)	Regimen (N = 196)	IRT (N =185)	OLAT (N = 145)	Regimen (N = 185)
Elapsed time	Mean (days)	65	37	80	16	58	62
	Median (days)	73	23	87	12	53	57
	Range (days)	2-288	1-128	3–288	1-85	1-129	1–135
Actual time	Mean (days)	65	36	79	14	55	57
	Median (days)	73	22	87	12	47	46
	Range (days)	2-288	1-128	3–288	1-84	1-129	1–135

The duration of treatment expressed in terms of elapsed time was similar to the actual time, although elapsed times tended to be slightly greater than actual times. This was especially the case in the amphotericin B group, because some investigators gave patients a break in their treatment, primarily to allow recovery from AEs (most frequently renal AEs).

In total, 177 patients who received study drug did not complete the study; 80 (41%) of patients in the voriconazole group and 97 (52%) of patients in the amphotericin B group. The main reason for discontinuation from the study (as determined by the investigator) was death.

Efficacy:

The survival for voriconazole treated patients was statistically significantly greater than that for amphotericin B treated patients and a clinically and statistically significant benefit was shown in favour of voriconazole for time to death and time to discontinuation due to toxicity.

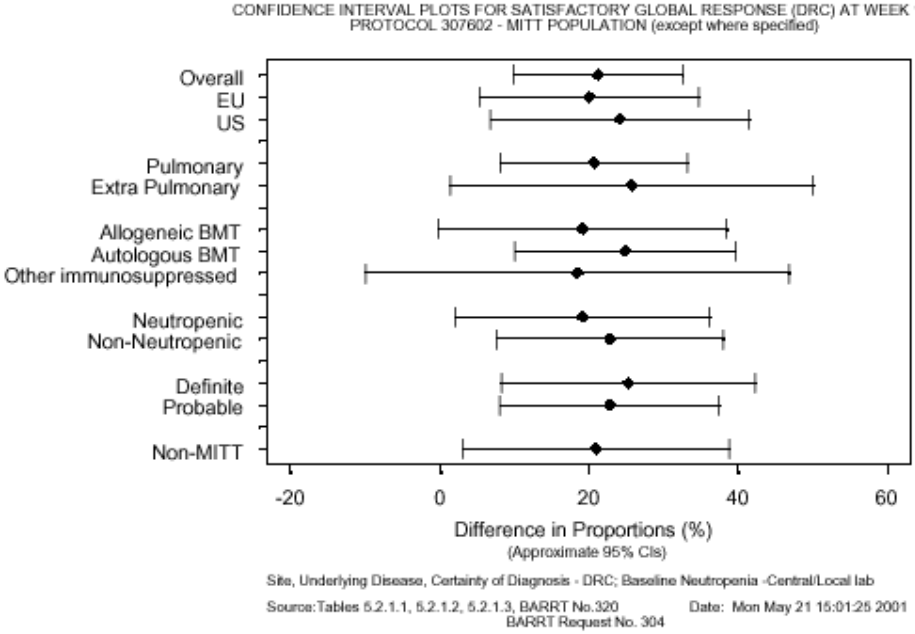
The positive outcome for the overall population (150-307/602) is reproduced within the individual protocol components (150-307 and 150-602) and subpopulations. Although more patients had a satisfactory global response in both treatment groups in protocol 150-307 (57.0% vs 36.9%) compared with protocol 150-602 (46.6% vs 22.5%), the treatment effects were not statistically different between the two protocols at the 5% level.

The table shows the outcome for the primary efficacy variable but remained consistent in other analyses:

Number of patients with satisfactory global responses (DRC assessment) at Week 12 by protocol and treatment group for the MITT population. (Primary Efficacy Analysis)

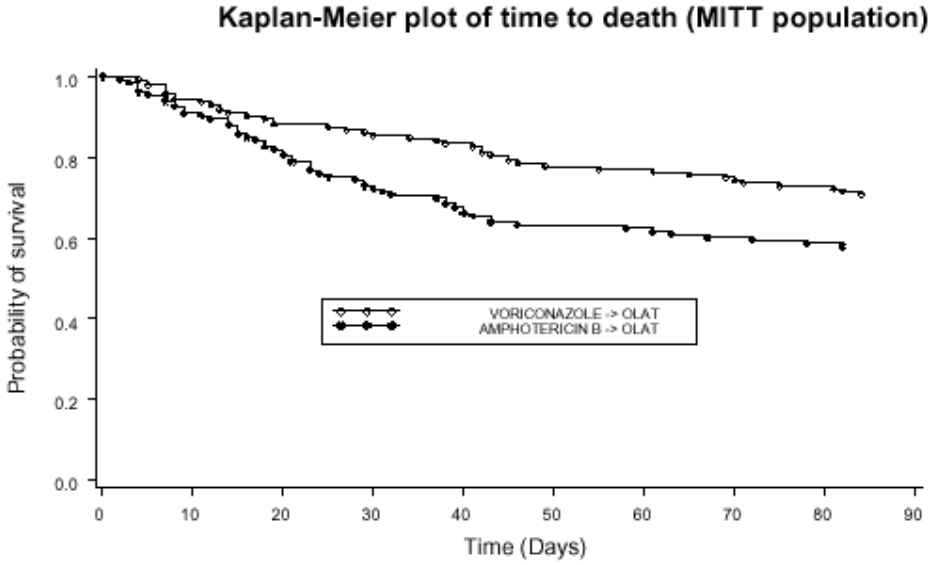
DRC Global Response	**Voriconazole group (N=144)**			**Amphotericin B group (N=133)**		
	150-307	150-602	Combined	150-307	150-602	Combined
Satisfactory	49 (57.0%)	27 (46.6%)	76 (52.8%)	31 (36.9%)	11 (22.5%)	42 (31.6%)
Unsatisfactory	37 (43.0%)	31 (53.5%)	68 (47.2%)	53 (63.1%)	38 (77.6%)	91 (68.4%)

Unsatisfactory response: included failures included (1) patients whose DRC response was given as failure, indeterminate or missing and had an assessment within the Week 12 window, (2) patients who died before the Week 12 assessment and (3) patients without a clinical, mycological or imaging assessment within the Week 12 window.



% success	
vori	amphoB
52.78%	31.58%
56.98%	36.90%
46.55%	22.45%
55.46%	34.82%
40.00%	14.29%
32.43%	13.33%
62.96%	38.10%
50.00%	31.58%
50.79%	31.67%
54.32%	31.51%
44.78%	19.51%
59.74%	36.96%
44.00%	23.08%

Analyses of time to death from the start of treatment and mortality on Day 84 data revealed a total of 98 deaths before Day 84 among patients in the MITT population; 42 patients (29.2%) in the voriconazole group and 56 (42.1%) patients in the amphotericin B group. Kaplan-Meier survival curves plotting time to death showed that the incidence of deaths in each treatment group tended to be highest early in the protocol, although this trend was most pronounced in the amphotericin B group. The proportion of patients surviving was consistently higher in the voriconazole group than the amphotericin B group throughout the study. Separation of the survival curves began soon after the start of treatment; the proportion of patients alive in the voriconazole group was higher than in the amphotericin B group at Day 14. The number of patients whose death was judged by the DRC to be caused by aspergillosis was approximately twice as high in the amphotericin B group compared with the voriconazole group.



Summary of cause of death for patients as assessed by the DRC (MITT population)

Cause of death	**Voriconazole group (N = 144)**	**Amphotericin B group (N = 133)**
Aspergillosis	22 (15.3%)	39 (29.3%)
Unrelated to aspergillosis but evidence of active Aspergillus infection	13 (9.0%)	9 (6.8%)
Unrelated to aspergillosis and no evidence of residual Aspergillus infection	8 (5.6%)	4 (3.0%)
Indeterminate	9 (6.3%)	4 (3.0%)

Serious *Candida* infections

In addition to the randomised, double blind, controlled oesophageal candidiasis study (150-305), a further 169 patients with candidiasis and treated with voriconazole were presented: 127 salvage cases (combined Studies 150-309/604 and other pooled data), and 42 primary therapy patients with systemic infection (from interim Study 150-608 and Study 150-603).

Serious infections caused by *Scedosporium* spp. and *Fusarium* spp.

Infections caused by fungi such as species of *Scedosporium* and *Fusarium* are encountered less frequently. The infection is often unresponsive to currently licensed antifungal agents. In the present application efficacy of voriconazole against such infections relied on the pooled efficacy analysis.

Clinical studies in special populations

Sixty-one paediatric patients aged 9 months up to 15 years who had definite or probable invasive fungal infections, were treated with voriconazole. This population included 34 patients aged 2 to <12 years and 20 patients 12 to 15 years of age. The number of paediatric patients (< 12years of age) evaluated is rather limited (n=34). However, based upon the submitted studies and population pharmacokinetic analysis, children have a higher elimination capacity than adults on a body weight basis. Therefore to achieve exposures (AUCs) in children consistent with those of adults following 3mg/kg, higher doses of 4mg/kg will be required. Higher doses have not been sufficiently nor systematically studied in children and the applicant will further investigate this as a post-approval commitment. In addition to studies regarding investigations of the pharmacokinetics and safety/efficacy investigations of the higher doses in children aged 2 to 12 years, a powder for oral suspension formulation is currently under development. Safety and effectiveness in children less than 2 years of age has not been established. See further relevant sections of the SPC.

Exploratory analysis performed across trials (pooled analyses).

Aspergillosis

Supportive pooled data analyses of results derived from different protocols across the clinical trial programme (including also compassionate use protocols but not the final results from main study *150-307/602*) were also provided for the invasive aspergillosis using the Voriconazole Efficacy Response Assessment. See the following table for the overall overview of outcome analyses.

Outcome of Voriconazole Therapy in Patients with aspergillosis

Pooled Across the Clinical Programme (excluding study 150-307/602)

Outcome	All cases (N=322)	Primary cases (N=84)	Salvage cases (N=238)
Success	140 (43.5%)	44 (52.4%)	96 (40.3%)
- Complete	50 (15.5%)	16 (19.0%)	34 (14.3%)
- Partial	90 (28.0%)	28 (33.3%)	62 (26.1%)
Failure	182 (56.5%)	40 (47.6%)	142 (59.7%)
- Stable	38 (11.8%)	9 (10.7%)	29 (12.2%)
- Failure	131 (40.7%)	29 (34.5%)	102 (42.9%)

This large database revealed an efficacy profile of voriconazole in invasive aspergillosis that was consistent with the profile from the prospective study 150-304.

Refractory invasive candidiasis

Voriconazole has been investigated as salvage treatment of fungal infections in Protocols 150-309/604. Along with data from refractory candidiasis patients in Study 150-303 and the compassionate programme the following patients were presented for the analysis:

Study	All Refractory Candidiasis Subjects*	Refractory Infection Groups	
		Candidaemia	Disseminated & other invasive candidiasis
Studies 150-	75	17	20
Study 150-303	9	0	2
Compassionate-use	22	4	12
Total	106	21	34

* - this column includes oesophageal candidiasis subjects

Prospectively defined criteria in studies 150-309/604 required that patients with invasive fungal infection had to have been efficacy failures having received treatment for at least 6 days with an appropriate systemic antifungal. Supportive data on 51 patients with oesophageal candidiasis who were considered efficacy failures after having received treatment prior antifungal therapy for at least 14 days were also discussed, their results will be mentioned briefly here.

Endpoints:

Complete response: Resolution of all clinical signs and symptoms, bronchoscopic and/or radiographic abnormalities attributable to fungal infection present at baseline, AND (where obtainable) mycological eradication

Partial response: Major improvement in clinical signs, symptoms, bronchoscopic and/or radiographic abnormalities attributable to fungal infection present at baseline.

The median duration of voriconazole treatment of the refractory candidiasis population varied between 54 to 65 days across the subgroups.

Outcome by infection category

The outcomes according to broad infection categories are presented in Table below.

Outcome According To Infection Category

Refractory infection category	Partial response	Complete response	Overall success
Candidaemia (n=21)	7/21	3/21	10/21 (47.6%)
Disseminated or other invasive candidiasis (n=34)	8/34	6/34	14/34 (41.2%)
Oesophageal candidiasis (n=51) (HIV/AIDS patients)	19/51	12/51	31/51 (60.8%)

Outcome by underlying condition:

Successful outcome in invasive refractory candidiasis patients according to primary underlying disease and infection group.

	Success at end of voriconazole treatment: Candidaemia			Success at end of voriconazole treatment: Disseminated or other invasive candidiasis			
	Complete response	Partial response	Success	Complete response	Partial response	Success	
Cancer	3/13	2/13	5/13	3/20	4/20	7/20	13/34 (38.2%)
♦ Haematological malignancy	2/11	2/11	4/11	2/16	4/16	6/16	10/27 (37.0%)
♦ Other malignancy	1/2	0/2	1/2	1/4	0/4	1/4	3/7
HIV/AIDS	1/2	0/2	1/2	-	-	-	31/52 (59.6%)
Other haematologic disorder	2/3	0/3	2/3	1/4	0/4	1/4	3/7
Prior solid organ transplantation	1/1	0/1	1/1	3/4	0/4	3/4	4/5
Other immunosupression	0/1	0/1	0/1	0/2	½	1/2	1/3
Other disorder or unknown	0/1	1/1	1/1	1/4	¼	2/4	3/5
All conditions	7/21	3/21	10/21	8/34	6/34	14/34	55/106* (51.9%)

* - this column includes oesophageal candidiasis subjects

Note: Grey shaded areas are subsets. 'Complete response' and 'Partial response' are combined for overall outcome of success.

Three of four liver transplant patients with candidaemia or disseminated infection had a complete response following voriconazole treatment; likewise a single lung transplant patient had a complete response.

Outcome by Haematologic Risk factors

Eight of the 11 patients with refractory systemic candidiasis who had undergone bone marrow transplantation, received allogeneic grafts, a recognised high risk group (three patients also had graft-versus-host disease). Of these allografts, 2/8 patients responded to treatment. Of patients with systemic infection, one with relapsed haematological malignancy had a partial response, and 3/12 patients with prolonged neutropenia responded successfully to voriconazole treatment.

Baseline Absolute Neutrophil Count

This information was not always available. However, 2/8 patients with an ANC of less than 500 cells/mm^3 treated with voriconazole for candidaemia or disseminated infection had a complete response. Of patients with ANCs of >1000 cells/mm^3 and refractory systemic infection, 14/25 (56%) had a successful outcome.

Outcome by prior antifungal exposure

The prior antifungal data indicate that exposure was extensive in the majority of the population. Of patients with candidaemia or disseminated/other invasive candidiasis 36 received more than 21 days prior treatment. Nineteen of 21 (90.5%) patients with refractory candidaemia had received prior antifungals for a minimum of eight days. In the combined candidaemia or disseminated/invasive candidiasis groups, 22/55 (40%) patients received more than one antifungal for a period exceeding 28 days.

Successful outcome following voriconazole treatment is summarised in Table below.

Successful Outcome According To Prior Antifungal Usage

Prior antifungals	Successful outcome at end of voriconazole treatment: Refractory candidaemia and disseminated or invasive candidiasis (combined)
Fluconazole alone	4/9
Fluconazole + amphotericin B	9/24
Fluconazole + any other combination	-
Amphotericin B alone	0/6
Amphotericin B + any other combination (excl. Fluconazole)	8/12
Itraconazole alone or in any other combination (excluding fluconazole or Amphotericin B)	2/3

Mycological aspects

C. glabrata and *C. krusei* were the most prevalent species in refractory candidaemia. It is noteworthy that in the refractory combined systemic candidiasis group, there were 39 non-*albicans Candida* species (including 16 infections with *C. glabrata* and 10 infections with *C. krusei*) at baseline, compared to 14 isolates of *C. albicans* and 14 unspeciated strains (in the refractory oesophageal group *C. albicans* was the predominant causative species).

Successful outcome in refractory candidiasis patients according to baseline *Candida* species

Baseline species and associated clinical outcome*	Success at end of voriconazole treatment: Candidaemia			Success at end of voriconazole treatment: Disseminated or other invasive candidiasis		
	Complete response	Partial response	Success	Complete response	Partial response	Success response
C. albicans	0/3	0/3	0/3	2/11	1/11	3/11
C. glabrata	1/6	1/6	2/6	4/10	0/10	4/10
C. krusei	3/6	0/6	3/6	1/4	1/4	2/4
C. tropicalis	0/4	1/4	1/4	2/5	2/5	4/5
C. parapsilosis	2/2	0/2	2/2	-	-	-
C. famata	1/1	0/1	1/1	-	-	-
C. kefyr	-	-	-	0/1	1/1	1/1
Candida species	1/3	1/3	2/3	1/6	2/6	3/6
Fungus unspecified	-	-	-	1/5	1/5	2/5

Note: Grey shaded areas are subsets: 'Complete response' and 'Partial response' are combined for overall outcome of success * The subject's overall outcome is linked to each organism listed: where patients had >1 infecting species, the corresponding subject outcome is listed more than once

The relation of response to mycological resistance data at baseline is difficult to assess. The susceptibility data are very limited due to confirmation by histology alone or the unavailability of original cultures prior to patients' entry into these salvage treatment studies. Success at the end of voriconazole treatment according to specified leading baseline *Candida* species with baseline susceptibility data for fluconazole is shown in the following derived table.

Species	Fluconazole MIC (mg/L)	Success in Candidaemia	Success in Disseminated or other invasive candidiasis
C. albicans	≥64	-	1/1
	16-32	-	-
	≤8	-	1/3
C. glabrata	≥64	2/3	1/1
	16-32	-	1/1
	≤8	0/2	0/2
C. tropicalis	≥64		1/1
	16-32		1/1
	≤8	1/2	1/2
C. krusei	≥64	-	-
	16-32	2/2	-

The available data do not suggest a consistent pattern in responsiveness according to baseline susceptibility of the *Candida* species in these limited numbers of patients and isolates.

Serious infections caused by *Scedosporium* spp. and *Fusarium* spp.

Efficacy of voriconazole in the treatment of *Scedosporium* and *Fusarium* infections was assessed in the pooled efficacy analysis:

In 19/38 (50%) *Scedosporium* cases success was noted, the majority were immunocompromised patients and had disseminated infections. A total of 15 cases with cerebral scedosporiosis received voriconazole and were included in the pooled analysis. In all cases the diagnosis was based either on the positive brain/CSF histology/mycology (definite infection) or on the typical brain CT/MRI findings accompanying a definite fungal infection in another site. The majority of these patients were immunocompromised and had failed previous antifungal therapies. A successful outcome was demonstrated in 9/15 patients. Nine of 21 patients with *Fusarium* spp. infections were successfully treated with voriconazole. Of these 7, 3 had eye, one had sinus and 3 had disseminated infection.

Supportive studies

Aspergillosis

Study 150-304 was a prospectively designed non-comparative, multicentre, international (European) study of voriconazole in (primarily adult) patients with acute invasive aspergillosis i.e. a diagnosis of definite or probable acute invasive aspergillosis (primary patients) or with definite acute invasive aspergillosis who had not responded to an adequate course of other anti-fungal therapy or were unable to tolerate previous anti-fungal therapy (e.g. IV amphotericin B) (salvage patients).

(A supportive historical control study (A1501003) including patients who were matched with those in the pivotal prospective study and during roughly the same period as the pivotal study was also provided).

'Primary' therapy patients were allowed to receive up to ten days of previous systemic anti-fungal drugs. Inclusion for salvage therapy with voriconazole was defined as follows: "patients aged 14-75 years with a diagnosis of definite acute invasive aspergillosis and who have not responded to an adequate course of other antifungal therapy, or were unable to tolerate intravenous amphotericin B therapy". Roughly 1/3 of the ITT patients were salvage therapy patients. The number of salvage treatment patients is thus very small which hampers the assessment

The predominant underlying disease was cancer, mainly haematological malignancies. The duration of treatment was to be a minimum of 4 weeks to a maximum of 24 weeks, depending on the response of the patient. The protocol set primary efficacy endpoint was the clinical response as assessed by the investigator at EOT.

The overall successful outcome rates were as follows: (study 150-304)

Response		ITT Population (N=137)[1]		PP Population (N=101)[1]	
Success		74	(54.0%)	54	(53.5%)
-	Complete	49	(35.8%)	37	(36.6%)
-	Partial	25	(18.2%)	17	(16.8%)

Clinical safety

Patient exposure

Overall, data from 1214 voriconazole-treated patients and 571 amphotericin B formulation- and 197 fluconazole-treated patients from prospectively designed clinical trials formed the basis of the safety assessment of voriconazole in the original submission. In addition, 289 normal volunteers received multiple doses of voriconazole in the Phase I programme, 258 patients received voriconazole on a compassionate use basis and 185 patients in Studies 150-302 and 95CK39-673 were also treated. The clinical experience in children aged <15 years is limited to 61 patients based on the pooled efficacy analysis.

Of the 1214 safety assessment patients who received voriconazole (therapeutic studies presented in the intial submission), 203 had a duration of voriconazole therapy of greater than 12 weeks, with 56 patients receiving voriconazole for over 6 months.

Adverse events and serious adverse event/deaths

AEs considered as treatment-related (TRAEs) and occurring in ≥ 5% of patients in any treatment group are summarised in the following table.

	THERAPEUTIC STUDIES		**ALL STUDIES**
	VORI	AMP	VORI
Total number treated	1 214	571	1 946
Number with AEs	667 (54.9%)	444 (77.8%)	1007 (51.7%)
Abnormal vision	251 (20.7%)	5 (0.9%)	439 (22.6%)
Fever	87 (7.2%)	138 (24.2%)	90 (4.6%)
Rash	80 (6.6%)	28 (4.9%)	105 (5.4%)
Nausea	70 (5.8%)	74 (13.0%)	85 (4.4%)
Vomiting	61 (5.0%)	67 (11.7%)	76 (3.9%)
Chills	60 (4.9%)	147 (25.7%)	61 (3.1%)
Headache	38 (3.1%)	27 (4.7%)	105 (5.4%)
Tachycardia	36 (3.0%)	47 (8.2%)	37 (1.9%)
Photophobia	29 (2.4%)	2 (0.4%)	98 (5.0%)
Hypertension	28 (2.3%)	37 (6.5%)	29 (1.5%)
Hypotension	27 (2.2%)	29 (5.1%)	29 (1.5%)
Hypokalaemia	25 (2.1%)	89 (15.6%)	26 (1.3%)
Vasodilatation	21 (1.7%)	49 (8.6%)	23 (1.2%)
Kidney function abnormal	6 (0.5%)	32 (5.6%)	7 (0.4%)

Creatinine increased	5 (0.4%)	57 (10.0%)	8 (0.4%)

Abnormal vision, headache, and sepsis (all causality) occurred more frequently in the voriconazole treated patients than patients in the control groups on the basis of the pooled analysis. Abnormal vision was the most frequently reported treatment related AE for voriconazole with a rate of 251/1214 (21%) vs. 5/571 (< 1%) for amphotericin B (3 and 0 cases respectively were severe).

This has been specifically monitored throughout the clinical trial programme on the basis of observation made during the phase I studies. In the latter studies there were specific investigations of the effects of voriconazole on the electrophysiology of the retina and visual cortex. There were no indications of organic damage; this has also not been the case in the prolonged exposure to the agent in the phase II-III studies and compassionate use programme. Phase I investigations addressed also potential cardiotoxicity of voriconazole since arrhythmias were occasionally observed in the preclinical pharmacology and toxicology studies in dogs. Hence, investigations included standardised measurements of QTc intervals in volunteer studies.

ECG data from eight studies where ECGs had been taken, were re-measured by an independent contractor. There was no visual evidence of a relationship between changes in QTc and either dose or plasma concentrations of voriconazole for single dose administration, for absolute values of QTc or changes from baseline.

As with other azoles, voriconazole can lead to the occurrence of skin reactions such as rash. However, the incidence of rash in the voriconazole group, when corrected by the treatment duration, was lower compared to Amphotericin B (1.94 versus 8.07).

Following the reporting of infusion related adverse events in four female volunteers participating in the voriconazole development programme, a full clinical review of potential infusion related adverse events across the programme has been performed. Batch relatedness seemed unlikely to explain these reactions that occurred at a higher rate per number of infusion exposures in healthy volunteers than in patients. The clinical data indicate that events of vasodilatation or anaphylactoid type events associated with infusion can occur at very low a frequency. These are however, unlikely to present a significant hazard to patients being treated for invasive aspergillosis or other serious fungal infections. Since there has been evidence to suggest that administration of the i.v. formulation of voriconazole could be associated with infusion-related reactions section 4.4 of the SPC reflects this potential risk. Furthermore, the company has committed to further investigate the mechanism of these infusion related reactions.

The safety phase I studies have shown major voriconazole side effects i.e., visual disturbances and liver function tests abnormalities were associated with the exposure to the antifungal agent (both Cmax and AUC).

The intravenous form containing the new excipient SBECD (160 mg/ml) did not appear to be associated with extra toxicity although caution in case of renal impairment is required. See relevant parts of the SPC.

A warning statement on the potential for photosensitivity reaction is included in SPC Section 4.4.

Many treatment related AEs reported in the voriconazole-group are expected (azole class effects), AEs may be due to concurrent diseases. Most cases have been considered as mild or moderate in intensity since in therapeutic studies only about 10% of VORI-patients (126 patients) experienced severe TRAEs (compared to 19% (111 patients) in the AMP-group). For the most frequent TRAEs such as abnormal vision, fever, rash, nausea, severe effects occurred in < 1% of patients.

The majority of the most frequently reported treatment related serious AE with voriconazole are related to hepatic effects. In addition to these events, other noteworthy SAEs occurring in patients taking voriconazole where a relationship to treatment could not be ruled out were pancreatitis (four cases), hepatitis (three cases), hepatic failure (four cases), hypoglycaemia (three cases), thrombocytopenia (five cases), erythema multiforme (one case), epidermal necrolysis (one case), leucopenia (three cases), bone marrow aplasia (one case), pancytopenia (two cases) and granulocytopenia (three cases). These cases were confounded by factors relating to progression of the underlying disease and the presence of numerous concomitant medications.

The liver was identified as the principal target organ in animal toxicology studies with voriconazole. These results have been confirmed in clinical studies. Hepatotoxicity risk is increased for Cmax at 5000-6000 ng/ml. Therefore, this correlation associated with the wide inter-subject variability of the voriconazole pharmacokinetics variability suggest that a therapeutic drug monitoring approach could help to avoid hepatic toxicity as further mentioned in the SPC. The monitoring of hepatoxicity in a targeted PMS strategy is part of the follow up measures post approval.

No deaths where a causal contribution of study drug could not be excluded have been reported.

Discontinuations

Hepatic effects (e.g. increased liver enzymes, bilirubinaemia, and cholestatic jaundice) were also the most frequently reported treatment related reason for discontinuation of voriconazole. Treatment related discontinuations due to cholestatic jaundice (7 cases), abnormal vision (7 cases) and hallucinations (5 cases) were reported only for voriconazole. Discontinuations due to elevated creatinine and abnormal kidney function were reported at a higher rate for patients treated with amphotericin B formulations than for patients given voriconazole.

Comparative safety assessment:

Study 150-305

In the double-blind study 150- 305 the rate of treatment related discontinuations in the voriconazole group was greater (6.0%) than in the fluconazole group (1.6%). The rates of treatment related adverse events reported were higher in the voriconazole group (30%) vs. approx. 14% in the fluconazole group, and tended to be more severe. The most frequent and distinguishing adverse effects of voriconazole occurring at higher rates were those related to abnormal vision and hepatic/metabolic effects.

Study 150-603

A similar trend was seen for the treatment related adverse events in the large study 150-603. This study compared voriconazole to liposomal amphotericin B in the empirical treatment of fungal infections in immunocompromised subjects. Patients receiving voriconazole had a higher rate of abnormal vision (23.8%) than in the control group (0.9%). Furthermore, hallucinations were also reported at a higher rate in the voriconazole group (4.3% vs. 0.5% in the control group); similarly this held also for headache. In this study the rates of serious hepatic effects were similar in both treatment groups, although higher rates of increased SGPT, SGOT, alkaline phosphatase and increased hepatic enzymes were reported in the voriconazole group. Cardiovascular effects seemed also to be reported at similar rates, for example treatment related bradycardia (1.9 % vs. 1.4 % in the voriconazole and control groups respectively). However, there were two patients with heart arrest with causality possibly attributed to voriconazole in this study. Reported cases of hyperkalaemia were also higher in the voriconazole group (0.5% vs. 0 in the control group) whereas hypokalaemia was more frequently reported in the control group (14.7% vs. 4.0% in the voriconazole group).

The rates of renal adverse events were similar in the two treatment groups. However, the proportion of patients who discontinued due to acute kidney failure was higher in the voriconazole group than in the control group (2.9% and 0.2%, respectively). There were 33 deaths (8.0%) in the voriconazole group and 25 (5.9%) in the control MITT treatment groups. Further review of these cases suggests that lack of antifungal efficacy of voriconazole was not responsible for the difference in deaths.

Study 150-307/602

In the comparative study (Study 150-307/602) against Amphotericin B, the latter was poorly tolerated and associated with more discontinuations. Voriconazole was better tolerated allowing for longer duration of therapy. The proportion of patients of experiencing drug-related AEs leading to discontinuation was consistently lower for voriconazole-treated patients than patients receiving amphotericin B (MITT population). The burden of amphotericin B toxicity was seen as renal dysfunction and infusion related reactions. Visual AEs were more frequent in the voriconazole group. Nearly all of the visual AEs were mild or moderate, did not lead to discontinuation, and resolved.

Incidence of treatment emergent AEs (all causalities) reported by >20% of patients in Any treatment group

	Voriconazole		**Amphotericin B**	
	IRT	Regimen	IRT	**Regimen**
	(N = 196)	(N = 196)	(N = 185)	**(N = 185)**
Abdominal pain	**27 (13.8%)**	35 (17.9%)	27 (14.6%)	**40 (21.6%)**
Abnormal kidney function	**18 (9.2%)**	28 (14.3%)	31 (16.8%)	**43 (23.2%)**
Abnormal vision	**65 (33.2%)**	65 (33.2%)	6 (3.2%)	**8 (4.3%)**
Chills	**9 (4.6%)**	11 (5.6%)	37 (20.0%)	**43 (23.2%)**
Creatinine increased	**10 (5.1%)**	14 (7.1%)	54 (29.2%)	**64 (34.6%)**
Diarrhoea	**34 (17.3%)**	43 (21.9%)	25 (13.5%)	**50 (27.0%)**
Fever	**56 (28.6%)**	70 (35.7%)	40 (21.6%)	**68 (36.8%)**
Hypokalaemia	**18 (9.2%)**	23 (11.7%)	37 (20.0%)	**47 (25.4%)**
Nausea	**46 (23.5%)**	54 (27.6%)	40 (21.6%)	**61 (33.0%)**
Peripheral oedema	**34 (17.3%)**	42 (21.4%)	17 (9.2%)	**36 (19.5%)**
Rash	**45 (23.0%)**	52 (26.5%)	21 (11.4%)	**40 (21.6%)**
Sepsis	**35 (17.9%)**	40 (20.4%)	7 (3.8%)	**25 (13.5%)**
Vomiting	**43 (21.9%)**	54 (27.6%)	31 (16.8%)	**53 (28.6%)**

Laboratory findings

In the voriconazole programme, clinically significant elevations in transaminases occurred at a rate of 160/1214 (13.2%) in the primary safety populations. With respect to the hepatic toxicity specific PK/PD analyses have shown hepatic enzyme elevations to be correlated with voriconazole plasma levels. The abnormalities are usually reversible on discontinuation of the drug. The incidence of clinically significant LFT abnormalities is unaffected by gender. Overall, the data do not suggest an age effect, although patients younger than 18 years of age are represented to a very limited extent.

5. Overall conclusions, benefit/risk assessment and recommendation

Quality

Voriconazole is presented as both film-coated tablets (two strengths) and as a powder for solution for infusion. The tablet formulation is a wet granulation common blend. The poor aqueous solubility of voriconazole was overcome in the parenteral product by its complexation with a novel excipient, SBECD, and subsequent lyophilisation to produce a sterile product suitable for parenteral use.

The quality dossier for both Vfend coated tablets and powder for solution for infusion indicates that the active substance and both finished products are manufactured and controlled in a relevant way, in compliance with current EU and ICH guidelines. Satisfactory information has been provided to demonstrate that these manufacture and control processes routinely and consistently generate a product of uniform quality when used in accordance with the conditions defined in the SPC.

Some outstanding GMP compliance issues at the parenteral manufacturing site (Catalytica, USA) remain. An undertaking has been provided by the applicant that the product will not be made commercially available until the remaining issues are satisfactorily resolved or an alternative manufacturing site is approved.

Also, at the time of the Opinion, the CPMP concluded that a number of minor quality issues remained to be resolved. These issues were considered to have no impact on the benefit/risk balance of the product when used according to the SPC. It was agreed that they should be resolved as follow-up measures to be submitted post-authorisation.

Preclinical pharmacology and toxicology

Voriconazole is a broad-spectrum antifungal agent with potent *in vitro* activity against the primary opportunistic pathogens: *Aspergillus spp., Candida spp.* and *Cryptococcus spp.*, fluconazole-resistant strains of *C. albicans*, as well as other *Candida spp.* which are inherently less sensitive to fluconazole *(e.g. C. krusei and C. glabrata*). Voriconazole is also active against a wide range of less common

pathogens, including organisms that are resistant to fluconazole, itraconazole and amphotericin B *(e.g. Fusarium spp., Scedosporium inflatum, Acremonium kilensii, Trichosporon spp).*

Repeat-dose oral studies in rats, mice and dogs have shown the liver to be the main target organ, with a range of adaptive and functional changes. The toxicology programme suggested that the potential for liver toxicity by voriconazole is comparable to other azoles. Based on the preclinical data there is virtually no margin of safety for the liver toxicity and by necessity, the safety has to be based mainly on clinical data. The Company has committed to perform studies into the genotoxic potential of the fluoropyrimidinedihydroxy metabolite and into developing a route of synthesis of SBECD in such a way that it does no longer contain 1,4 butane sultone. This information has been included in the SPC.

Efficacy

Invasive aspergillosis

Critically reviewed data in the original MAA (study 150-304) together with the requested results of the comparative studies (150-307/602) are convincingly supportive of the clinical benefit of voriconazole in the treatment of immunocompromised patients with invasive aspergillosis. In the latter study versus conventional amphotericin B the blinded expert assessment of the results showed that global response for voriconazole-treated patients was superior to that for amphotericin B (53% versus 31%). The survival for voriconazole was statistically significantly greater than that for conventional amphotericin B and a clinically and statistically significant benefit was shown in favour of voriconazole for time to death and time to discontinuation due to toxicity.

Serious invasive *Candida* infections

With focus on the refractory population the combined candidaemia or disseminated/invasive candidiasis groups, 22/55 (40%) patients received more than one antifungal for a period exceeding 28 days. The majority of the refractory population had prior therapy with fluconazole or fluconazole plus amphotericin B and successful clinical outcome was observed in 13/33 (39.4%) of these cases. Eight of 12 subjects who had previously received amphotericin B plus any other anti-fungal except fluconazole, were successfully treated with voriconazole, and in the total refractory systemic candidiasis population successful outcome was seen in 24/55 (43.6%) subjects. In the majority of successful cases (15/24) the response was partial. The response was, as expected, influenced by the underlying disease and degree of neutropenia. Success was limited to 3/12 (25%) patients with prolonged neutopenia and 2/8 cases with neutrophil count <500 cells/$mm^{3.}$

Scedosporiosis and Fusariosis

The data are supportive of the benefit of voriconazole in these rare life threatening serious infections in immunocompromised patients for whom there is very limited, if any alternative therapy. Success with voriconazole was described in 19 (50%) of 38 cases of scedosporiosis, and 9 (42%) of 21 cases of fusariosis. The beneficial effects of voriconazole in a few cases of cerebral infection is noteworthy.

Safety

Many treatment related AEs reported with voriconazole are rather expected (azole class effects). Most cases have been considered as mild or moderate in intensity. For the most frequent treatment related AEs such as abnormal vision, fever, rash, and nausea, severe effects occurred in < 1% of patients.

The safety studies have shown that side effects to voriconazole such as visual disturbances and liver function tests abnormalities were associated with the exposure levels of the antifungal agent (both Cmax and AUC).

The liver was identified as the principal target organ in animal toxicology studies with voriconazole. These results have been confirmed in patient studies. The monitoring of hepatoxicity in a targeted PMS strategy is part of the follow-up measures post approval.

Benefit/risk assessment

Matters related to the efficacy of the drug in (1) *Candida* infections, (2) use in children and (3) safety in particular with regard to hepatic safety and anaphylactoid reactions, were discussed during on oral explanation before the CPMP. The CPMP was in favour of approving voriconazole for the treatment of fluconazole resistant *Candida* infections in patients with invasive candidiasis.

The susceptibility data in conjunction with the clinical efficacy, support a role for voriconazole in the treatment of serious invasive infections caused by both *C. albicans* or non-*albicans* species that have failed to respond, and that may have reduced susceptibility, to fluconazole.

In invasive aspergillosis there is a favourable efficacy of the voriconazole treatment regimen compared to amphotericin B across different subgroups of patients - with or without prior antifungal therapy and severe neutropenia.

Data are supportive of the benefit of voriconazole in rare life threatening *Scedosporium* and *Fusarium* infections in immunocompromised patients for whom there is very limited, if any, alternative therapy.

The safety concerns with voriconazole, primarily related to hepatotoxic effects generally compares favourably with other alternative treatments. These abnormalities are usually reversible on discontinuation of the drug but will be further monitored and assessed in the post marketing phase. The safety aspects have been adequately reflected in the SPC and will be further addressed by the Company following a positive CPMP opinion.

The Benefit/Risk for voriconazole for treatment of the suggested indications was thus found to be positive.

Recommendation

Based on the CPMP review of data on quality, safety and efficacy, the CPMP considered by consensus that the benefit/risk profile of Vfend in the treatment of invasive aspergillosis, fluconazole-resistant serious invasive *Candida* infections (including *C. krusei*) and serious fungal infections caused by *Scedosporium* spp. and *Fusarium* spp. was favourable and therefore recommended the granting of the Marketing Authorisation.