SCIENTIFIC DISCUSSION

1. Introduction

Fungal infections have increased in recent decades due to the increasing use of iatrogenic immunosuppression in connection with treatment of cancer and organ transplantation, widespread use of broad-spectrum antibiotics and the increasing number of patients with HIV infection.

Two systemically available triazoles - fluconazole and itraconazole – have been marketed for more than a decade and have made a major contribution to the management of both superficial and invasive fungal infections. Most recently, voriconazole has been approved in the EU for the treatment of aspergillus, candida and some other fungal infections as specified in the current Summary of Product Characteristics (SPC). Whereas there is now very considerable clinical experience with the triazoles, their use does carry some considerable potential for interactions with other medicinal products and has sometimes been associated with hepatotoxicity, QTc prolongation and *Torsades de Pointes* and resistance.
The echinocandin class of antifungal agents currently includes only one authorised agent. Caspofungin has been authorised in the EU for the treatment of fungal infections as specified in the current SPC.

Posaconazole is a novel broad-spectrum antifungal agent of the triazole class that has been developed for the treatment of invasive fungal infections.

Noxafil is available as an oral suspension containing 40 mg/ml posaconazole to be administered at a dose of 400 mg twice a day with a meal or with 240 ml of a nutritional supplement. In patients who cannot tolerate a meal or a nutritional supplement, posaconazole can be administered at a dose of 200 mg four times a day.

The approved indication is for use in the treatment of the following invasive fungal infections in adults:
- Invasive aspergillosis in patients with disease that is refractory to amphotericin B or itraconazole or in patients who are intolerant of these medicinal products;
- Fusariosis in patients with disease that is refractory to amphotericin B or in patients who are intolerant of amphotericin B;
- Chromoblastomycosis and mycetoma in patients with disease that is refractory to itraconazole or in patients who are intolerant of itraconazole;
- Coccidioidomycosis in patients with disease that is refractory to amphotericin B, itraconazole or fluconazole or in patients who are intolerant of these medicinal products.

Refractoriness is defined as progression of infection or failure to improve after a minimum of 7 days of prior therapeutic doses of effective antifungal therapy.

2. Quality aspects

Introduction

Noxafil is formulated as a multidose oral suspension containing 40 mg/ml of posaconazole as active substance.

The other ingredients include polysorbate 80, simeticone, sodium benzoate, sodium citrate, citric acid monohydrate, glycerol, xanthan gum, liquid glucose, titanium dioxide, artificial cherry flavour and purified water.

It is presented in an amber glass bottle closed with a polypropylene child-resistant cap. A polystyrene measuring spoon with a 2.5 and a 5 ml graduation is provided.

Active Substance

Posaconazole is a triazole antifungal agent containing 4 chiral centres. It is synthesised solely as the (R,R,S,S) enantiomer. Three polymorphic forms of posaconazole have been observed during development, but the synthetic process is designed to constantly produce form I. Moreover, the crystal form is controlled as part of the drug substance specification and there has been no evidence of polymorphic transition on storage as micronised powder, during manufacture or as formulated in the finished product. Posaconazole is lipophilic, highly permeable, and practically insoluble in water. Therefore, the rate of drug dissolution is likely to be important to the rate and possibly to the extent of absorption.

- Manufacture

Posaconazole is prepared from commercially available starting materials via a three-step synthesis followed by a micronisation step.
Satisfactory specification and associated methods have been provided for the starting materials, key intermediates, reagents and solvents.
During development, different variants of the commercial synthesis have been used to produce posaconazole batches used in non-clinical and clinical studies. Batch analytical data provided for posaconazole obtained from all routes of synthesis show a comparable quality.

- Specification

The active substance specification includes tests for appearance, identity (IR and chiral HPLC), optical rotation (PhEur), assay (chiral HPLC), impurity (chiral and achiral HPLC), residual solvents, heavy metals (PhEur), sulphated ash (PhEur), loss on drying and particle size.
Batch analysis data provided for lots manufactured according to the commercial synthesis process at the commercial site confirm satisfactory compliance and uniformity with the proposed specification.

- Stability

Stability data have been provided for 3 primary stability batches synthesised using the commercial process at the commercial site. Samples were tested in line with shelf-life specification including all parameters liable to change during storage.
Under accelerated conditions (40°C/75% RH - commercial packaging) 6-month data have been provided. Under long-term conditions (25°C/60% RH - commercial packaging), 3-year data are available for 1 batch and 2-year data for the two other batches. The photostability study performed did not show any significant change in all stability indicating parameters.

The proposed retest period is supported by the presented data when pozaconazole is stored in double polyethylene bags in a sealed fiber drum.

Medicinal Product

- Pharmaceutical Development

The rationale for formulating the finished product considered principally the low solubility of posaconazole in aqueous media and the acceptability for the patient population of an oral dosage form containing a relatively high dosage (400 mg twice a day). Based on superior bioavailability an oral suspension has been selected as commercial formulation over prototype tablets/capsules formulations. Posaconazole dissolution rate is enhanced by micronisation at the end of synthesis and the particle size is further reduced during manufacture of the finished product.

The excipients were chosen based on their compatibility with posaconazole. A non-ionic surfactant was found to be necessary to wet the hydrophobic poorly soluble active substance and to stabilise the suspension. Development studies have confirmed that xanthan gum is an effective suspending agent providing good product uniformity for extended periods of time on standing, and permitting redispersion of active substance that may have sedimented during long-term storage. The selected and maintained by a citrate buffer system is satisfactory for the stability of posaconazole and maintains the antimicrobial efficacy of sodium benzoate, which has been demonstrated according to PhEur. Acceptable taste and organoleptic properties are ensured by the incorporation of liquid glucose as sweetener, titanium dioxide as opacifier and artificial cherry flavour
. All the excipients comply with the PhEur requirements except the flavour, which is adequately controlled according to a different standard and is in compliance with the European legislation. Regarding the TSE risk, the oral suspension. does not include any components of ruminant origin.

Physical characterisation of the suspension included studies of rheology, settling rate, redispersibility and minimum and maximum fill volume tolerances. The product settles very slowly, remains homogeneous for extended period of time and is readily redispersed by shaking the bottle for a few seconds.

The amber glass bottle and the high-density polyethylene closure liner coming in contact with the suspension are of PhEur quality. Satisfactory testing was performed in order to define any potential extractable from the liner and no leachable was identified during stability studies when storing the bottles in inverted position. The compatibility of the container/closure system was verified through the primary stability program. The polystyrene measuring spoon is suitable for contact with food, CE marked and it has been approved for its intended use. The accuracy of the dose delivered by this medical device has been demonstrated according to PhEur.

The oral suspension formulation used in the pivotal clinical study (P00041) was slightly different of the commercial formulation. However, comparative in vitro dissolution data indicate that posaconazole dissolution and the product performance are comparable.

- Manufacture of the Product

The manufacturing process involves the following steps: preparation of an aqueous dispersion of posaconazole, homogenization, final compounding, and primary packaging.
Satisfactory operating parameters and in-process controls have been defined at each stage of manufacture. Holding times for the posaconazole manufacturing process have been adequately justified.
The process will be validated prior to commercialization

- Product Specification

The product specification includes tests for appearance, identity (achiral HPLC and TLC), identity of sodium benzoate (HPLC), identity of titanium dioxide, assay (achiral HPLC), sodium benzoate content (HPLC), degradation products, particle size, pH, microbial quality (PhEur – skip testing), viscosity, deliverable volume, homogeneity, simeticone particles and dissolution.

Batch analysis data provided for batches made at the commercial manufacturing scale and . batches manufactured at the commercial site comply with the specifications and indicate consistent and reproducible manufacture.

- Stability of the Product

Stability studies have been conducted on 3 batches using the commercial process.

Stability of the Product before first opening

Chemical and physical stability-indicating parameters were tested.
Under long-term conditions (25ºC/60% R.H. - packaging intended for commercialisation – upright and inverted position), 2-year data are available. Up to 6-month data under accelerated conditions are available for these batches (40ºC/75% R.H. - packaging intended for commercialisation – upright and inverted position).
A photostability study performed has shown that the finished product is not light sensitive.
The results presented support the proposed shelf life and storage conditions defined in the SPC.

In-use stability of the suspension
The product has been shown to be chemically, physically and microbiogically stable during the proposed in-use shelf life and under the storage conditions defined in the SPC.

3. Non-clinical aspects

Introduction

All pivotal studies were performed in compliance with the principles of international Good Laboratory Practice (GLP) regulations and were consistent with the International Committee on Harmonisation (ICH) guidelines for conduct of toxicology studies.

Pharmacology

- Primary pharmacodynamics (*in vitro/in vivo*)

Mechanism of action

Posaconazole, like other azoles, inhibits the enzyme lanosterol 14α-demethylase that is necessary for ergosterol biosynthesis in yeasts and filamentous fungi. This enzyme is also known as CYP51A or Erg11p and is encoded by the *ERG11* gene.

In-vitro studies showed a direct correlation between the ability of posaconazole to inhibit the enzyme and the minimum inhibitory concentration (MIC) of substance for an organism.
Homology models of the *A. fumigatus* and *C. albicans* CYP51 proteins predicted that the long side chain of posaconazole occupies a specific channel within CYP51 that is not utilised by fluconazole or voriconazole. This additional interaction may stabilise binding of posaconazole to CYP51 proteins that have amino acid substitutions near the haem binding site and so may account for some aspects of the spectrum of susceptible fungi and for some activity against certain azole-resistant strains.

Antifungal activity in vitro

In-vitro studies of antifungal activity were performed in 45 laboratories using National Committee for Clinical Laboratory Standards (NCCLS) methodology. Approximately 18,000 unique strains collected from around the world have been tested, including organisms from 66 genera and 157 species of moulds and yeasts, as well as one algal and six protozoan species.
In these tests, posaconazole showed activity against some organisms with reduced susceptibility to alternative anti-fungal agents (see table 1 for a summary). In-vitro studies with posaconazole in combination with amphotericin B, caspofungin or voriconazole against 30 *Candida* and *Cryptococcus* isolates and 75 *Aspergillus* and *Fusarium* isolates revealed no antagonism of activity for any of the antifungal combinations tested.

Table 1: Activity against isolates resistant to other anti-fungals

	N	**Posaconazole**		**Fluconazole**		**Itraconazole**		**Voriconazole**		**Amphothericin**	
		MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}
Aspergillus fumigatus											
AMB resistant	15	NA	0.25	NA		NA	0.5	NA	1	NA	8
ITZ resistant	25	NA	0.5	NA		NA	16	NA	1	NA	0.5
VOR resistant	12	NA	0.5	NA		NA	0.5	NA	8	NA	0.5
Candida species											
	12										
Candida glabrata	18	1	2	8	64	1	4	0.25	2	1	1
	18										
Candida krusei	9	0.5	1	32	64	1	1	0.25	0.5	1	2
Candida guilliermondii	26	0.25	1	4	32	0.5	4	0.063	8	0.5	1
	16										
Candida dubliniensis	4	0.031	0.125	0.25	32	0.063	0.5	0.016	0.125	0.5	1
Zygomycetes											
All zygomycetes	86	0.5	4	NA		1	32	16	128	0.25	2
Rhizopus	32	1	8	NA		4	32	16	128	1	2
Mucor	18	1	16	NA		2	32	64	128	0.25	1
Absidia	16	0.125	0.25	NA		0.125	0.5	16	128	0.25	0.5

Antifungal activity in vivo

In 41 different animal models (immunocompetent or immunosuppressed mice, guinea pigs or rabbits), posaconazole was compared to other antifungal agents (amphotericin, fluconazole, itraconazole, voriconazole or caspofungin) against one or more of *Absidia, Aspergillus, Blastomyces, Candida, Cladophialophora, Coccidioides, Cryptococcus, Fusarium, Histoplasma, Mucor, Pseudallescheria, Ramichloridium, Rhizopus, Wangiella, Leishmania,* and *Trypanosoma*.

In vivo studies in mice using posaconazole in combination with either amphotericin B or caspofungin against *C. albicans*, *A. flavus*, and *A. fumigatus* confirmed that there was no antagonism of activity or efficacy.
In pre-clinical studies, the posaconazole 24-hr AUC/MIC and free drug AUC/MIC were predictive of efficacy in neutropenic mice infected with *Candida albicans*. Posaconazole free-drug AUC/MIC values associated with ED_{50} were similar (p-value 0.42) for 12 *C. albicans* isolates with posaconazole MICs in the range 0.015 – 0.12 µg/ml. The posaconazole free drug AUC/MIC ratio was approximately 17.

Non-clinical PK/PD studies investigated the dose-response relationship for posaconazole against *Aspergillus flavus* in immunocompromised mice infected by inhalation of conidia and against *C. albicans* in immunocompetent mice infected systemically. Survival increased with posaconazole dose and both AUC/MIC and dose showed a sigmoidal relationship with survival. In the *A. flavus* study, maximum survival was achieved at 5 mg/kg posaconazole, with best results on splitting the dose into four rather than two or on administration as a single dose.

In a neutropenic rabbit model of pulmonary *A. fumigatus*, the maximum concentration of posaconazole in serum greatly exceeded the MIC at doses of 6 and 20 mg/kg/day and the $t_{1/2}$ of 7-10 hours maintained plasma levels above MIC. A sustained level of 1000 ng/ml posaconazole correlated with high activity in plasma.

Resistance

Resistance to posaconazole in laboratory and clinical strains of *A. fumigatus* and *C. albicans* appeared to be rare. In the laboratory, spontaneous *A. fumigatus* mutants with decreased susceptibility to

posaconazole arose at a frequency of approximately 1 in 10^8. This decrease in susceptibility was due to a single amino acid substitution in CYP51 (Gly54). In *C. albicans*, multiple amino acid substitutions in CYP51 were required to confer major reductions in susceptibility to posaconazole. In addition to amino acid substitutions, a second mechanism of resistance involved increased expression of efflux pumps and resulted in a decreased intracellular concentration of the drug.

A third mechanism of resistance was identified in clinical *C. albicans* isolates that exhibited reduced susceptibility to all azoles but did not have amino acid substitutions in CYP51 or increased expression of the efflux pump genes. These isolates had nonsense mutations in the *ERG3* gene resulting in a non-functional $\Delta^{5,6}$-sterol desaturase, thereby abrogating the toxicity of the methylated sterol intermediates. This mechanism of resistance was rarely observed.

- Safety pharmacology

No secondary pharmacodynamic studies with posaconazole were conducted which was considered acceptable.

- Safety pharmacology

Safety pharmacology studies in rats (oral doses up to 30 mg/kg posaconazole) did not reveal any specific findings regarding, gastrointestinal, central nervous system and renal function. . In a respiratory safety pharmacology study in rats (intravenous doses of a lipid containing formulation up to 60 mg/kg) there were no effects on respiratory function.

The effects of posaconazole on ventricular repolarisation were evaluated *in vitro* by measuring both the action potential and the recombinant hERG channel current. In isolated Purkinje fibre system, exposure to posaconazole at measured concentrations of ≥25 ng/ml (36 nM) induced a small (<10%), but statistically significant, increase in action potential duration at 60% (APD_{60}) and/or 90% (APD_{90}) repolarisation. There were no effects regarding the other action potential parameters.
In the recombinant hERG channel, posaconazole at a concentration of 770 ng/ml (1100 nM) induced a decrease in hERG current of 7%. When taking into account the protein binding (98.5%), the concentration in the hERG assay was approximately 18-times the free posaconazole C_{max} value in healthy volunteers. The magnitude of these changes was considered unlikely to elicit QT interval prolongation *in vivo*.

Cardiovascular parameters were investigated in rats and monkeys. Rats administered an oral dose of 90 mg/kg/day for 4 weeks had a minimal increase in systolic and mean arterial blood pressures, a decreased intraventricular systolic diameter and increased fractional shortening. No changes in heart rate and stroke volume were observed. The blood pressure change was considered to be a response to increased vascular resistance. In monkeys, 2 safety pharmacology studies with a lipid-containing *iv* formulation of posaconazole (with doses up to 40 mg/kg/day) showed no treatment-related effects on heart rate, diastolic blood pressure, ECG intervals (RR, PR, QRS, QT, QTc), or ECG morphology and rhythm

- Pharmacodynamic drug interactions

No pharmacodynamic drug interaction studies were conducted.

Pharmacokinetics

The pharmacokinetics profile of posaconazole was assessed following administration of single and repeated oral dose to mice, rats, pregnant rats and rabbits, dogs and monkeys. Additional pharmacokinetics data were obtained after intravenously administration of single dose to mice, rats, and dogs.

In most studies, oral administration of posaconazole was as a suspension in 0.4% aqueous methylcellulose or by dietary admixture. Intravenous administration used posaconazole as a solution in 40% hydroxypropyl-β-cyclodextrin.

Sensitive and selective HPLC and LC-MS/MS bioanalytical methods were used to determine plasma and urine concentrations.

- Absorption

Posaconazole was slowly absorbed and slowly eliminated in all species including humans. Tmax ranged from 6 to 8 h in fed mouse, 3 to 12 h in fed rat, 6 to 28 hour in fed dog, 3 to 8 h in fed monkey and 5-24 in human. In mice, following *iv* administration of 10 mg/kg, posaconazole was eliminated with clearance (CL) and t½ values of 0.097 l/hr/kg and 6.86 hr, respectively. In rats, following *iv* administration of 20 mg/kg, posaconazole was slowly eliminated with clearance values of 0.207 and 0.123 l/hr/kg in males and females, respectively. Values for t½ were 10.8 and 20.1 hr for males and females, respectively.

Absolute bioavailability accounted for 44 to 49 % in fed mouse, 6.7 % in fasted male rat, 11.8 % in fasted female rat, 11 % and 27 % respectively in fasted and fed dog.
The difference of exposure between sexes in rats was due to greater bioavailability and slower clearance of posaconazole in female.

Bioavailability of posaconazole following oral administration exhibited a very high food effect.
Exposure increased after oral administration to rats fed *ad libitum* (4- to 7-fold greater than fasted rats) and fed dogs (4-fold greater than fasted dogs). Dietary administration of posaconazole to rats increased exposure by about 2.5 times that of fed rats dosed by gavage.

Exposure to posaconazole increased with the dose but in a less than proportional manner.

Exposure to posaconazole in pregnant rats was lower than that observed in non gravid rats. The reason for this difference is unknown at the present time. Exposure to posaconazole in pregnant rabbits increased with increasing dose and was dose proportional.

- Distribution

After administration of a single oral dose of ^{14}C-posaconazole to fed, fasted albinos and pigmented rats and fed pregnant rats, radiocarbon was widely distributed and the pattern of tissue distribution of radiocarbon was the same in pregnant and non pregnant rats. The combined contents of the gastrointestinal tract in the first 8 to 12 hr contained up to ~81% (females) and ~86% (males) of the total dose. The maximum concentration of radiocarbon in all tissues was observed between 4 and 12 hr postdose. By 168 hr after a single oral dose, radiocarbon was below the limit of detection in most tissues.

The same pattern was observed after once daily administration for 21 day, however, radiocarbon was still present in most tissues 240 hr after the final dose.

Posaconazole was transferred across the placental barrier and is secreted to milk.

Posaconazole is highly bound to plasma proteins in mouse, rat, rabbit, dog and human ranging from 97.9 % to 99.2 %, primary to HSA, and independently of posaconazole concentration over the range of 0.05 to 20 µg/ml. In addition there was no difference between serum and plasma protein binding of ^{3}H-posaconazole.

- Metabolism and excretion

In vitro human microsomal enzyme studies showed that posaconazole is an inhibitor of CYP3A4 with a Ki of 290 ng/ml, which is within the human plasma concentration range. However, there was no induction of any CYP450 enzymes and no inhibition of CYP1A2, CYP2A6, CYP2C9, CYP2C19, or CYP2D6 at concentrations less than 210 µg/ml.
In-vivo metabolism studies have been conducted in mice, rats, dogs and humans with ^{14}C-posaconazole.

Posaconazole undergoes direct glucuronidation, oxidation, cleavage (N- and O-dealkylation), and conjugation (glucuronidation and sulfonation) of cleavage and oxidative products. In all species, the majority (53.0 to 100%) of the radiocarbon observed circulating in plasma was associated with parent compound. No chiral inversion was observed in rat and dog serum or monkey and human plasma after single oral administration.
Single oral dosing in all species revealed that 80.3% to 100% of the radiocarbon in faeces co-eluted with posaconazole. In contrast, 1.85% or less of the radiocarbon in urine co-eluted with posaconazole. Two minor human metabolites, called "M11" and"M10", were identified in human urine and faeces that did not appear to be found in rats and dogs. However, the radio chromatograms of urine and faeces of both rats and dogs had small peaks that eluted in a region of the chromatogram consistent with the location of M10 and M11. Thus, it is likely that these species were exposed to small amounts of both of these metabolites, but due to differences in the limit of detection of the different instruments used for analysis they were not identified in the earlier animal studies.

After *iv* administration, the metabolite profiles in faeces were similar to those observed after oral, but in contrast the profiles of urine samples collected after *iv* administration appeared to be significantly different to that seen after oral dosing. Although the reason for these differences has not been firmly established, possible reasons include a facilitation of posaconazole renal clearance when administered *iv* as a solution in hydroxypropyl-β-cyclodextrin (HPβCD), or that *iv* administration of posaconazole circumvents first pass metabolism that might occur after oral administration.
After intraduodenal (ID) administration of 5 ml bile from male *iv*-dosed donor rats to male recipient rats, approximately 40% of the administered radiocarbon was in the bile and urine combined, indicating enterohepatic circulation of posaconazole. In contrast, clearance and t½ values were not different in dogs with and without bile collection after *iv* dosing, suggesting that enterohepatic circulation of posaconazole or its metabolites is not significant in dogs.

Fed male rats treated with oral doses of 80 mg/kg/day posaconazole for 8 days had significant decreases in hepatic benzphetamine N-demethylase and 7-ethoxyresorufin O-deethylase activities.

Toxicology

- Single dose toxicity

The single dose toxicity studies have been carried out in mice, rats and dogs by oral and intravenous route.
After oral administration, posaconazole showed low acute toxicity in all tested species. The no-effect oral doses were 2000 and 1500 mg/kg in male and females mice, respectively and were >5000 and <4000 mg/kg in males and female rats, respectively.
After intravenous administration as a solution in hydroxypropyl-β-cyclodextrin, the no-effect doses were 22.5 and 15 mg/kg for male and female mice, respectively and 20 mg/kg in rats.
The non-lethal oral dose in dogs was 2000 mg/kg, with the no-effect doses being 480 and 240 mg/kg for males and females, respectively.

- Repeat dose toxicity (with toxicokinetics)

Repeated-dose toxicity studies have been conducted in mice for up to 3 months with oral doses up to 90 mg/kg, in rats for up to 6 months with oral doses up to 45 mg/kg and in dogs for up to 1 year with oral doses up to 30 mg/kg. Results of a 1-year neuropathology study in cynomolgus monkeys have also been submitted.

Posaconazole caused several toxicological effects that are also observed with other antifungal substances in the azole class.

Phospholipidosis, defined as vacuolisation of cells of monocyte/ macrophage lineage, was observed in all species studied. The main findings were foamy alveolar macrophages or accumulation of vacuolated macrophages in lungs, vacuolated histiocytes in spleen, thymus, lymph nodes and other lymphoid tissues and vacuolated Kupffer cells in the liver. Posaconazole-induced phospholipidosis occurred without apparent functional effects, with the exception of pulmonary phospholipidosis seen in rats in the 2-year carcinogenicity study. In contrast to the other species tested, the rat had the greatest severity of pulmonary phospholipidosis to the degree that the phospholipid-filled macrophages occupying the alveoli obstructed the alveoli and resulted in effects on respiration.

The lungs of mice, dogs and monkeys exposed to posaconazole at exposures comparable to or greater than those achieved in rats in the 2-year carcinogenicity study, also had accumulations of vacuolated or foamy macrophages typical of phospholipidosis. However, in mice, dogs and monkeys, the pulmonary phospholipidosis seen was less severe and there were no clinical observations, necropsy or histopathological findings suggestive of overt functional changes related to pulmonary phospholipidosis. The no effect dose levels for phospholipidosis in cells of monocyte/ macrophage lineage in dogs, rats, mice and monkeys were 1, <5 (dietary administration), <10 (dietary administration) and <15 mg/kg respectively.

Acute coagulopathy syndrome was recorded in 1 and 6 month studies in dogs. In a 19-day investigational study, most of treated dogs had increased plasma von Willebrand Factor (vWf).

Posaconazole also caused hypertrophy or hyperplasia of the adrenal glands in mice (at ≥ 30 mg/kg), rats (all doses) and dogs (≥ 30 mg/kg), a well-known effect of azoles on adrenal cortical steroidogenesis.

In dogs, but not in the other species, phospholipidosis in neural tissue, as indicated by vacuolation of neurones in the brain and Auerbach's plexus of the intestine, and swelling of axons in the brain and spinal cord, was observed in the 6 and 12 months repeated-dose toxicity studies. Neuronal and axonal changes occurred at 10 and 30 mg/kg. At 3 mg/kg, only neurones of Auerbach's plexus were affected.
A 12 months neurotoxicity study, designed to specifically investigate posaconazole effects, did not show functional changes in the central and peripheral nervous system based on neurologic examinations and electrophysiological measurements. The highest dose at which neuronal phospholipidosis without functional effects were observed in dogs was 30 mg/kg, which represents animal to human exposure multiples of approximately 3 fold. The lack of functional changes in the central and peripheral nervous system in the parameters examined in both dogs and monkeys indicates that neuronal phospholipidosis observed in dogs is, therefore, unlikely to be of clinical significance in humans.

In the one-month repeated dose toxicity study in dogs, doses of 45 and 90 mg/kg^{-}/day^{-} resulted in minor increased QT intervals, reversal of T waves, STj point depression, deep negative T waves and increased U wave amplitude in precordial leads. All these findings were reversible at the end of an 8-week recovery period. These electrocardiographical changes correlated with moderate decreases in serum potassium at the same doses.

- Genotoxicity *in vitro* and *in vivo*

Posaconazole was not mutagenic in in vitro studies (gene mutation in bacteria, hamster ovary cells and human peripheral blood lymphocytes assays) nor clastogenic in vivo (micronuclei bone marrow assay in mice with doses up to 180 mg/kg).

- Carcinogenicity (with toxicokinetics)

The carcinogenic potential of posaconazole has been investigated in long term oral studies in rats with doses up to 30 mg/kg/day and in mice with doses up to 90 mg/kg/day.
In rats, the incidence of adrenal cortical (cortical cell adenoma or carcinoma) and adrenal medullary tumours (benign and malignant pheochromocytomas) was increased in the high-dose in males (30 mg/kg/day) and females (20 mg/kg/day). Adrenal cortical tumours are attributed to the posaconazole-induced interruption of steroidogenesis, with consequent increased secretion of ACTH, leading to chronic proliferation of cortical cells. Adrenal medullary tumours were considered consequence of altered calcium homeostasis. The effect on the adrenal glands in the rat is a known class effect of azole antifungals.

In mice, histiocytic hyperplasia was observed in the lymph nodes. This finding was a hyperplastic (non-neoplastic) change due to proliferation of fixed macrophages (histiocytes) in several organs including lymph nodes. The affected cells stained for lysozyme immunohistochemically, indicating that they were of histiocytic origin. Ultrastructurally, they were large interdigitating cells containing primary and secondary lysosomes consistent with cells of histiocytic origin. There was no evidence of phospholipidosis (membranous lamellar inclusions) within the proliferative cell population as demonstrated by transmission electron microscopy. The no effect dose for histiocytic hyperplasia in lymph nodes in mice was 10 mg/kg. The animal-to-human exposure multiple at this dose is 1.51-fold and 5.17-fold for healthy subjects and patients, respectively. The animal-to-human exposure multiples for 30 mg/kg, a dose at which histiocytic hyperplasia in lymph nodes was seen, were 3.69-fold and 12.7-fold in healthy subjects and patients, respectively.

- Reproductive and developmental studies

Posaconazole had no effects on male fertility (doses up to 180 mg/kg) or on female fertility in rats (up to 45 mg/kg).
In embryo-foetal development studies in rats, doses of 27 mg/kg led to foetuses with skeletal variations and malformations. In rabbits, there were increases in resorptions and skeletal variations (predominantly reduced ossification of the sternebrae and an extra pair of thoracic ribs). These effects are, however, known to correlate with treatment related effects on steroidogenesis. The NOEL was $\underline{\geq}$ 80 mg/kg for maternal toxicity and 20 mg/kg for embryo-foetal toxicity.
In the peri- and post-natal development study in rats, deaths occurred in females treated at $\geq$ 18 mg/kg/day, due to drug-related dystocia. Increased length of gestation and dystocia occurred at doses of $\geq$ 18 mg/kg/day. Reduced F_1 mean live litter size and F_1 postnatal viability also occurred at $\geq$ 18 mg/kg/day. Foetal abnormalities, consistent with those seen in the embryo-foetal development studies, were observed at 36 mg/kg/day.

- Local tolerance (if applicable)

The acute dermal toxicity was evaluated in male and female rats administered a single topical application at 2000 mg/kg. Only slight dermal irritation was observed and this cleared in all animals by Day 4. Posaconazole was not considered a dermal sensitiser in guinea pigs.
Posaconazole did not cause any irritation to the skin in rabbits. Posaconazole was slightly irritating to the rinsed eyes of rabbits and practically not irritating to the unrinsed eyes of rabbits.

- Other toxicity studies

A series of immunotoxicology studies in mice indicated minimal changes in immune function at 30 or 90 mg/kg/day after one and 3 months of dosing. The changes in the immune system parameters in the

immunotoxicity studies were minimal and reversible, indicating that administration of posaconazole had no permanent effect on the function of the immune system. The no effect level was between 10 and 30 mg/kg/day.

There were no posaconazole-related neurotoxicity or neuropathology findings in monkeys administered daily doses of 180 mg/kg/day for 12 months.

Ecotoxicity/environmental risk assessment

An assessment of the risk was performed and no significant risk to the environment related to the use of posaconazole is anticipated.

4. Clinical aspects

Introduction

The pharmacology programme consisted of 23 studies involving 531 subjects.

The clinical programme in refractory invasive fungal infections (rIFI) comprised one main study (P00041) and a control study (P02387) to be used as external control to the main study. An overview of these studies is displayed in table 2.

Table 2: Overview of the clinical studies in rIFIs

Study number	**Design** **Regimen**
P00041	Open label, multicentre Phase III study n = 330 patients (≥ 13 years) with proven/probable invasive fungal infections refractory to or intolerant of standard antifungal therapy Posaconazole 200 mg x 4/day while hospitalised, followed by 400 mg x 2/day as outpatient for up to 12 months
P02387	Retrospective chart review to provide external control study, n=279 patients (≥ 13 years) with proven/probable invasive fungal infections refractory to or intolerant of standard antifungal therapy
P02952	Review committee analysis for the comparison of data from P00041 & P02387
P01893	Open Phase II study, n=98 from 18 to 74 years Loading dose (800 mg/day or 1600 mg/day given in divided doses) for 2 days followed by 800 mg/day (as a single dose or in divided doses) or 1200 mg/day.

In addition the results of an open label pilot study (C/I97-280) in first line treatment of non-meningeal coccidiodomycosis were submitted.

All clinical studies were claimed to have been performed according to Good Clinical Practice.

Pharmacokinetics

The studies are listed in table 3. Several formulations of posaconazole were used as shown below.

Table 3: Overview of the pharmacology studies

Bioavailability/Bioequivalence Studies			
N=21	I95-099	Tablet / 100 mg Capsule / 100 mg	Relative bioavailability (RBA) of Tablet/Capsule in Fed and Fasted Conditions
N=20	I96-099	Tablet / 100 mg Suspension / 40 mg/ml	High-Fat/Non fat and Fasted conditions and RBA of Suspension vs Tablet
N=24	I96-172	Tablet / 100 mg Capsule / 100 mg	RBA of Two Optimised Tablet and Capsule Formulations
N=23	P02812	Suspension / 40 mg/ml	RBA With/Without Oral Nutritional Supplement
Pharmacokinetic Characteristics			
N=54	I95-098	Tablet / 50 mg-100 mg	Rising Single-Dose Safety/Tolerance
N=48	I96-089	Tablet / 50 mg-100 mg	Rising Multiple-Dose Safety/Tolerance
N=8/8	C96-104, P02418	^{14}C-Suspension / 40 mg/ml	Radiolabeled ^{14}C-AME Studies
N=18	C97-444	Suspension / 40 mg/ml	Compared BA of 3 Dose Regimens
Intrinsic Factors			
N=16	I97-195	Suspension / 40 mg/ml	Effect of Hepatic Disease on PK
N=24	P01940	Suspension / 40 mg/ml	Effect of Renal Disease on PK
N=64	P02810	Suspension / 40 mg/ml	Effect of Age and Gender on PK
N=56	P02811	Suspension / 40 mg/ml	Effect of Race on PK
Drug Interaction			
N=12	I97-016	Tablet / 100 mg	Effect on Drug Metabolizing Enzymes
N=12	C96-120	Tablet / 100 mg	PK Interaction with Antacid
N=12	C96-173	Tablet / 100 mg	PK Interaction with Cimetidine
N=24	I96-207	Tablet / 100 mg	PK Interaction with Rifabutin
N=36	C96-201	Tablet / 100 mg	PK Interaction with Phenytoin
N=4	C96-247	Tablet / 100 mg	PK Interaction with Ciclosporin
N=17	C96-190	Tablet / 100 mg	PK Interaction with Nucleoside Analogues (zidovudine or lamivudine) and Protease Inhibitors (ritonavir or indinavir)
N=34	P02862	Suspension / 40 mg/ml	PK Interaction with Tacrolimus
N=12	P02489	Suspension / 40 mg/ml	PK and PD Interaction with Glipizide
Pharmacokinetics in Patients			
N=31	C96-421	Suspension / 40 mg/ml	PK in Neutropenic Autologous Bone Marrow Transplant Patients

- Absorption

Following oral administration, peak plasma concentrations were reached within 3-4 hours and 4-10 hours in fasted and fed states, respectively.
Due to the absence of an intravenous formulation, the absolute oral bioavailability could not be determined.

With the oral suspension, it was shown in a 3-way crossover study in the fasting state that the AUC of posaconazole could be increased in healthy volunteers by dividing the total daily dose of 800 mg into either 400 mg twice daily (x 1.7) or 200 mg four times daily (x 2.6) (table 4).

Table 4: Compared bioavailability of 3 dose regimens (C97-444)

Parameter	Ratio[a]	Relative Bioavailability (%)	90% Confidence Interval
Cmax (ng/ml)	B/A C/A C/B	174 275 158	129 - 234 204 - 370 118 - 213
AUC(0-48 hr) (ng·hr/ml)	B/A C/A C/B	165 261 159	127 - 214 201 - 339 122 - 206

a: A = 800 mg posaconazole administered QD.
B = 400 mg posaconazole administered Q12 hr.
C = 200 mg posaconazole administered Q6 hr.

When posaconazole was administered as the suspension with a non-fat meal or nutritional supplement, the AUC was 2.6 times that seen in the fasted state. When administered with a high fat meal the posaconazole exposure is approximately 3.4 to 3.9 higher than in fasted state.

Bioequivalence

Bioequivalence was not demonstrated between the co-precipitate tablet *vs* research capsule, research capsule *vs* the size-optimised tablets, research *vs* size-optimised capsules or co-precipitate tablet *vs* suspension when administered with a high-fat meal. In a *post hoc* evaluation of the cumulative dataset the point estimates for AUC and Cmax under fed conditions for the comparison of the suspension to research capsule AUC[I] were estimated at 109.7% and 96.9%, respectively, which should not be clinically significant.

In another bioequivalence study, oral suspensions with particle sizes of 1.7 and 2.3 µm were not bioequivalent. The median particle size for the suspension used in the main study of efficacy (P00041) was in the range of 1.6 - 1.8 µm. Further investigations did not show any clear relationship between steady state AUC and particle size. The original proposed specifications for particle size were wider than those used for the production of clinical batches. Because of the uncertain clinical implication, the applicant was requested to tighten the specifications. In addition the applicant undertook to further investigate pharmacokinetic variability of posaconazole with the intention of development of optimised method that would be suitable for further investigation of the effect of particle size distribution on posaconazole bioavailability.

- Distribution

Posaconazole had a large apparent volume of distribution (mean 1744 l and range 774 to 5845 l), indicating high tissue penetration. Posaconazole is highly protein bound (98.2%), mainly to albumin and binding is concentration-independent. Posaconazole is a substrate for and an inhibitor of p-glycoprotein (P-gp) mediated efflux from cells.

- Excretion

In vitro human microsomal enzyme studies showed that posaconazole is an inhibitor of CYP3A4 with a Ki of 290 ng/ml, which is within the human plasma concentration range. However, there was no induction of any CYP450 enzymes and no inhibition of CYP1A2, CYP2A6, CYP2C9, CYP2C19, or CYP2D6 at concentrations greater than 210 µg/ml.

Posaconazole is mainly metabolised via UDP-glucuronidation.

In a mass balance study, 77% and 14% of a ^{14}C labelled oral dose were recovered in faeces and urine respectively (total 91%). The major component in plasma was associated with posaconazole (50% of profiled radioactivity). The major plasma metabolite was monoglucuronide of posaconazole which constituted 18-28% of the profiled radioactivity. In addition, at 24 hours post-dose, a di-glucuronide and an oxidative metabolite of posaconazole constituted 9% and 8% of the percent of radiocarbon in the profiled plasma, respectively.
The urine contained two mono-glucuronide conjugates and a di-glucuronide conjugate of posaconazole but these metabolites together accounted for no more than 4% of the dose. The remaining urinary radioactivity was present as trace amounts of oxidative metabolites. Faecal radioactivity was composed mainly of parent compound (93.8% of the radioactive profile; 66.3% of the dose) and minor oxidative metabolites. The presence of parent drug in the faeces was consistent with unabsorbed drug, non-metabolised drug, drug actively secreted into the gut or glucuronide conjugates hydrolysed to the aglycone by gut flora.

The mean half-life was approximately 25 hours following administration of single doses of 200-1200 mg, indicating that the metabolism of posaconazole is not saturable across this dose range. After multiple dosing for 14 days in the fed state in study I96-089, the mean steady-state elimination t½ was long 19 to 31 hours and Vd/F was 343 to 486 l indicating extensive tissue penetration.

- Dose proportionality and time dependencies

In a single dose study (after a high fat meal), plasma concentrations increased approximately in proportion to doses from 50 mg to 800 mg. The 1200 mg dose yielded slightly lower plasma concentrations than the 800 mg dose.
On dosing at up to 400 mg twice daily with standardised high-fat meals for 14 days in healthy volunteers, an approximate dose proportional increase in exposure was observed on day 14. Steady-state concentrations were achieved by day 10 of dosing. The accumulation ratio of 6.6 to 8.3 was greater than would be expected based on the half-life value of 19-31 hours.

- Intra- and inter-variability

The variability in AUC and Cmax values between subjects was higher in patient studies (71% - 86%) relative to healthy volunteer studies (~35% - 50%). In addition, exposure to posaconazole in the majority of healthy volunteers was ~3 times higher than in patients administered the same dose. This was thought likely due to reliable consumption with food in healthy subjects and more variable conditions of dosing in patients.

At present there is no explanation for the inter-individual variability seen in posaconazole exposures and there is no indication that the dose of posaconazole should be tailored according to gender, age, P-gp, MDR-1 genotype or weight.
Due to the inter-individual variability and effect of food on posaconazole exposures, the applicant committed to further evaluate the pharmacokinetics of posaconazole in various types of patients under various dosing conditions.

- Special populations

Impaired renal function

Following a single 400 mg dose of posaconazole suspension with a high fat meal, there was no effect of mild and moderate renal insufficiency on posaconazole pharmacokinetics (n = 18; 6 per group Clcr $\geq$ 20 ml/min/1.73 m^2). In subjects with severe renal insufficiency on haemodialysis (n = 6; Clcr < 20 ml/min/1.73 m^2) no definitive conclusion could be drawn due to the high variability exposure (> 81 %) compared to the exposure in other groups (< 49 %).
No effect of mild renal insufficiency on the pharmacokinetics of posaconazole is expected and therefore no dose adjustment is necessary. As posaconazole is not significantly renally eliminated, an effect of severe renal insufficiency is not expected and therefore no dose adjustment is warranted. Posaconazole is not removed by haemodialysis.

Impaired liver function

In a study of single 200 mg dose of posaconazole oral suspension with a standardised high-fat meal, there was a trend towards decreased Cmax and increased AUC values with the increased severity of hepatic dysfunction (table 5). There was also an increase in half-life associated with a decrease in hepatic function.

Table 5: Mean (%CV) Pharmacokinetic Parameters for Posaconazole Following a Single 200 mg Oral Dose to Subjects With Normal Liver Function and With Mild, Moderate, and Severe Chronic Liver Disease

Parameter	Mean (%CV)			
	Normal (n=4)	Mild (n=4)	Moderate (n=4)	Severe (n=4)
Cmax (ng/ml)	508 (35)	545 (34)	414 (16)	347 (28)
Tmax (hr)[c]	7.5 (5-12)	5 (5-6)	11 (10-24)	18 (5-36)
AUC(tf) (ng·hr/ml)	18220 (50)	26490 (45)	23497 (35)	24238 (45)
AUC(I) (ng·hr/ml)	18944 (51)	25805[a] (60)	23535[a] (41)	30521[b] (NC)
CL/F (l/hr)	12.5 (42)	9.61[a] (50)	9.65[a] (45)	6.91[b] (NC)
Vdarea/F (l)	381 (39)	334[a] (31)	431[a] (26)	473[b] (NC)
t½ (hr)	22.1 (22)	26.6[a] (32)	35.3[a] (55)	46.1[b] (NC)

a: n=3; t½, CL/F, AUC(I), and Vd/F could not be determined for some subjects as the number of samples collected during the terminal elimination phase were not sufficient.

b: n=2, CV not calculated; t½, CL/F, AUC(I) and Vd/F could not be determined for some subjects as the number of samples collected during the terminal elimination phase were not sufficient.

A pharmacokinetic model similar to the one used for renal impairment suggested higher mean and geometric mean Cmax and AUC(τ) values (by 2-fold or more) in severe hepatic insufficiency for 200 mg qid or 400 mg bid regimens and regardless of food. Although clear dose recommendations cannot be given, the SPC describes the findings and advises caution on the use in patients with severe hepatic impairment. The applicant has committed to acquire more data on use in individuals with hepatic insufficiency.

Gender, Race, Age and Weight

There were no clinically relevant effects of gender, weight and race (Caucasians and African-Americans) on the pharmacokinetics parameters. A significant increase in Cmax and AUC up to 49 % was found in the elderly, nonetheless it was not considered necessary to require any dose adjustment.

No specific pharmacokinetics study was conducted in children.

Pharmacokinetics in target population

The results from study P00041 in which patients were to be dosed with food (but may not always have complied with this recommendation) suggested that responders tended to have greater mean plasma posaconazole concentrations than non-responders, although the range of plasma concentrations was large (table 6).

Table 6: Summary Statistics of Posaconazole Concentration *vs* Global Response – DRC, mITT subset

Response Status		Concentration (ng/ml)				
	n	Median	Mean	SD	Minimum	Maximum
All Subjects (n=158)						
Responder[a]	93	804	927	655	0	2990
Non-responder	65	480	637	605	14	3490
Subjects With *Aspergillus* Infection (n=66)						
Responder[a]	34	704	746	454	60	2010
Non-responder	32	398	500	406	57	1880

a: Subjects with a global response of "complete response" or "partial response," as adjudicated by the DRC.

The relationship between positive clinical response and the plasma concentration natural logarithm was statistically significant according to this model for all subjects combined (n=158; p = 0.01), and for subjects with *Aspergillus* infection (n=66; p = 0.02). Even when baseline MIC was included in the analysis, with a smaller sample size, the association of plasma concentration with global response

remained statistically significant for all subjects combined (n=78; p = 0.021), and for subjects with *Aspergillus* infection (n=33; p = 0.012).

- Pharmacokinetic interaction studies

The majority of the interaction studies were carried out in healthy volunteers with a multiple dose regimen that was most often 200 mg (as tablets) once daily to steady state administered with a meal or nutritional supplement. Since it has been shown that data obtained in healthy volunteers with 200 mg daily as tablets taken with a high fat meal are likely to be close to those that will be achieved in patients with suspension at 400 mg bid, the findings of these studies were considered relevant.

Posaconazole administered at 200 mg once daily with food increased the midazolam AUC by 83% after intravenous administration to healthy volunteers. Due to the potential for inhibition of intestinal CYP3A4 by posaconazole, an even greater effect on the AUC midazolam is expected following oral administration of posaconazole. Therefore a recommendation has been added in the Summary of Product Characteristics to consider dose adjustments for all benzodiazepines that are metabolised through CYP3A4 during co-administration with posaconazole. In addition the applicant agreed to undertake to conduct an interaction study with oral midazolam, the results of which will be submitted as part of the follow-up measures to be fulfilled post-authorisation.

Antacid (Mylanta Double-Strength Liquid with 25.4 mEq acid neutralising capacity per 5 ml) was given with posaconazole under either fed (high-fat meal; 54 g fat) or fasted conditions. The antacid slightly increased the relative oral bioavailability of posaconazole in the fasted state (by 15%) but decreased bioavailability in the fed state (by 12%).

Concomitant administration with cimetidine 400 mg twice daily decreased the Cmax and AUC(τ) of posaconazole by ~40% but posaconazole Tmax and t1/2 did not change. The effect on posaconazole exposure is most likely due a pH-mediated decrease in absorption and so the SPC also mentions co-administration with proton pump inhibitors.

Rifabutin 300 mg once daily for 7 days reduced posaconazole AUC and Cmax values by 51% and 57% with a doubling in clearance. Rifabutin Cmax and AUC(τ) increased by 31% and 72%, respectively, with a 40% decrease in rifabutin CL/F. Three subjects discontinued this study due to leukopenia (one after rifabutin but prior to posaconazole and two after combination dosing). Therefore a statement has been included in the SPC to avoid the co-administration of posaconazole and rifabutin and similar inducers such as rifampicin.

At steady state, co-administration of posaconazole with phenytoin resulted in reductions of approximately 50% in posaconazole Cmax and AUC(0-24 hr) values with a 99% increase in clearance of posaconazole. Mean steady state phenytoin Cmax and AUC(0-24 hr) values were both increased by 15.5% on co-administration. Therefore a statement has been included in the SPC to avoid the co-administration of posaconazole and phenytoin and similar inducers such as carbamazepine, phenobarbital and primidone.

Four male heart transplant recipients on ciclosporin for at least 15 months with a stable dose for at least 6 weeks received 200 mg posaconazole (tablets) once daily for 10 days with a high-fat meal. Doses had to be lowered based on ciclosporin blood levels in 3/4 subjects by 14%-29%. Based on the findings and on a model to extrapolate the data to 400 mg bid, the increase in ciclosporin AUC on co-administration with the recommended doses for invasive fungal infections is likely to be in the range 1.5 to 2-fold depending on whether posaconazole is taken with food, particularly with a high fat food. Monitoring of ciclosporin levels is recommended and dose adjustment should be based on individual ciclosporin concentrations.

Single doses of tacrolimus 0.05 mg/kg on Days 1 and 14 with posaconazole 400 mg suspension twice daily on Days 7 through 14 gave increases in tacrolimus AUC(I) and Cmax values of 458% and 221%,

respectively, but Tmax did not change. The t½ of tacrolimus increased by ~7 hours and the CL/F decreased 80% on co-administration. Therefore a statement has been included in the SPC recommending dose adjustment (e.g. a reduction in the tacrolimus dose to about one third of the current dose) and close monitoring of blood levels during treatment. The applicant committed to obtain data on sirolimus.

In 17 HIV-infected patients already on treatment with zidovudine and lamivudine or another NRTI plus ritonavir or indinavir and receiving 200 mg posaconazole (tablets) once daily for 14 days with a non-fat breakfast, the posaconazole mean AUC value was consistent with that observed previously in a study where 200 mg QD was given with a non-fat meal, suggesting no significant metabolism by CYP3A4. Posaconazole did not notably affect the pharmacokinetics of indinavir, zidovudine, or lamivudine (AUC changes by 7%-16%). There was a 30% increase in exposure to ritonavir (30%). A statement has been included in the Summary of Product Characteristics to draw the attention of the prescribers that because protease inhibitors are CYP3A4 substrates, it is expected that posaconazole will increase plasma levels of these anti-retroviral agents. The applicant committed to perform a study to evaluate the interaction between posaconazole and a boosted PI (atazanavir) as well as efavirenz (CYP3A4 inducer), the results of which will be submitted as part of the follow-up measures to be fulfilled post-authorisation.

When 10 mg glipizide was given on Days 1 and 11 and 400 mg posaconazole suspension was given twice daily from Days 2-11 with a high-fat meal, glipizide had a small effect on the pharmacokinetics of posaconazole that was not thought to be clinically significant. Co-administration had a small effect on the pharmacokinetics of glipizide but there was a mean decrease in glucose concentrations with statistically significant differences in the log-transformed glucose AUC(0-24 hr), Cmin, and Cmax values. Also, 6 of the 11 evaluable subjects in this study had a decrease in Cmin glucose values on co-administration. However, there was no definitive correlation between individual glipizide and glucose concentrations. Because the effects on glipizide and glucose levels might be significant in diabetics**,** monitoring of glucose concentrations is recommended in diabetics taking sulphonylureas.

Pharmacodynamics

- Mechanism of action

See the preclinical part of this document. The applicant committed to continue to support programmes of surveillance of resistance and to provide regular updates on the occurrence of resistance to posaconazole.

Relationship between plasma concentration and effect

Data from 6 Phase 2/3 clinical studies with orally administered posaconazole were analysed to explore the correlation between susceptibility (MIC), pharmacokinetics (PK), pharmacodynamics (PD), and clinical outcome. Data were available for 924 isolates from 810 posaconazole-treated subjects, including many strains with MICs greater than 2 µg/ml posaconazole but it has not been possible to determine susceptibility testing breakpoints.

In animal studies the PK/PD parameter that was found to correlate best with triazole efficacy was the AUC of free unbound drug/MIC. An analysis of clinical cases for which there were PK, MIC and clinical outcome data (n=189) showed a correlation between susceptibility, total drug AUC/MIC and clinical outcome. The AUC/MIC ratio associated with a successful clinical outcome (complete or partial clinical response) in subjects infected with *Aspergillus* (n=33) was higher (~200) than that (~15) observed for *Candida* (n=45). Most of the patients with *Candida* had refractory OPC while all of the patients with *Aspergillus* had invasive disease. For those subjects achieving these respective ratios, 88% (15/17) of the *Aspergillus*-infected subjects and 90% (26/29) of the *Candida*-infected subjects had a successful outcome. Although numbers are small, the results suggest that it is important to ensure that the maximal plasma levels are achieved, especially for patients infected with *Aspergillus*.

Due to the inter-individual variability and effect of food on posaconazole exposures, the applicant committed to further explore whether there is a discernible relationship between exposure and outcome.

- Secondary pharmacodynamics

Some potential for prolongation of the QTc interval might be anticipated as for other azoles, although the data in healthy subjects did not suggest that taking 400 mg bid of the suspension with food would produce notable changes in conduction. Since plasma concentrations achieved by this dose regimen are higher in volunteers than in patients, there seemed to be little potential for clinically significant QTc prolongation during routine clinical use (see also clinical safety for further discussion on QTc).

With respect to liver function, approximately 1% of healthy volunteers had elevations greater than 2.5 times the upper limit of normal (CTC Grade 2) for alanine transaminase (ALT), aspartate transaminase (AST) and/or gamma-glutamyl transferase (GGT). The relationship between LFT elevation by CTC grade and posaconazole AUC was evaluated using AUC[τ] for multiple-dose studies and AUC[I] for single-dose studies assuming linear kinetics. Where there were multiple LFT elevations, the highest single value was included and crossover periods were counted separately. Although, the majority of the LFT elevations (CTC Grade 1) were observed in the 400 mg twice daily group (gives highest mean exposure), there was no clear association between CTC grade elevations in any of ALT, AST, or GGT and exposure to posaconazole in these studies.

Clinical efficacy

- Dose response

The choice of the dose is mainly based on pharmacokinetics data which showed that increasing the dose above 800 mg does not further enhance exposure to posaconazole.
The data clearly indicated a major food effect that was seen with all formulations tested and which reduced the degree of inter-subject variability (coefficient of variation 26-43 % compared to 31-75 % in the fasted state). In the fasting state, splitting the dose into 200 mg four times a day increased plasma concentrations in healthy volunteers (58 % over 48 hours) and it is expected that the effect would occur in patients.

Although the exact dosing conditions employed in P00041 are not known, the analyses of patient samples from this study did demonstrate a correlation between mean plasma levels and outcomes for *Aspergillus* and for other infections. In addition the results support a benefit over other therapies, as elaborated below including injected therapies, in the treatment of *Aspergillus*. What the patient pharmacokinetic data cannot determine, due to the design of the study, is whether the two regimens (400 mg BID or 200 mg QID) would or would not result in similar plasma profiles in patients with similar food intakes, disease features and other potentially important variables affecting exposure. Also, the clinical data cannot determine if the BID regimen is more or less efficacious than the QID regimen.

Overall there seem to be sufficient data to suggest that recommending 200 mg QID for those unable to take the suspension with food is a reasonable reflection of the data thus far. Also, recommending 400 mg BID when it is possible to take posaconazole with food, even if not a high fat meal, should provide satisfactory blood levels.

- Main Studies

Study P00041 was an open-label, multicentre and non-comparative study primarily intended to evaluate posaconazole oral suspension for treating patients with invasive fungal infections that were refractory or resistant to standard antifungal therapies.

Study P02387 was a retrospective study based on medical chart review of patients with invasive fungal infections either refractory or intolerant to standard therapy. These patients constituted an external control group that was mainly contemporary P00041.

An independent Data Review Committee (DRC) composed of 15 experts in the diagnosis and treatment of fungal infections and 2 expert radiologists was assembled to review the cases from P00041 and P02387 in a simultaneous, blinded fashion. The DRC assessed patient eligibility and global responses.

Study Participants

Study P00041
This study enrolled adults (> 18 years of age) and children (> 13 years of age) with:

- proven or probable invasive fungal infection which was refractory (according to prespecified criteria, see below) to standard antifungal therapies
- or a proven invasive *Aspergillus* species infection diagnosed by a brain biopsy
- or a proven invasive *Aspergillus terreus* infection
- or a positive blood culture for *Fusarium* within 7 days prior to start of study drug and temporally related clinical symptoms compatible with a *Fusarium* infection
- or a tissue histopathology within 7 days prior to start of study drug showing dichotomously branching septate hyphae in tissue specimens obtained by a needle aspiration or biopsy (excluding mucous membranes) and with isolation of *Fusarium* species from the same site

or
- a proven or probable IFI with a prior history of serious, severe, or life-threatening toxicity while receiving standard antifungal therapy
or
- a proven or probable IFI with preexisting organ dysfunction (such as renal dysfunction) that precludes the administration of standard antifungal therapy.

There are no standardised guidelines to define refractoriness, but the criteria used by the DRC were:
- Patients must have had treatment for an appropriate duration (≥ 7 days for *Aspergillus* and fusariosis, > 90 days for chromoblastomycosis and mycetoma and CNS coccidioidomycosis, and > 180 days for non-CNS coccidioidomycosis) with an effective (DRC opinion) antifungal agent prior to entry into the study.

and
- Require a change in mycological therapy (in agent, regimen, route or an additional agent)

accompanied by
- Failure to improve or progression of disease (with detailed definitions supplied).

Study P02387
To be considered as eligible, all following criteria were to be met:
- Adult (age ≥ 18 years) and children (age ≥ 13 years)
- Treatment of IFI between April 30, 1996 and April 30, 2001 at one of the centres participating in P00041 or at other centres
- Diagnosis of proven or probable IFI based on MSG/EORTC criteria
- Refractory IFI or intolerance to standard therapy
- The case must have enough post baseline information to assess global response

Several valid reasons have been provided to explain why patients identified from medical records as being eligible for P02387 had not been enrolled into P00041 itself in the sites that participated in both studies.

Treatments

Study P00041
Patients who began treatment in hospital received 200 mg of posaconazole oral suspension (40 mg/ml) 4 times daily (q.i.d.) followed by 400 mg of posaconazole oral suspension b.i.d. from the time of discharge from the hospital. Those not hospitalised at the beginning of treatment received posaconazole 400 mg b.i.d. throughout. All dosing was to be with food or nutritional supplement.

The maximum total duration of treatment was to be 12 months. Also, if the investigator, subject, and sponsor agreed, maintenance therapy with posaconazole could be continued under a separate study protocol (P02095).

Study P02387
The treatments that had been given were recorded.

Outcomes/endpoints

Study P00041
The primary efficacy end-point was the subject's global response status at the end of treatment as assessed by the Data Review Committee.

The end of treatment was defined as 7 days after either day 365 day on study, the last dose of posaconazole or the last dose before the first interruption in dosing of at least 14 days.

The definitions of responder/non responder as determined by the DRC based on clinical signs and symptoms attributable to IFI, radiographic assessment and mycology testing were:

Responders
- **Complete Response:** resolution of all attributable symptoms, signs, and radiographic, mycological, or bronchoscopic abnormalities, if present at baseline
- **Partial Response:** clinically meaningful improvement in attributable symptoms, signs, and radiographic, mycological, or bronchoscopic abnormalities, if present at baseline

Non responders
- **Stable Disease:** no improvement in attributable symptoms, signs, and radiographic, mycological, or bronchoscopic abnormalities, if present at baseline
- **Failure:** deterioration in attributable clinical or radiographic abnormalities necessitating alternative antifungal therapy or resulting in death
- **Unable to Determine:** If for any reason the global response cannot be assessed (e.g., insufficient medical records to determine outcome)

When applicable, the cause of death was also assessed.

There were a number of secondary endpoints including time to death from the beginning of posaconazole.

Since the data collection for the external controls in P02387 was retrospective, it was not possible to collect follow-up information in any sort of standardised fashion as it was done in P00041. Therefore, the global response rate at the end of treatment was chosen as the primary endpoint that could be assessed blindly and compared between P00041 and P02387 patient populations by the DRC.

Statistical methods

Study P00041

For this uncontrolled study, the global response rate was estimated and a 95% confidence interval was provided.

The final analysis plan referred to the following subsets of patients:
Intent to treat (ITT): All patients who received at least one dose of posaconazole between April 30, 1996 and April 30, 2001.
Modified Intention to Treat Subset (= "eligible patients" mITT)**:** Subset of ITT with a proven or probable IFI as determined by the DRC based on 2001 MSG/EORTC criteria [Ascioglu *et al*. 2002] and evidence of a refractory IFI or intolerance to standard antifungal agents as determined by the DRC. The primary analysis is based on this subset.
Efficacy Evaluable Subset (= evaluable patients)**:** Subset of mITT patients who have at least one assessment of global response that is not "Unable to Determine" as determined by the DRC.
Per Protocol Efficacy Subset: Subset of efficacy evaluable who has not received any prohibited medications or any concomitant systemic antifungal therapy for more than 5 consecutive days or for more than 20% of the total duration of the Treatment Period. Patients received ≥ 80% of the scheduled days of dosing during the Treatment Phase.

Report P02952
This report on the comparison of the results between P00041 and P02387 must be viewed with considerable caution since P02387 constituted an external control group. However, the applicant performed a primary analysis that was based on the MITT subset ("eligible" subjects with proven or probable invasive aspergillosis).
A logistic regression model was used to compare posaconazole-treated and control groups with respect to the global response rate at the end of treatment in subjects with IFI due to Aspergillosis.
The odds ratio for the treatment effects based on this model provides an estimate of the efficacy of posaconazole relative to control, and a two-sided test (alpha=0.05) was used to assess the significance of the treatment effect.

Clinical outcomes

Table 7: Patient disposition

	Number (%) of subjects	
	P00041 (N=330)	**P02387 (N=279)**
Disposition of subjects during the treatment phase - ITT subset		
Discontinued	193 (58)	109 (39)
Adverse events	102 (31)	5 (2)
Treatment failure	47 (14)	
Lost of follow-up	2 (1)	
Did not wish to continue	17 (5)	
Non-compliance with protocol	17 (5)	
Did not meet protocol eligibility	3 (1)	
Administrative	5 (2)	8 (3)
Death	*	96 (34)
Completed treatment phase	**137 (42)**	**170 (61)**

* *death reported separately.*

With respect to baseline data, the overall major characteristics of the study (P00041) and control (P02387) populations are shown below.

For the majority of characteristics, the groups were well matched, including proportions of patients with malignancy and bone marrow transplant (BMT) as well as sites of infections.

Table 8: Baseline data

ALL PATHOGENS Baseline Characteristic or Subgroup	Posaconazole (P00041) N	(%)	Control (P02387) N	(%)
ALL PATIENTS HAVING A PRIMARY PATHOGEN	**238**	**(100.0)**	**218**	**(100.0)**
DEMOGRAPHY				
Age (y)				
<18 y	11	(5)	6	(3)
18 to 64 y	202	(85)	190	(87)
≥65 y	25	(11)	22	(10)
Mean (SD)	44.1 (16.1) y		42.4 (15.9) y	
Female	77	(32)	68	(31)
Male	161	(68)	150	(69)
Caucasian	143	(60)	96	(44)
non Caucasian	95	(40)	122[a]	(56)
<65 kg	106	(45)	71	(33)
≥65 kg	114	(48)	77	(35)
Missing	18	(8)	70	(32)
N	220		148	
Mean (SD)	66.48 (15.96) kg		67.81 (16.24) kg	
Time Interval of Enrollment				
30 APR 1996 to 31 DEC 1998	NA		57	(26)
01 JAN to 31 DEC 1999	33	(14)	57	(26)
01 JAN to 31 DEC 2000	151	(63)	79	(36)
01 JAN to 30 APR 2001	54	(23)	25	(11)
P00041 and P02387	170	(71)	192	(88)
P00041 only	68	(29)	NA	
P02387 only	NA		26	(12)
Large Site	60	(25)	38	(17)
Other Sites Combined	178	(75)	180	(83)
USA	165	(69)	117	(54)
non USA	73	(31)	101	(46)

Global response

Analysis of the global response at the end of treatment for patients with refractory /intolerant fungal infection is presented in table 9.

Table 9: Global Response at End of Treatment mITT

ALL PATHOGENS	Posaconazole (P00041) N	(%)	Control (P02387) N	(%)
Total Number (%) of Patients	**238**	**(100.0)**	**218**	**(100.0)**
Responders	119	(50.0)	96	(44.0)
Non-responders	119	(50.0)	122	(56.0)
Treatment versus Control[a]				
P Value	0.0459			
Odds Ratio	1.75			
95% Confidence Interval for the Odds Ratio	(1.01, 3.02)			

Outcome by pathogens

Aspergillus

The majority of the patients were refractory (88% of 107 in the posaconazole group and 79% of 86 controls) or refractory and intolerant to standard therapy (36% and 23%. respectively). Few patients were intolerant only and most patients who were intolerant had renal dysfunction as a result of amphotericin B therapy. There were more control group patients who received less than 30 days of previous therapy than in the posaconazole group (83% *versus* 64%) and the median duration of prior therapy among mITT patients with refractory disease was 23 days in the posaconazole group and

16 days in the control group. More than 90% of the patients in both groups had received some formulation of amphotericin B and itraconazole had been administered to 40% to 50%. The median number of days of prior amphotericin B for the entire mITT population was 17 days for the posaconazole group and 11.5 days for the control group.

Table 10: Response according to prior antifungal therapy

Prior Effective Antifungal Therapy[a]	Posaconazole (P00041) n	Mean	SD	Median	Range	Control (P02387) n	Mean	SD	Median	Range
Refractory (With or Without Intolerance)										
	(N=94)					(N=68)				
Amphotericin B	33	19.8	23.5	12.0	1 to 109	31	11.3	7.1	10.0	1 to 33
Lipid Amphotericin	71	27.6	36.1	16.0	1 to 193	41	23.0	26.3	12.0	1 to 141
Any Amphotericin	86	28.6	35.3	17.0	1 to 193	64	20.1	22.8	12.5	1 to 141
Itraconazole	48	30.4	40.9	17.0	1 to 190	31	23.6	25.4	14.0	1 to 106
Voriconazole	5	33.2	25.4	30.0	3 to 65	0				
Any Azole	53	30.7	39.6	17.0	1 to 190	31	23.6	25.4	14.0	1 to 106
Echinocandins	5	73.2	74.2	74.0	7 to 187	0				
Any Antifungal (Days)	92[b]	36.3	42.3	23.0	1 to 203	68	25.7	29.0	16.0	4 to 141
Any Antifungal (Duration)	92[b]	41.3	69.1	23.0	1 to 583	68	26.1	29.9	16.0	4 to 151
Intolerant Only										
	(N=13)					(N=18)				
Amphotericin B	4	4.0	2.2	3.5	2 to 7	14	10.1	12.0	4.0	1 to 42
Lipid Amphotericin	12	23.6	26.1	10.5	2 to 83	3	6.0	4.4	8.0	1 to 9
Any Amphotericin	12	23.9	25.8	10.5	4 to 83	16	9.9	11.2	5.5	1 to 42
Itraconazole	3	8.3	4.0	9.0	4 to 12	3	4.7	1.5	5.0	3 to 6
Any Azole	3	8.3	4.0	9.0	4 to 12	3	4.7	1.5	5.0	3 to 6
Any Antifungal (Days)	12	24.4	26.0	12.0	4 to 83	17	9.8	10.8	5.0	2 to 42
Any Antifungal (Duration)	12	29.3	33.3	12.0	4 to 97	17	9.8	10.8	6.0	2 to 42

The primary analysis controlled for pre-determined prognostic variables, of which race, enrollment time, non-malignant haematological disorder, renal disease, and hepatic disease were imbalanced between study groups. A logistic regression analysis that adjusted for imbalances in these variables gave an estimate of the adjusted odds ratio for the treatment effect of posaconazole relative to the control regimens of 4.06 (p = 0.006).

Table 11: Primary Efficacy Analysis *Aspergillus*: mITT

ASPERGILLUS Analysis	Posaconazole (P00041) Total N	Responders n	(%)	Control (P02387) Total N	Responders n	(%)
ALL PATIENTS HAVING *ASPERGILLUS* AS A PRIMARY PATHOGEN	**107**	**45**	**(42.1)**	**86**	**22**	**(25.6)**
Treatment versus Control	Estimated Odds Ratio	95% CI for the Odds Ratio		P Value		
Primary Efficacy Analysis	4.06	(1.50, 11.04)		0.006		
Unadjusted Efficacy Analysis	2.11	(1.14, 3.92)		0.018		

Most of the patients had partial responses, which can be expected with this disease (table 12).

Table 12: Global Response by Sub-category at EOT *Aspergillus*: mITT

ASPERGILLUS	**Posaconazole (P00041)**		**Control (P02387)**	
Response Category	N	(%)	N	(%)
Total Number (%) of Patients	**107**	**(100.0)**	**86**	**(100.0)**
Responder	**45**	**(42.1)**	**22**	**(25.6)**
Complete Response	7	(6.5)	8	(9.3)
Partial Response	38	(35.5)	14	(16.3)
Non-responder	**62**	**(57.9)**	**64**	**(74.4)**
Stable Disease	10	(9.3)	7	(8.1)
Failure	39	(36.4)	52	(60.5)
Unable to Determine	13	(12.1)	5	(5.8)

Global response rates by species were numerically higher in the posaconazole group regardless of species (table 13).

Table 13 Overall response by *Aspergillus* species: mITT

	Posaconazole (P00041)		**External Control Group (P02387)**	
Overall Response	45/107 (42 %)		22/86 (26 %)	
Success by Species All mycologically confirmed *Aspergillus* spp.	34/76	(45 %)	19/74	(26 %)
A. fumigatus	12/29	(41 %)	12/34	(35 %)
A. flavus	10/19	(53 %)	3/16	(19 %)
A. terreus	4/14	(29 %)	2/13	(15 %)
A. niger	3/5	(60 %)	2/7	(29 %)

The table 14 present the global response by baseline characteristics or clinically relevant groups.

Table 14: Global Response at EOT *Aspergillus*: mITT

ASPERGILLUS	**Posaconazole**			**Control**		
Baseline Characteristic or Subgroup	Total N	Responders n	(%)	Total N	Responders n	(%)
ALL PATIENTS HAVING *ASPERGILLUS* AS A PRIMARY PATHOGEN	**107**	**45**	**(42.1)**	**86**	**22**	**(25.6)**
DEMOGRAPHY						
Neutropenia (Baseline ANC < 500/mm^3)	21	5	(23.8)	26	2	(7.7)
Bone Marrow Transplant	55	21	(38.2)	38	7	(18.4)
Allogeneic	48	15	(31.3)	34	7	(20.6)
Autologous	7	6	(85.7)	4	0	(0.0)
Solid Organ Transplant	12	7	(58.3)	7	5	(71.4)
Duration of Prior Effective Antifungal Therapy						
≤30 days	69	31	(44.9)	71	17	(23.9)
31 to 60 days	21	8	(38.1)	8	4	(50.0)
61 to 90 days	7	2	(28.6)	3	1	(33.3)
91 to 180 days	7	3	(42.9)	4	0	(0.0)
>180 days	3	1	(33.3)	0		
Enrolment Reason						
Refractory	55	24	(43.6)	48	10	(20.8)
Intolerant	13	5	(38.5)	18	9	(50.0)
Refractory and Intolerant	39	16	(41.0)	20	3	(15.0)
All Refractory	94	40	(42.6)	68	13	(19.1)
All Refractory With Proven Infection	62	27	(43.5)	36	10	(27.8)
General Site of Infection						
Pulmonary	79	31	(39.2)	67	17	(25.4)
Extrapulmonary	19	10	(52.6)	11	5	(45.5)
Disseminated With Pulmonary Involvement	3	1	(33.3)	3	0	(0.0)
Disseminated Without Confirmed Pulmonary Involvement	6	3	(50.0)	5	0	(0.0)
Haematological Malignancy	79	29	(36.7)	70	16	(22.9)
Non-haematological Malignancy	13	6	(46.2)	5	1	(20.0)

ASPERGILLUS	Posaconazole			Control		
Baseline Characteristic or Subgroup	Total N	Responders n	(%)	Total N	Responders n	(%)
Non-malignant haematological Disorder	91	36	(39.6)	52	11	(21.2)
Aplastic Anemia	2	0	(0.0)	3	1	(33.3)
Myelodysplastic Syndrome	7	1	(14.3)	9	1	(11.1)
Immunocompromised - Acquired	28	13	(46.4)	19	6	(31.6)
Renal Disease	68	27	(39.7)	21	5	(23.8)
Hepatic Disease	43	16	(37.2)	6	0	(0.0)
Study Center Location						
USA	94	38	(40.4)	68	16	(23.5)
non USA	13	7	(53.8)	18	6	(33.3)
Time Interval of Enrollment						
30 APR 1996 to 31 DEC 1998	NA			26	7	(26.9)
01 JAN to 31 DEC 1999	20	8	(40.0)	23	6	(26.1)
01 JAN to 31 DEC 2000	64	26	(40.6)	29	7	(24.1)
01 JAN to 30 APR 2001	23	11	(47.8)	8	2	(25.0)
Centers Contributing Data to						
P00041 and P02387	73	30	(41.1)	76	19	(25.0)
P00041 only	34	15	(44.1)	NA		
Study Center Size						
Large Site	42	13	(31.0)	36	6	(16.7)
Other Sites Combined	65	32	(49.2)	50	16	(32.0)
P02387 only	NA			10	3	(30.0)

Success rates were lower in the neutropenic and allogeneic bone marrow transplant subgroups although still numerically higher for posaconazole than for comparators. There was no obvious difference for outcomes by age between treatments but females did worse than males irrespective of treatment. However, the treatment difference was greater in females than males.

Most patients were from centres that contributed patients to both studies (68% in P00041 and 88% in P02387). Centres that enrolled into P02387 only had a higher percentage of global responders (30%) than those that contributed patients to both studies (25%). One centre enrolled > 10% of mITT patients - 39% (42/107) posaconazole and 42% (36/86) controls. Response rates were lower for this centre in both studies probably because it had about three times as many patients with haematological malignancies and about twice as many patients with a history of BMT as the other centres.

In addition, successful response rates at US sites for posaconazole and other treatments were lower by about 10% than at non-US centres. However, non-US patients were relatively few in number (13/107 posaconazole and 18/86 controls). The wider use of the *Aspergillus* antigen assay in Europe may have led to earlier institution of therapy and a higher rate of success.

Patients in the control group could have had several additional agents added as salvage therapy either concomitantly or sequentially prior to being declared a success or a failure. The overall success rate for the different treatments used in the external control study ranged from 20% to 31% compared with 42% for posaconazole (80/86 (93%) in the control group received some formulation of amphotericin B as salvage and that 45/86 (52%) received both an amphotericin B formulation and itraconazole.

Table 15: Global Response by Salvage Therapy at EOT *Aspergillus*: mITT

ASPERGILLUS		Responders	
Salvage Therapy	N	n	(%)
Posaconazole	107	45	(42.1)
Control: All Salvage Therapies	86	22	(25.6)
Control: Amphotericin B[a]	80	16	(20.0)
Control: Itraconazole[b]	49	14	(28.6)
Control: Amphotericin B and Itraconazole[c]	45	10	(22.2)
Control: Other Therapies[d]	36	11	(30.6)

a: Patients who received any amphotericin B, including lipid formulations (regardless of any other salvage therapy they may have received).

b: Patients who received itraconazole (regardless of any other salvage therapy they may have received).

c: Patients who received any amphotericin B, including lipid formulations, and itraconazole (regardless of any other salvage therapy they may have received).

d: Patients who received other therapies which included: terbinafine, nystatin, fluconazole, caspofungin and unspecified investigational agents. All patients, except two, who received other therapies also received amphotericin B and/or itraconazole.

It appeared that the overall results were driven by those for the sub-group with infections already refractory to amphotericin although they suggested that posaconazole could also be active against itraconazole-refractory infections. There were too few data for any conclusions regarding activity in voriconazole-refractory infections.

The DRC-assigned response rates for the other defined populations were very similar as shown in table 16. The Efficacy Evaluable patients accounted for 94-95% of the MITT subset.

Table 16: Global Responses at EOT *Aspergillus*: Other Subject Subsets (P00041)

	Total	Responses	
Subject Analysis Subset	N	n	%
Intent-to-Treat	141	56	39.7
Modified Intent-to-Treat	**107**	**45**	**42.1**
Efficacy Evaluable	101	45	44.6
Per Protocol	89	41	46.1

Survival curves suggested an advantage for posaconazole compared to the retrospectively collected external control group. However, the CHMP viewed these results with caution due to the comparison against a retrospectively identified external control group.

Fusariosis

In P00041, 18 cases of invasive fusariosis were included in the mITT population whereas there were only 4 in the control study. Most in the posaconazole group had haematological malignancies (13/18), 6/18 were neutropenic at baseline, 6/18 had a history of BMT (three had graft versus host disease) and 9/18 had disseminated disease. Most (14/18) had refractory disease, with or without intolerance, to previously treatment with amphotericin B.

The global response rate as assessed by the DRC at the end of treatment in the mITT subset was 39 % (7/18, 95 % CI 17-64 %) in the posaconazole group and 50 % (2/4, 95 % CI 7-93 %) in control group. Out of the 7 responders, 3 had a complete response (16.7 %), including one with fusariosis and phaeohyphomycosis of the eye. However, only 1/6 with neutropenia, 1/6 BMT patients and 2/9 with disseminated disease responded.

Table 18: Global Response at EOT *Fusarium*: mITT

FUSARIUM	**Posaconazole (P00041)**			**Control (P02387)**		
	Total	Responders		Total	Responders	
Baseline Characteristic or Subgroup	N	n	%	N	n	%
ALL PATIENTS HAVING *FUSARIUM* AS A PRIMARY PATHOGEN	**18**	**7**	**(38.9)**	**4**	**2**	**(50.0)**
Enrollment Reason						
Refractory	12	4	(33.3)	4	2	(50.0)
Intolerant	4	2	(50.0)	0		
Refractory and Intolerant	2	1	(50.0)	0		
Haematological Malignancy	13	4	(30.8)	2	1	(50.0)
Non-haematological Malignancy	2	0	(0.0)	1	1	(100.0)
Non-malignant Haematological Disorder	16	5	(31.3)	4	2	(50.0)

a: For each type of fungal infection, a set of potentially effective antifungal medications was specified.
b: Other Disease subgroups were summarised from the medical history data.

In the ITT population there were 24 *Fusarium* infections treated, of which 11/24 completely or partially responded, for an overall positive global response of 45.8%. Of these 11, most had localised disease while most of the 13 non-responders had disseminated disease..

Chromoblastomycosis or mycetoma

In P00041 there were 11 patients with proven or probable chromoblastomycosis (6) or mycetoma (5) compared to 2 patients in the control study (mITT subset). All of them were refractory to standard therapy and had extrapulmonary infections. Patients were middle-aged Hispanic men without significant underlying medical conditions who were treated in Latin America for refractory invasive disease of the skin and subcutaneous tissue. Previous antifungal treatments included azoles for all patients, with treatment periods of several months to several years, and additional antifungal agents for six. Of the 11, 9 had received itraconazole.

The global response to posaconazole was 82 % (9/11, 95 % CI 48-98 %). Of the 9/11 deemed responders, 4/9 had complete resolution of disease and the two non-responders had stable disease.

Coccidioidomycosis

There were 16 patients with proven coccidioidomycosis in P00041 and 7 in the control study (mITT subset). These patients were aged 17 to 65 years, about half were Hispanic and slightly more than half female. Most had no predisposing immunocompromising condition.

Eight of the 15 with refractory infections had been treated with an amphotericin B-based regimen for a median of 29 days and 14 had received an azole for a median of 335 days. The patient judged to be intolerant of standard therapy (only) received fluconazole for 11 days followed by a lipid formulation of amphotericin B for 16 days after diagnosis of the current episode.

The global response rate to posaconazole was 69 % (11/16, 95 % CI 41-89 %). Of the 11 responders, 4/9 had complete resolution of disease.

Table 19: Global Response at EOT *Coccidioides*: mITT

COCCIDIOIDES	**Posaconazole (P00041)**			**Control (P02387)**		
	Total	Responders		Total	Responders	
Baseline Characteristic or Subgroup	N	n	%	N	n	%
ALL PATIENTS HAVING *COCCIDIOIDES* AS A PRIMARY PATHOGEN	**16**	**11**	**(68.8)**	**7**	**3**	**(42.9)**
History of Bone Marrow Transplant	1	0	(0.0)	0		
Allogeneic	1	0	(0.0)	0		
Duration of Prior Effective Antifungal Therapy						
≤30 days	1	0	(0.0)	3	1	(33.3)
31 to 60 days	2	1	(50.0)	2	1	(50.0)
61 to 90 days	1	1	(100.0)	0		
91 to 180 days	2	2	(100.0)	1	1	(100.0)
>180 days	10	7	(70.0)	1	0	(0.0)
Enrolment Reason						
Refractory	13	10	(76.9)	3	2	(66.7)
Intolerant	1	0	(0.0)	4	1	(25.0)
Refractory and Intolerant	2	1	(50.0)	0		
General Site of Infection						
Pulmonary	8	5	(62.5)	6	3	(50.0)
Extrapulmonary	4	2	(50.0)	0		
Disseminated Without Confirmed Pulmonary Involvement	4	4	(100.0)	1	0	(0.0)

All four patients with disseminated disease responded to posaconazole, as did 5/8 with pulmonary disease and the one case with CNS infection.

In the ITT population, 19 *Coccidioides* infections were treated with posaconazole, of which 12/19 completely or partially responded, for an overall positive global response of 63.2%. The investigators judged that 81.3% (13/16) of the MITT patients infected with *Coccidioides* infection were responders.

Additional data were provided from a pilot study (study C/197-280) in which patients with chronic active pulmonary or non-meningeal but disseminated primary coccidioidomycosis received 400 mg posaconazole once daily as capsules taken with food with treatment limited to 6 months. Before closure of the study, 20 patients had been enrolled at nine sites in the US and Mexico. The mean coccidioidomycosis score at baseline was 11 (range 5-27) and responders were to have at least a 50% reduction in score at month 6. Of the 20 patients, 15 (75%) were responders and 5 failed. Among evaluable patients 12/15 (80%) were responders, of which 3 had chronic active pulmonary disease at baseline, 3 skeletal disease, 5 soft tissue disease and 1 had both the latter.

Zygomycosis

There were 11 patients with proven or probable zygomycetes infection (8 in the control group) aged 14 to 74 years and all except one was treated in the US. Overall the data were considered insufficient to support an indication for use.

Candidiasis

There were 23 patients with proven or probable Candida infections refractory or intolerant to standard therapy treated with posaconazole in P00041 and 30 in the control study.
The number of cases was considered too low and the patients studied too heterogeneous to support a clear indication for use.

Cryptococcosis

There were 31 patients treated with posaconazole in P00041 and 64 in the control study that had DRC-determined proven or probable cryptococcal infection and nearly all the infections were proven.

The DRC global success rates at the end of treatment for cryptococcal infections were 48% (15/31) for posaconazole and 58% (37/64) for in the control group. There was also a higher declared failure rate with posaconazole (8/31 25.8 % versus 12/64, 18.8 %). The data did not support the use of posaconazole against cryptococcal infections.

Use in children

There were only 16 patients less than 18 years (range 8-17) enrolled into study P00041. The data were too limited to establish the efficacy of posaconazole in children.

Clinical safety

- Patient exposure

As of 1 September 2003, posaconazole had been administered to over 2300 subjects in completed and ongoing studies. Out of this number, 952 subjects, including 225 healthy volunteers, received posaconazole oral suspension at 800 mg/day in divided doses.

The numbers included several studies in oropharyngeal candidiasis, but as this was not a sought indication, the following sections will concentrated on the 428 IFI patients treated with 800 mg/day.

More males than females were included in the studies (~ 65 %) and the mean age was 44 years. Patient population was severely immunocompromised at risk for invasive fungal infections and had severe underlying diseases. The treatment duration is presented in table 21.

Table 21: Treatment Duration with Posaconazole (rIFI Pool)

	Number (%) of Subjects: POS All Doses		
Treatment Duration	BMT (n=124)	Non-BMT (n=304)	Overall rIFI Pool (n=428)
0-<3 months	84 (68)	154 (51)	238 (56)
≤7 days	20 (16)	30 (10)	50 (12)
0-1 month	65 (52)	96 (32)	161 (38)
3-<6 months	17 (14)	59 (19)	76 (18)
6-<9 months	14 (11)	44 (14)	58 (14)
9-<12 months	4 (3)	20 (7)	24 (6)
≥12 months	4 (3)	23 (8)	27 (6)

BMT: Bone marrow transplant

Adverse events

At least 1 treatment-emergent adverse event (TEAE) was reported by 96% of subjects in the IFI Pool. Analyses of TEAEs by age, sex, and race revealed no significant trends related to these characteristics. Fever was most frequently reported (36%) followed by nausea, diarrhoea, vomiting and abdominal pain in 20%-29% and headache in 26% (latter influenced by HIV-infected subjects with cryptococcal meningitis).

Treatment-related TEAEs were reported for 38 % of patients in the overall rIFI pool with the most common related to gastro-intestinal disorders (table 22).

Table 22: Treatment-Related TEAEs Reported by ≥ 2% IFI Pool

Adverse Events	Number (%) of Subjects: Posaconazole All Doses					
	BMT (n=124)		Non-BMT (n=304)		Overall rIFI Pool (n=428)	
Subjects Reporting any Adverse Event[a]	**37**	**(30)**	**127**	**(42)**	**164**	**(38)**
Body as a Whole - General Disorders						
Anorexia	2	(2)	6	(2)	8	(2)
Dizziness	1	(1)	6	(2)	7	(2)
Drug Level Altered	2	(2)	5	(2)	7	(2)
Fatigue	4	(3)	3	(1)	7	(2)
Headache	3	(2)	17	(6)	20	(5)
Central and Peripheral Nervous System Disorders						
Convulsions	2	(2)	0		2	(<1)
Paresthesia	1	(1)	5	(2)	6	(1)
Disorders of the Reproductive System and Breast						
Menstrual Disorder	0		2	(2)	2	(1)
Gastrointestinal System Disorders						
Abdominal Pain	3	(2)	15	(5)	18	(4)
Diarrhoea	3	(2)	12	(4)	15	(4)
Mouth Dry	0		6	(2)	6	(1)
Nausea	10	(8)	25	(8)	35	(8)
Vomiting	7	(6)	18	(6)	25	(6)
Heart Rate and Rhythm Disorders						
QTc/QT Prolongation	0		6	(2)	6	(1)
Liver and Biliary System Disorders						
Hepatic Enzymes Increased	2	(2)	5	(2)	7	(2)
SGOT Increased	1	(1)	8	(3)	9	(2)
SGPT Increased	2	(2)	9	(3)	11	(3)
Metabolic and Nutritional Disorders						
Phosphatase Alkaline Increased	1	(1)	5	(2)	6	(1)
Renal & Urinary System Disorders						
Blood Creatinine Increased	0		5	(2)	5	(1)
Skin and Subcutaneous Tissue Disorders						
Rash	2	(2)	8	(3)	10	(2)

No clear relationship has been established between plasma levels and adverse events.

Serious adverse events (SAEs)

In the IFI Pool, 68% of patients reported SAEs, most commonly fever (20%), respiratory insufficiency and dyspnoea (both 10%). Hypotension, acute myelogenous leukaemia aggravated, sepsis, pneumonia, diarrhoea and vomiting were reported in 6%-8%.
Treatment-related SAEs occurred in only 8% of patients; those reported by more than 2 patients (1%) were altered drug level (increased levels of cyclosporin, tacrolimus and digitalis,) increased hepatic enzymes, nausea, rash and vomiting.

Deaths

In the IFI Pool, 157 subjects (37%) died. Most deaths were attributed to complications or progression of the underlying diseases (table 23).

Table 23: Summary of Deaths (IFI Pool)

Cause of Death	Number (%) of Subjects: POS All Doses					
	BMT (n=124)		Non-BMT (n=304)		Overall rIFI Pool (n=428)	
Total Number of Deaths	**65**	**(52)**	**92**	**(30)**	**157**	**(37)**
Adverse Event	**29**	**(23)**	**48**	**(16)**	**77**	**(18)**
Related	1	(1)	1	(<1)	2	(<1)
Unrelated	28	(23)	47	(15)	75	(18)
Complications Related to Disease Under Investigation	**19**	**(15)**	**20**	**(7)**	**39**	**(9)**
Progression of Disease Under Investigation	**17**	**(14)**	**21**	**(7)**	**38**	**(9)**
Other[a]	**0**		**3**	**(1)**	**3**	**(1)**

a: Other="AIDS complications" (P00041-02/0203); "unknown cause" of death, as subject discharged to inpatient hospice (P00041-06/0639); "end-stage COPD" (P00041-41/4106).

Discontinuation due to AEs

In the IFI Pool, 46% had AEs that led to drug discontinuation, study discontinuation or death. Treatment-related AEs that led to study-drug discontinuation, study discontinuation, or death were reported in 6% and included nausea and vomiting (5 subjects each), increased LFTs, rash (3 subjects each), convulsions, dizziness, and increased gamma-GT (2 subjects each). Most others involved only one patient.

Specific AEs

Cardiac events

In the IFI Pool, 158 subjects (37%) had any cardiovascular TEAE, mainly hypotension (15%), hypertension (12%), cardio-respiratory arrest (4%), cardiac failure (4%), hypertension aggravated (3%) and pericardial effusion (3%). These and the Grade 3 or Grade 4 events seen in 8%-9% were mostly considered unlikely related to posaconazole. Atrial fibrillation, QTc/QT prolongation and SVT were reported in 3%-4% but other ECG abnormalities occurred in <1%-2%.
Data pooled from the five studies in 173 healthy volunteers that employed multiple, time-matched centrally read ECGs collected over a 12 hour period obtained before and during administration of posaconazole (400 mg bid with high fat meals) did not reveal any clinically relevant change in the mean QTc (Fridericia) interval from baseline.
In the IFI Pool, there were 11/428 patients (3%) with an adverse event of QTc/QT prolongation reported by the investigator and 6 cases were considered possibly related to treatment although none resulted in discontinuation. There were predisposing reasons for cardiac conduction disturbances seen in all of these subjects and most had reasons to be predisposed to QTc prolongation. There were 6 % (17/265) of patients with baseline and post-baseline recordings with $\geq$ 60 ms change in QTcF from baseline but only 2/265 (1 %) had a change > 500 ms.
There was one case of *Torsade de Pointes* in which the contribution of posaconazole to this arrhythmia could not be excluded.
Overall the data point a low potential for posaconazole to prolong the QT prolongation. However, appropriate warnings have been included in the SPC.

Neurological effects

Detailed neurological examinations were incorporated in four clinical studies (P01893, P00041, P00298, and C/I97-280). In the IFI Pool, treatment-related neurological AEs reported in more than two subjects were paraesthesiae, confusion and somnolence (1% each). Frequencies were generally higher in the BMT group than in the non-BMT group, probably mainly due to concomitant medications, psychological effects of long-term/ICU hospitalisation and the complications and morbidity. Of the 17 patients who reported convulsions, (7 in BMT patients and 10 in non-BMT patients) only 2 were considered to be posaconazole related. Of the 10 non BMT patients, 5 were infected with HIV and 3 subjects had IFI affecting the CNS. Of the remaining 2, 1 had a history of convulsions prior to starting posaconazole and 1 had severe hypoxia due to pulmonary haemorrhage. Although the causality is

difficult to determine, the data do not seem to indicate any major safety concern with respect to neurological effects of posaconazole.

Hepatobiliary function

In the IFI pool, 113 subjects (26%) reported TEAEs of the liver and biliary system, mainly increased enzymes (7%), hyperbilirubinaemia and increased SGPT (6% each). Increased alkaline phosphatase was noted in 6% of subjects. Grade 3 events were reported by 6% (n=25) and Grade 4 events were reported by 1% (n=5). Hepatic necrosis was reported in two subjects (<1%) as Grade 3 events but neither case was considered to be related to posaconazole or resulted in discontinuation or death. The rate of hepatobiliary AEs was higher for BMT (33%) than non-BMT patients (24%) but, as expected from clinical experience, more in the BMT group had a history of hepatobiliary conditions relative to the non-BMT group.

Hepatic failure was reported in 8 subjects (1 BMT and 6 non-BMT), of which 6 had an outcome of death and 1 was lost to follow-up. All had a history of conditions related to the hepatobiliary system that could be fatal. One of the 6 deaths was considered to be possibly related to treatment. It is not possible to rule out a contribution from posaconazole to hepatocellular damage and failure. Appropriate warnings have been added in the SPC.

Haematological effects

In the IFI studies, 144 (34%) had TEAEs classified as disorders of the blood and lymphatic system and 117 (27%) had TEAEs classified as platelet, bleeding and clotting disorders. The most frequent were anaemia, thrombocytopenia and neutropenia (6%-13%). Treatment-related TEAEs occurred in 1% and included anaemia (n=4), thrombocytopenia (n=2), eosinophilia, pancytopenia, haematoma and decreased platelet count (one case each). Many had a variety of haematological and other types of malignancy and were undergoing intensive chemotherapy. The contributing factor of posaconazole cannot be excluded.

Hypocalcaemia
In the preclinical studies, there were findings of bone thinning/fractures in rats as well as adrenal medullary tumours. In the IFI Pool, hypocalcaemia was reported in 28 patients (7%), fractures in 4 (1%) and renal calculi were reported in 2 (<1%) but none was considered treatment-related.
Although the data do not indicate any association between posaconazole and decreased calcium levels a warning has been included on the need to monitor electrolytes disturbances, especially those involving potassium, magnesium or calcium levels and correct them as necessary before and during posaconazole therapy.

Others

In the IFI Pool, 6% of subjects had reports of blurred vision and 2% had reports of abnormal vision but there were no Grade 3 or Grade 4 events and most were of relatively short duration. There is therefore no evidence for an effect of posaconazole on vision.

Skin and subcutaneous tissue disorders were reported by 192 subjects (45%), with similar proportions in BMT and non-BMT groups. These were mainly rash (14%) and pruritus (8%). As with other azoles posaconazole can lead to the occurrence of skin reactions such as rash. There were 2 cases of Stevens-Johnson syndrome (SJS), both considered to be unlikely to be treatment related and neither patient discontinued posaconazole.

Safety in special populations

Renal or hepatic impairment

The data are limited but it appears that pre-existing elevations in transaminases might be associated with a greater risk of severe hepatic problems while on posaconazole therapy. Patients who have some degree of renal insufficiency before starting treatment related or unrelated to prior therapy might also be more at risk of adverse events. Appropriate warnings have been included in the SPC.

Children

There were only 16 patients aged 8 to 17 years enrolled in P00041 and 8 completed treatment. The very limited data would suggest that similar proportions had SAEs or other clinically significant AEs compared with the overall IFI population.

Safety related to drug-drug interactions and other interactions

In study P00041, drug interactions were reported as adverse events in 21 (5%) patients of which 9 were considered treatment-related and 6 were SAEs. The most clinically relevant interactions were those with tacrolimus and ciclosporin. Adequate warnings have been included in the SPC.

Safety data from study P02095

As of 18 March 2005, data were available on 420 patients from this extended use protocol. Overall the safety profile has been similar to that reported in the IFI population with fever, nausea, vomiting and headache being the most commonly reported AEs. The applicant undertook to provide further safety data from this study as a follow-up measure to be fulfilled post-authorisation.

5. Overall conclusions, benefit/risk assessment and recommendation

Quality

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

Non-clinical pharmacology and toxicology

Posaconazole is an antifungal agent from the triazoles class. It inhibits the enzyme lanosterol 14α-demethylase (CYP51), which catalyses an essential step in ergosterol biosynthesis.
Posaconazole has been shown *in vitro* to have an antifungal activity against *Aspergillus* species (*Aspergillus fumigatus*, *A. flavus*, *A. terreus*, *A. nidulans*, *A. niger*, *A. ustus*), *Coccidioides immitis*, *Fonsecaea pedrosoi*, and species of *Fusarium*. *In vitro* there was no antagonist activity when use in combination with other antifungal agents, however, there is currently no clinical evidence that combination therapy will provide an added benefit.

With respect to pharmacokinetics, the bioavailability of posaconazole exhibited a high food effect.
Protein binding was high. Posaconazole underwent direct glucuronidation and also oxidation and cleavage followed by conjugation. Posaconazole was mainly eliminated via faeces as unchanged compound.

Reproduction, peri- and postnatal development studies were conducted in rats. At exposures lower than those obtained at therapeutic doses in humans, posaconazole caused skeletal variations and malformations, dystocia, increased length of gestation, reduced mean litter size and postnatal viability. In rabbits, posaconazole was embryotoxic at exposures greater than those obtained at therapeutic doses. As observed with other azole antifungal agents, these effects on reproduction were considered related to a treatment-related effect on steroidogenesis. Posaconazole must therefore not be used during pregnancy

as indicated in the SPC. It is excreted in the milk of lactating rats. In the absence of data in human, women should not breast-feed while taking posaconazole.

Posaconazole was not genotoxic in in-vitro and in-vivo studies. Carcinogenicity studies did not reveal special hazards for humans.

Clinical

Food has a marked effect on the AUC of posaconazole and the suspension should be administered with food or a nutritional supplement whenever possible as recommended in the SPC. If the patient cannot take the suspension with food, based on data from healthy volunteers dosed under fasting conditions, the dose should be divided into 200 mg four times daily since this increased the AUC of posaconazole compared to 400 mg twice daily. In view of the high inter-individual variability and effect of food on posaconazole exposures, the applicant undertook to further evaluate the pharmacokinetics specific to the marketed formulation in patients under various dosing conditions. In particular, the applicant will further explore the effect of different dosing conditions, such as timing of meals, meal characteristics and pH, on the absorption of posaconazole.

Renal impairment does not affect the pharmacokinetics of posaconazole. Limited pharmacokinetic data showed that hepatic impairment increases exposure associated with prolonged half-life. The influence of hepatic impairment on the pharmacokinetics of posaconazole will be further evaluated in the post-authorisation phase. In the meantime, the SPC recommends that posaconazole should be used with caution in patients with severe hepatic impairment. There are very limited pharmacokinetic data available from children aged at least 8 years and there are insufficient data on safety or efficacy in children to recommend the use of posaconazole in persons aged less than 18 years.

Posaconazole is an inhibitor of CYPA3A4, is metabolised through UDP glucuronidation and is an inhibitor and substrate for P-gp. A number of potential interactions between posaconazole and other medicinal products has been identified and reflected in the SPC. Results from further interaction studies with oral midazolam, anti-retroviral protease inhibitors, efavirenz and sirolimus are expected to be submitted post-authorisation.

Clinical isolates with decreased susceptibility to posaconazole-have been identified. The principle mechanism of resistance is the acquisition of substitutions in the target protein, CYP51. The applicant undertook to provide regular updates on the occurrence of resistance to posaconazole as part of the follow-up measures to be fulfilled post-authorisation.

The demonstration of the efficacy of posaconazole in the treatment of invasive fungal infections that had not responded to specific licensed antifungal therapies or which occurred in patients intolerant of such antifungal agents (as detailed in the indications for use) is based on the results of the study P00041. This was an open-label, multi-centre and non-comparative study involving 330 patients with different type of infections receiving 800 mg posaconazole daily in divided doses.

A retrospective chart-review study (P02387) in a similar patient population as in P00041 but treated with a salvage regimen other than posaconazole was conducted to provide external control data. A blinded external committee (DRC) reviewed the data from these two studies. Nevertheless, the lack of a prospective randomised control group means that all comparisons between the posaconazole-treated patients and external controls must be viewed with caution.

In the treatment of aspergillosis, a successful response (complete or partial resolution) at the end of treatment was seen in 42% (45/107) of posaconazole-treated patients compared to 26% (22/86) of the external group. Most of the cases of aspergillosis were considered to be refractory to prior therapy in both the posaconazole group (88%) and in the external control group (79%).

Fusariosis

A successful response (complete or partial resolution) at the end of treatment was seen 39 % (7/18) patients treated with posaconazole group.

Chromoblastomycosis/Mycetoma:
A successful response (complete or partial resolution) at the end of treatment was seen in 9 /11 patients treated with posaconazole..

Coccidioidomycosis
A satisfactory response (complete or partial resolution of signs and symptoms present at baseline**)** was achieved for 69 % (11/1) of patients in posaconazole group. Data from a pilot study supported the efficacy of posaconazole against this fungus.

Safety

The safety database pertaining to dosing at 800 mg daily in divided doses is currently limited and is derived from the invasive fungal infections pool of 428 patients, most of whom were treated for up to 3 months. The severity of the invasive fungal infections, the underlying diseases and multiple concomitant medications may confound the safety profile. The most commonly reported adverse events with posaconazole were gastrointestinal disorders such as nausea, diarrhoea, vomiting and abdominal pain, fever and headache.
Posaconazole appears to have a low potential to prolong QTc interval. However warnings against use in highly predisposed patients, as well as use with other compounds known to prolong QTc have been included in the SPC. As with other azoles cases of hepatic disorders, such as elevated transaminases, and cutaneous reactions have been reported.

Benefit/risk assessment

Overall the efficacy data were considered sufficient to support an indication for use in aspergillosis refractory to amphotericin B or itraconazole or in patients intolerant of these alternative antifungal agents. The study was initiated prior to the release of the CHMP Points to Consider document on the Evaluation of New Antifungal agents for invasive fungal infections. In addition, the timing of the study precluded direct comparison against voriconazole and/or caspofungin or the evaluation of posaconazole in patients who had not responded to or were intolerant of these agents due to the timing of the marketing authorisations. However, the lack of a prospective randomised comparative study in patients with invasive aspergillosis limited the reliability of the assessment of the risk benefit relationship. Therefore, the applicant has agreed to undertake a prospective randomised and controlled study against caspofungin in aspergillosis refractory to amphotericin B or itraconazole and in patients with aspergillosis who are intolerant of these antifungal agents.

Due to the recognised difficulties in treating fusariosis and chromoblastomycosis and mycetoma, the CHMP considered that the efficacy data were sufficient to support an indication in these infections as well as in Coccidioidomycosis. These indications are limited to use in patients who have not responded to or are intolerant of the anti-fungal agents specified for each type of fungus in the SPC. The indications closely reflect the treatment histories of the patients that were enrolled into P00041.

The CHMP agreed that the duration of therapy should be based on the severity of the patient's underlying disease, recovery from immunosuppression and clinical response.

In view of the indications, the CHMP recommended that treatment with posaconazole should be initiated only by physicians experienced in the management of invasive fungal infections.

With respect to safety, further data with the use of posaconazole will be provided as part of the follow-up measures to be fulfilled post-authorisation. In the forthcoming Periodic Safety Update Reports,

several reactions reported in the clinical studies will particularly be monitored such as QTc prolongation/torsades de pointes, hepatic failure, coagulation abnormalities, thrombotic events, convulsions and drug interactions. Also, due to concerns raised by the pre-clinical findings, events that might represent pulmonary phospholipidosis will be especially monitored.

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the benefit/risk ratio of Noxafil was favourable and therefore recommended the granting of the marketing authorisation for the following indications.

"treatment of the following invasive fungal infections in adults:

- Invasive aspergillosis in patients with disease that is refractory to amphotericin B or itraconazole or in patients who are intolerant of these medicinal products;
- Fusariosis in patients with disease that is refractory to amphotericin B or in patients who are intolerant of amphotericin B;
- Chromoblastomycosis and mycetoma in patients with disease that is refractory to itraconazole or in patients who are intolerant of itraconazole;
- Coccidioidomycosis in patients with disease that is refractory to amphotericin B, itraconazole or fluconazole or in patients who are intolerant of these medicinal products.

Refractoriness is defined as progression of infection or failure to improve after a minimum of 7 days of prior therapeutic doses of effective antifungal therapy."