

London, 23 September 2004  
Product name: **VFEND**  
Procedure No. **EMEA/H/C/387/X/09**

## **SCIENTIFIC DISCUSSION**

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## 1. INTRODUCTION

Voriconazole is a second generation triazole and is the result of a discovery programme aimed at improving the potency and spectrum of fluconazole. In order to enhance the spectrum, one triazole moiety with a 4-fluoropyrimidine group was substituted and an  $\alpha$ -methyl group was added to provide activity against *Aspergillus* species and a range of other moulds.

Voriconazole is a broad spectrum triazole antifungal agent and is indicated as follows :

- *treatment of invasive aspergillosis*
- *treatment of fluconazole-resistant serious invasive Candida infections (including C. Krusei).*
- *Treatment of serious fungal infections caused by Scedosporium spp. and Fusarium spp.*

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

The applicant submitted an application for a line extension for VFEND, containing the active substance voriconazole via a Centralised Procedure. This line extension is a powder for oral suspension (POS) containing 40 mg/ml voriconazole following reconstitution.

VFEND film coated tablets 50 mg and 200 mg and powder for solution for infusion 200 mg (equivalent to 10 mg/ml) were registered via the Centralised Procedure in March 2002.

The high oral bioavailability (96%) of voriconazole enables switching between intravenous and oral treatment. Current therapy using either the IV or oral tablet formulations allows flexibility in patient care and the possibility of prolonged treatment with a single, effective agent. The tablet formulation, however, may not meet the needs of all patients, *e.g.* those who may have difficulty in swallowing, paediatric patients, or those who dislike taking tablets. This is of particular importance considering the debilitated patient population experiencing serious fungal infections. Voriconazole POS has been designed to fulfil this medical need.

This application is based on the bioequivalence of the powder for oral solution dosage form with previously authorised tablet formulation. The proposed posology for the oral suspension is similar to the posology of the already authorised tablets. Cross-reference is made to the non-clinical and clinical data previously presented in the original marketing application for the tablets.

## 2. PART II: CHEMICAL, PHARMACEUTICAL AND BIOLOGICAL ASPECTS

### 2.1 Composition

Vfend is formulated as a multidose powder for oral suspension containing, after reconstitution, 40 mg/ml of voriconazole as active substance.

The other ingredients include sucrose, silica colloidal, titanium dioxide, xanthan gum, sodium citrate, citric acid anhydrous, sodium benzoate, and natural orange flavour.

It is presented in a high-density polyethylene (HDPE) bottle with a child-resistant polypropylene closure. A 5 ml polypropylene oral syringe, calibrated with respect to volume and voriconazole dose, and a press-in bottle adaptor are provided. The powder is to be reconstituted with water prior first use by using the polypropylene cup supplied.

### 2.2 Active substance

No change has been made to the oral grade active substance already authorised for Vfend film-coated tablets (EU/1/02/212/01-24).

Voriconazole has a low aqueous solubility, its maximum solubility being in acidic conditions (2.7 mg/ml at pH 1.2). The particle size distribution specification acceptance criteria of the drug substance

used for this new formulation was based on development studies and (see product development and finished product) is consistent with the current specification for voriconazole oral grade.

### **2.3 Other ingredients**

All the excipients comply with the Ph. Eur. requirements except the natural orange flavour, which is adequately controlled according to a different standard.

Regarding the TSE risk, the oral suspension does not include any components of ruminant origin.

Satisfactory specifications have been provided for the HDPE bottle and the child-resistant polypropylene closure. The compatibility of the powder and of the constituted suspension with the primary packaging has been satisfactorily demonstrated.

The oral syringe and the measuring cup are CE marked and have been approved for their intended use. The accuracy and reproducibility of the volume delivered by these medical devices have been satisfactorily demonstrated.

### **2.4 Product development and finished product**

This new oral formulation has been mainly developed for patients who have difficulties or dislike swallowing tablets, this being of particular importance considering the debilitated patient population experiencing serious fungal infections.

A dry powder formulation to be reconstituted has been chosen over a “ready-to-use” liquid formulation based on the active substance properties: low solubility and instability in aqueous environments, and good stability in the solid state.

It has been demonstrated that the particle size of the active substance has no influence on manufacturing process, suspension properties and stability of the finished product. However, an apparent relationship between this parameter and *in vitro* dissolution was observed, but batches with a wide range of particle size distribution have been shown to be clinically acceptable. Based on these data, an appropriate particle size specification for voriconazole drug substance has been established (see active substance).

All the excipients selected are commonly used. The reconstituted suspension has a pH of 4 which is satisfactory for the stability of voriconazole and maintains the antimicrobial efficacy of sodium benzoate, which has been demonstrated according to Ph. Eur.

Development studies have investigated the potential for particle growth in the constituted suspension, constitution time, redispersibility and dose uniformity at first use and throughout the in-use shelf life. The particle size did not change significantly during the in-use shelf life of the finished product. Following constitution or resuspension, a satisfactory dose could be withdrawn after shaking for a few seconds. Dose volumes were found to have uniform content of active substance both at constitution and throughout the in-use shelf life of the product.

The overfill of 5 ml is suitable to allow the label claim volume to be withdrawn.

Bioequivalence of the “proposed commercial powder for oral suspension” formulation versus the commercial tablet formulation has been satisfactorily demonstrated.

The finished product is produced using a standard process comprising the following steps: initial blending of the excipients, milling of the excipients, post milling blending, addition of voriconazole and of the flavour, blending, screening, final blending and primary packaging.

The milling of the excipients has been identified as a critical step, the milling speed influencing particle size distribution in the excipient blend.

### ***Specification***

The product specification include tests for appearance of powder, identity (IR), assay (HPLC, 95-105% release and end of shelf life), fill weight, sodium benzoate content and identity, degradation products, appearance of constituted suspension, pH, viscosity, titanium dioxide, microorganism count (Ph. Eur.).

No specification has been included for the new impurity arising due to an interaction between a degradation product of voriconazole and a known degradation product of sucrose taking into account the non significant concentration (<10 ppm) found in samples stored under long term and accelerated conditions and the results of the genetic toxicology assays (see Part III: Toxicopharmacological aspects). Based on the development studies, no specification has been included so far for particle size distribution, constitution time and redispersibility. No dissolution test is included as the performance of the finished product is more appropriately assessed by controlling the particle size distribution of the active substance and the viscosity of the constituted suspension.

Batch analysis data provided for 9 batches (2 manufactured at the intended manufacturing site) met the specification at the time of release and confirm the robustness and reproducibility of the manufacturing process.

## **2.5 Stability of the Product**

### *Stability of the product before reconstitution*

Under long-term conditions (5°C - packaging intended for commercialisation), 12-month data and 6-month data are respectively available for 1 batch produced at the intended manufacturing site and for three batches manufactured at another site. Up to 12-month data are available under accelerated conditions (25°C/60% R.H. - packaging intended for commercialisation). Stress testing studies as well as a photostability study have been performed and showed 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 reconstituted suspension*

In-use stability of the reconstituted suspension was tested (upright and inverted positions). The reconstituted suspension was shown to be chemically and physically stable during the in-use period, either directly after reconstitution with water or after storage. Stress testing studies as well as a photostability study have been performed and showed that the product is not light sensitive.

The results presented support the proposed in-use shelf life and storage conditions defined in the SPC.

## **2.6 Discussion on chemical, pharmaceutical and biological aspects**

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

The active substance is well characterised and documented. The pharmaceutical form selected is adequate taken into account the properties and stability of the active substance. The excipients are commonly used in this kind of formulation and the packaging material is well documented. The manufacturing process has been shown to be capable of producing reproducible finished product batches. Stability tests under ICH conditions indicate that the product is stable for the proposed shelf life. At the time of the CPMP opinion there were some outstanding quality issues which had no impact on the benefit/risk profile. The applicant committed to provide the necessary information as follow-up measures within an agreed timeframe, and to submit variations if required following the evaluation of this additional information.

### 3. PART III: TOXICO-PHARMACOLOGICAL ASPECTS

#### 3.1 Pharmacology

The pharmacology has been thoroughly characterized and presented to support the oral and IV Vfend formulations. As the new formulation is not expected to affect the pharmacology of voriconazole, **no new studies have been performed.**

#### 3.2 Pharmacokinetics

As pharmacokinetics have been thoroughly characterized and presented to support the oral and IV Vfend formulations, no new pharmacokinetic studies have been conducted with voriconazole powder oral suspension (POS).

The new pharmaceutical form, POS, may potentially affect absorption rate and therefore show different pharmacokinetics. Bioequivalence, however, was studied in humans and is assessed in the Clinical Critical Assessment Report. It is therefore accepted that **no new pharmacokinetic studies were performed in animals.**

#### 3.3 Toxicology

The toxicology profile has been thoroughly characterized and presented to support the oral and IV Vfend formulations. The only additional toxicology data, to those included in the previous voriconazole submissions, are two genotoxicity studies conducted with UK-519,140, which was not present in the original voriconazole formulations:

- Microbial reverse mutation assay at 0.06 mg/plate (Study No. 02-2532-01)
- Mouse micronucleus assay mice at 2 mg/kg (Study No. 02-2532-02)

#### *Studies on impurities*

Type of test/Study ID/GLP	Test system	Concentrations/ Concentration Metabolising system	Results range/ Positive/negative/equivocal
Gene mutations in bacteria	Salmonella <i>typhimurium</i> TA98, TA100, TA1535, TA 1537; <i>E. coli</i> WP2 uvrA pKM101	+/- S9, 0.06 mg/plate	negative
Chromosomal aberrations in vivo	Mouse, micronuclei in bone marrow	2 mg/kg orally by gavage	negative

In voriconazole POS, UK-51,060 is the primary degradation product of voriconazole, while 5-hydroxymethylfurfuraldehyde (5-HMF) is a potential degradation product of the sucrose excipient. UK-51,060 has been qualified in the previous voriconazole submission and 5-HMF is a recognized impurity in a number of food products (e.g. caramel, jam, preserved fruit) at concentrations up to 1 mg/g. A safe oral dose of 5-HMF is reported to be 2 mg/kg (cited in Ulbricht et al, 1984).

The two degradation products (UK-51,060 and 5-HMF) have been found to react in stressed samples of voriconazole POS to form an impurity UK-519,140. However, further testing demonstrated no significant concentration (<10 ppm) of UK-519,140 in samples stored at 5°C (long term storage) or 25°C/60%RH (accelerated storage). UK-519,140 was not present in voriconazole tested in the toxicology program for the original filing.

The applicant demonstrated that a new impurity, UK-519,140, may be formed in stressed samples of voriconazole POS. In accordance with ICH Q3B, the applicant was prompted to perform genotoxicity testing when a substituted vinyl ketone was identified as a structural alert for genotoxicity. **The**

**applicant performed a microbial reverse mutation assay and an oral in vivo micronucleus assay in mice. This is considered an acceptable screen for genotoxic potential of a new impurity.**

The toxicology of voriconazole has been previously assessed in the Marketing Authorisation Application for Vfend IV and tablet formulations. Compared to the marketed formulations the only toxicological issue regards the formation of UK-519,140 in stressed samples of the POS formulation. The repeat dose toxicity of this impurity has not been addressed by the applicant. However, as the level of this impurity remains below 10 ppm when stored under refrigerated conditions, as is prescribed, the lack of such studies is accepted. The applicant identified a structural alert for genotoxicity in UK-519,140, which prompted the applicant to perform a genotoxicity screen for this impurity consisting of a microbial reverse mutation assay and an in vivo micronucleus assay in mice. Both studies were negative, but the bacterial assay is considered less adequate as only one concentration was tested (0.06 mg/plate), whereas the OECD guidelines indicate that a range of concentrations should be tested with a maximum of 5 mg/plate, and the micronucleus assay is considered inconclusive, since exposure of the target tissue was not demonstrated. **Nevertheless, UK-519,140 is considered of no toxicological concern in view of the negative findings in the studies performed and the lack of significant concentration (<10 ppm) of UK-519,140 in samples stored at 5°C (long term storage) or 25°C/60%RH (accelerated storage).**

### 3.4 Discussion on toxico-pharmacological aspects

Considering that a favorable safety profile has been previously established for Vfend for the treatment of fungal infections and, in view of the negative results of the two additional genetic toxicology studies conducted, informations given are acceptable. There is no need for more studies.

The proposed wording of the sections 4.3, 4.6, 4.9, 5.1 (non-clinical data), and 5.3 of the Summary of Product Characteristics is identical to the concurrent sections of the SPC for Vfend oral tablet formulation, and is agreed.

## 4. PART IV: CLINICAL ASPECTS

### 4.1 Clinical pharmacology

#### Pharmacodynamics

Voriconazole is a second generation triazole with a close structural similarity to fluconazole. Like other azole antifungals, voriconazole acts by inhibiting the cytochrome P450-dependent 14- $\alpha$ -sterol demethylase required for ergosterol biosynthesis. Fungi are therefore depleted of ergosterol and accumulate 14- $\alpha$ -methylated sterols that are thought to disrupt membrane structure and function, thereby inhibiting fungal growth.

#### Pharmacokinetics

- Bioequivalence studies

Three bioequivalence studies were conducted, one pivotal study (**A1501028**) using two batches of the proposed commercial POS formulation (these two batches differed only in terms of particle size distribution of the in going drug substance), and two formulation development studies [**A1501019** (using a similar suspension formulation compared with the to be marketed formulation, but the volume of water used for constitution of the proposed marketed formulation was changed) and **150-248** (research formulation; this latter study was submitted with the original marketing application)]. Reference was the marketed 200 mg voriconazole tablet.

**Study 150-248:** In this study 14 healthy male volunteers (aged 20 – 29 years, 13 homozygote extensive metabolisers (EM) and one homozygote poor metaboliser (PM)) were included. There were 2 treatment periods. Each subject received at day one 400 mg BID voriconazole and at the subsequent 5.5 days 200 mg BID voriconazole. Plasma samples (obtained at the last day of the treatment period)

were analysed for voriconazole by a validated HPLC method with a quantitation limit of 10 ng/ml and a calibration curve of 10 – 3000 ng/ml. The results at steady state showed bioequivalence for  $C_{max}$  (ratio 1.02, 90% confidence interval 0.89 – 1.18) and  $AUC\tau$  (ratio 1.04, 90% confidence interval 0.97 – 1.12).

The research powder for oral suspension formulation is **bioequivalent** with the tablet formulation.

**Study A1501028:** In this study 45 healthy males, aged 18 – 35 years were included. Each subject received at day one 400 mg BID voriconazole and at the subsequent 5.5 days 200 mg BID voriconazole in the fasted state (2 treatment periods, reference tablet and test suspension). In a third period, subjects received also the suspension, but from another batch. Plasma samples (obtained at last day of each treatment period) were analysed for voriconazole by a validated HPLC method with a quantitation limit of 10 ng/ml and a calibration curve of 10 – 3000 ng/ml. The results at steady state and the statistical analysis are shown in table PK 1.

**Table PK 1.**

	tablet	suspension to be marketed (batch 1)	suspension to be marketed (batch 2)	ratio (90% CI)	ratio (90% CI)
$C_{max}$ (ng/ml)	2367 ± 1272	2455 ± 1146	2686 ± 1120	susp.batch 1/tablet 1.04 (0.98 – 1.11)	susp. batch2/tablet 1.15 (1.08 – 1.22)
$AUC\tau$ (ng.h/ml)	14640 ± 13482	14869 ± 12530	15618 ± 13505	1.02 (0.99 – 1.06)	1.05 (1.02 – 1.09)
$t_{max}$ (h)	1.5 (0.5 – 4.0)	1.0 (0.25 – 2.5)	0.5 (0.25 – 2.0)	--	--
$C_{min}$ (ng/ml)	635 ± 941	608 ± 863	652 ± 939	0.95 (0.90 – 1.01)	0.97 (0.91 – 1.03)

as mean ± sd ;  $t_{max}$  as median (range); batch 1: no. 7877-055, batch 2: no. 7877-056

The suspension formulation to be marketed and the marketed tablet formulation are **bioequivalent** with regard to the rate and extent of absorption.

**Study A1501019:** In this study 26 healthy volunteers (15 males and 11 females, aged 18 – 43 years were included. Pharmacokinetics were obtained from 24 subjects. Each subject received at day one 400 mg BID voriconazole and at the subsequent 5.5 days 200 mg BID voriconazole in the fasted state (2 treatment periods). In a third period, subjects received the suspension in the fed state (high fat meal, dose taken within 5 min of completing the meal). Plasma samples (obtained at last day of each treatment period) were analysed for voriconazole by a validated HPLC method with a quantitation limit of 10 ng/ml and a calibration curve of 10 – 3000 ng/ml. The results at steady state showed that bioequivalence between the suspension and the tablet formulation (fasting) could only be proven for  $AUC\tau$  (ratio 0.99, 90% confidence interval 0.94 – 1.05), and not for  $C_{max}$  (ratio 1.15, 90% confidence interval 1.04 – 1.27).

In addition, food decreased the rate ( $C_{max}$ ) and extent (AUC) of absorption of voriconazole from the suspension with 58 and 37%, respectively.

In study A1501019 bioequivalence could not be proven for  $C_{max}$ , including a total of 24 male and female subjects. Also bioequivalence could not be proven in the subgroup of 15 male subjects. However, in study A1501028, in which a similar dosing scheme was used as in study A1501019, but including a much higher number of subjects (45 male subjects) bioequivalence could be proven for AUC and  $C_{max}$ . The results of the latter study prevail, as the power of this study is higher.

In conclusion, the tablet and suspension are **bioequivalent with regard to  $C_{max}$  and AUC**.

- Conclusion on pharmacokinetics

The to be marketed suspension is bioequivalent with the marketed tablet formulation. Food decreased the rate and extent of absorption from the suspension with 58 and 37%, respectively. This effect was more pronounced than observed for the tablet formulation (34 and 24%, respectively). The food effect was not studied with the to be marketed formulation. However, taken into account the similarity between the suspension used in the food interaction study and the to be marketed suspension, it is



considered that the results obtained in the food interaction study can be extrapolated to the to be marketed suspension.

Overall, the SPC is in accordance with that of the tablet formulation. However, **the oral suspension should be taken at least one hour before, or two hours following a meal**, whereas the tablet should be taken at least one hour before or one hour following a meal.

Based upon the earlier studies for the tablets and IV formulation, children have a higher elimination capacity than adults on a body weight basis. Therefore, to achieve exposures in children consistent with those of adults higher doses will be required. **The applicant committed in March 2002 then (post approval commitment number 13) to conduct a paediatric trial to investigate the pharmacokinetics of higher doses of voriconazole. The results of the latter trial are awaited in 3-4Q 2004.**

#### 4.2 Clinical efficacy

No efficacy studies have been conducted using voriconazole POS. **Efficacy is claimed on the basis of bioequivalence with the previously approved voriconazole tablets.**

#### 4.3 Clinical safety

Extensive safety data for subjects exposed to voriconazole have been submitted previously to support the approval of the intravenous and oral formulations. The current application contains the safety data of the three POS bioequivalence studies.

##### **Patient exposure**

A total of 88 healthy volunteers (77 males, 11 females; age range 18-43 years) received at least one dose of voriconazole in the three open label, cross-over bioequivalence studies. Eighty-five subjects received at least one dose of POS whilst 84 received the commercial tablet. The dosing regimen for voriconazole POS and tablet was the same for all three bioequivalence studies, i.e. 400mg bid on Day 1 followed by 200mg bid for 5.5 days.

### Summary of Studies Included in the POS Safety Database

Study	Design	Dose	Total exposure (days)	Number of subjects	
				POS	Tablet
A1501028	Open, randomised, two-treatment crossover study; three 7-day treatment periods, minimum 7-day washout between periods,	Proposed commercial POS Batch 1: 400mg bid Day 1, 200mg bid for 5.5 days, fasted state	6.5	44	45
		Proposed commercial suspension Batch 2: 400mg bid Day 1, 200mg bid for 5.5 days	6.5		
		Commercial tablet: 400mg bid Day 1, 200mg bid for 5.5 days	6.5		
A1501019	Open, randomised, two-treatment crossover study; three 7-day treatment periods, minimum 7-day washout between period, fasted and fed states for suspension formulation	Initial multi-dose POS: 400mg bid Day 1, 200mg bid for 5.5 days (fasted and fed states)	13	25/26*	25
		Commercial tablet: 400mg bid Day 1, 200mg bid for 5.5 days	6.5		
150-248	Open, randomised, two-treatment crossover study; two 7-day treatment periods, minimum 7-day washout between treatments, fasted state	Research suspension: 400mg bid Day 1, 200mg bid for 5.5 days	6.5	14	14
		Commercial tablet: 400mg bid Day 1, 200mg bid for 5.5 days	6.5		

\*N=25 for POS administered in fasted state and N=26 for POS administered after food

### Adverse events and serious adverse event/deaths

The table below shows the adverse events (all causality and treatment related) occurring at an incidence of  $\geq 5\%$  for the POS and for the tablet reported during the three bioequivalence studies.

### **Incidence of Treatment Emergent Adverse Events In Bioequivalence Studies (incidence $\geq 5\%$ )**

Adverse event	POS (N=84)		Tablet (N=84)	
	All causality	Treatment related	All causality	Treatment related
Abnormal vision	36 (42%)	36 (42%)	32 (38%)	32 (38%)
Headache	28 (33%)	22 (26%)	15 (18%)	14 (17%)
Photophobia	25 (29%)	25 (29%)	22 (26%)	22 (26%)
Dry skin	16 (19%)	7 (8%)	10 (12%)	3 (4%)
Taste perversion	12 (14%)	12 (14%)	0	0
Dizziness	10 (12%)	9 (11%)	4 (5%)	1 (1%)
Abdominal pain	10 (12%)	5 (6%)	3 (4%)	2 (2%)
Abnormal dreams	9 (11%)	9 (11%)	10 (12%)	10 (12%)
Nausea	9 (11%)	5 (6%)	2 (2%)	2 (2%)
Gastrointestinal disorder	8 (9%)	8 (9%)	4 (5%)	4 (5%)
Back pain	8 (9%)	0	5 (6%)	1 (1%)
Pharyngitis	8 (9%)	0	2 (2%)	0
Respiratory tract infection	8 (9%)	0	2 (2%)	0
Insomnia	6 (7%)	6 (7%)	1 (1%)	1 (1%)
Urinary frequency	5 (6%)	5 (6%)	3 (4%)	3 (4%)
Eye pain	4 (5%)	4 (5%)	4 (4%)	4 (5%)
Palpitation	4 (5%)	3 (4%)	0	0
Rhinitis	4 (5%)	1 (1%)	1 (1%)	0
Bruise	4 (5%)	0	1 (1%)	0

Source: Table 6.3 Studies 150-248, A1501019 and A1501028

Across all three studies, the treatment related adverse events occurring in  $\geq 10\%$  of subjects receiving POS were **abnormal vision, headache, photophobia, taste perversion, dizziness and abnormal dreams**; and the treatment related events occurring in  $\geq 10\%$  of subjects receiving the commercial tablet were photophobia, abnormal vision, headache and abnormal dreams.

Since the experience with voriconazole (tablets / iv) in paediatric patients is limited, the applicant should provide a safety update in paediatric patients for voriconazole as was committed during first registration (postapproval commitment number 20). The applicant informed us that it would provide a paediatric safety update using data from the two completed paediatric IV studies (150-249 and A1501007) which were already submitted with the main filing, and the new paediatric IV and POS study (A150137) when this study is completed. The applicant should commit to provide Reports of the paediatric trials 150-249, A1501007 and A1501037 by 3-4Q 2004.

Although the pattern of events was consistent with the known safety profile of voriconazole, the frequency of adverse events in these bioequivalence studies was higher than in the previously reported trials. The scientific discussion of VFEND (CPMP/4049/01) reported the following percentages of treatment related adverse events in 1 946 subjects (patients and volunteers) treated with voriconazole: abnormal vision 22.6%, headache 5.4% and photophobia 5.0%.

Since the Powder for Oral Suspension (POS) was studied in healthy volunteers, the applicant provided a comparison between the frequency of adverse events in the POS studies and the MAA Clinical Pharmacology population (N=289). The frequencies of treatment emergent, treatment related adverse events reported in at least 3 subjects ( $\geq 4\%$ ) of the POS population are compared with those in the MAA Clinical Pharmacology population below:

Adverse event	Incidence of adverse event, n(%)		
	POS studies		MAA Clinical Pharmacology (N = 289)
	POS (N = 84)	Tablet (N = 84)	
Abnormal vision	36 (42%)	32 (38%)	143 (49.5%)
Photophobia	25 (29%)	22 (26%)	64 (22.1%)
Headache	22 (26%)	14 (17%)	56 (19.4%)
Taste perversion	12 (14%)	0%	1 (0.3%)
Dizziness	9 (11%)	1 (1%)	17 (5.9%)
Abnormal dreams	9 (11%)	10 (12%)	0%
Gastrointestinal disorder	8 (9%)	4 (5%)	0%
Dry skin	7 (8%)	3 (4%)	0%
Insomnia	6 (7%)	1 (1%)	10 (3.5%)
Abdominal pain	5 (6%)	2 (2%)	10 (3.5%)
Nausea	5 (6%)	2 (2%)	7 (2.4%)
Urinary frequency	5 (6%)	3 (4%)	2 (0.7%)
Eye pain	4 (5%)	4 (5%)	9 (3.1%)
Palpitation	3 (4%)	0%	0%

Source: POS submission, Module 2.7.4, in-text Table 6 and MAA Safety Summary Table 2.6.4

The applicant appropriately considered the occurrence of **taste perversion** related to the oral suspension and the SPC was changed accordingly. All **gastrointestinal disorders** included a waxy sensation in the mouth. The incidence was 9% for the POS and 5% for the tablet, so apparently there is no clear relation with the POS. **Abnormal dreams** and **urinary frequency** were reported in the POS trials in both groups the POS and tablet group in comparable percentages, which makes it unlikely that these adverse events could be attributed to the POS. The higher frequency compared to the previous reported frequency is most likely caused by a higher reporting rate during the POS trials. The same is likely to be true for the incidence of dry skin, although the frequency in the POS group seemed a little higher (8% vs 4% for POS vs. tablet, respectively).

**Palpitations** were only reported for the POS. As mentioned in the day 70 assessment report arrhythmia's have been observed previously in the voriconazole programme, in particular associated with the intravenous formulation. From the description of the present cases it seemed that the relation of the occurrence of palpitations with the voriconazole suspension is remote or unlikely.

Several events occurred more frequently with the POS compared to the tablet: **headache, taste perversion, palpitations, dizziness, insomnia, gastrointestinal disorders** and **nausea**. All except headache (26% vs. 17% for POS vs. tablet, respectively) were sufficiently discussed by the applicant at the time of the submission of the dossier. Therefore, the applicant discussed the difference in **frequency of headache** between POS and tablets in its response to the List of Questions adopted in July 2003.

According to Table 6 of Module 2.7.4 Summary of Clinical Safety, the frequency of treatment related headache for the POS was 26% (22/84 subjects) compared with 17% (14/84 subjects) for the tablet. This table, however, does not take into account that, for Studies A1501019 and A1501028, subjects were exposed to the POS for two treatment periods and the tablet for only one treatment period. The frequency of treatment related headache during each individual POS study is presented in the following table:

	Study 150-248		Study A1501019			Study A1501028		
	POS	Tablet	POS*	POS**	Tablet	POS#	POS##	Tablet
n/N (%)	0/14	0/14	7/25 (28%)	6/26 (23%)	6/25 (24%)	5/43 (12%)	4/44 (9%)	8/45 (18%)

\* Initial multi dose POS fasted

\*\* Initial multi dose POS fed

# Proposed commercial POS Batch 1

## Proposed commercial POS Batch 2

Source: Tables 6.2.3, Studies 150-248, A1501019 and A1501028

The apparent increase in frequency of headache in the summary of frequency across all three POS studies combined is due to the way the data are presented, as some subjects contributed twice to the number of events in the POS arms of studies A1501019 and A1501028 but only once to the overall subject numbers. No correction for duration of exposure was made in the overall presentation.

Furthermore, the increased frequency of central nervous system adverse events associated with the POS formulation raises some concern, Considering the limited number of subjects assessed for safety, the applicant should commit to **closely monitor CNS events in the subsequent PSURs**.

#### Serious adverse events and deaths

No subjects died during the bioequivalence studies.

One serious adverse event was reported. A female subject in Study A1501019 experienced palpitations on Days 3 and 7 of POS dosing in the fed state (her first treatment period). Her ECG taken on Day 3 was normal with no evidence of arrhythmia, however, telemetry on Day 7 showed ventricular extrasystoles (with no prolongation of the QT interval). Dosing was permanently discontinued due to the extrasystoles, and the event was considered to have resolved approximately 15 minutes after the extrasystoles had been detected. The investigator attributed the event to voriconazole and the sponsor could also not exclude a causal association. The subject did not experience any further episodes of palpitation, and Holter monitoring at the final follow up visit showed no ventricular ectopic beats.

Arrhythmia's have been observed previously in the voriconazole programme, in particular associated with the intravenous formulation. From the description of the present cases it seems the relation with the voriconazole suspension is remote or unlikely. Currently a type II variation has been adopted for the tablets and IV solution to add QT interval prolongation to section 4.8. Therefore, "**torsade de pointes, QT interval prolongation**" are added in the Vfend POS SPC as rare adverse events in section 4.8.

#### Laboratory findings

Overall, the rate of laboratory abnormalities was low for all formulations of the POS and for the tablet formulation. Only one abnormality, raised alanine transaminase (ALT) led to discontinuation of dosing for one subject receiving tablets.

#### Discontinuation due to AES

A total of seven subjects discontinued from the three studies. Two subjects discontinued due to safety reasons. A female subject was discontinued because she experienced ventricular extrasystoles (see serious adverse events). A male subject from Study A1501028 was discontinued on Day 5 of his first dosing period (commercial tablet formulation) due to raised ALT, which was considered to have resolved after discontinuation of dosing. The other five discontinued due to reasons unrelated to

safety (two subjects due to protocol violation, two subjects were no longer willing to participate and one subject had to leave the country due to family emergency).

#### Post-marketing experience

In addition to the three equivalence studies completed for the POS formulation, the applicant has submitted postmarketing data for the tablet formulation.

These data consist of the **first periodic safety update report** (PSUR) for VFEND tablet and powder for solution for infusion. The PSUR covered the period from 1 March 2002 to 31 August 2002. The assessment report from the rapporteur circulated in January 2003 and was adopted at the January meeting of the CPMP.

It is estimated that 875 patients received voriconazole in clinical trials during the reporting period. Using unit sales trends and average days of therapy trends from the 2002 voriconazole Baseline Launch Tracking Study (July 2002), an estimated 2,147 patients were exposed to all formulations of voriconazole during the reporting period. Some of these patients may have been exposed to both the oral and intravenous formulations. There were 21 voriconazole cases (containing 53 events) included in the PSUR, nineteen of which were classified as serious. The safety experience with all cases indicated that most of the frequently reported events were labelled or were label compatible. Approximately one-half of the total events were contained in four body systems (body as a whole, gastrointestinal, liver/biliary and skin/appendages). Based on a review of these cases, no changes to the core data sheet were necessary.

#### Discussion on clinical safety

In the three bioequivalence studies, the treatment related adverse events occurring in  $\geq 10\%$  of subjects receiving oral suspension (powder for oral suspension: POS) were abnormal vision, headache, photophobia, taste perversion, dizziness and abnormal dreams. Although the safety profile of both products (POS and tablets) was consistent with the known safety profile of voriconazole the frequency of adverse events was higher in these three trials compared to previous submitted trials. This was most likely caused by a difference in reporting rate that in an actual difference. **The overall safety profile of POS appeared comparable to the tablets.** However, several events occurred more frequently with the POS compared to the tablet: taste perversion, palpitations, dizziness, insomnia, gastrointestinal disorders and nausea. 14% of the subjects receiving POS reported taste perversion, while it was reported by none of the subjects receiving tablets. **As taste perversions appeared to be an adverse event obviously related to the oral suspension, it is mentioned in the SPC (section 4.8).** Three female subjects experienced palpitations during POS dosing, and one of these subjects also experienced ventricular extrasystoles. Arrhythmia's have been observed previously in the voriconazole programme, in particular associated with the intravenous formulation. From the description of the present cases it seems the relation with the voriconazole suspension is remote or unlikely. **CNS adverse events will be closely monitored in the subsequent PSURs.**

The suspension appeared to be bioequivalent to the tablet, because the oral tablet is already authorised for children aged 2 to 12 years and the suspension did not contain excipients, which could be harmful for children, **the suspension can also be authorised for children aged 2 to 12 years.** Furthermore, the applicant informed the rapporteur that it would provide a paediatric safety update using data from the two completed paediatric IV studies (150-249 and A1501007) which were already submitted with the main filing, **and the new paediatric IV and POS study (A150137) when this study is completed in the 3-4Q 2004.**

## **5. OVERALL CONCLUSIONS, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION**

### **5.1 Quality**

The quality of this product is 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 are controlled in a satisfactory way.

Viral Safety and Batch to batch consistency has been documented and the relevant test will be performed according to the agreed specifications

### **5.2 Preclinical pharmacology and toxicology**

Overall, the primary pharmacokinetics studies provided adequate evidence that tablet and suspension are bioequivalent.

Overall, the toxicology programme revealed that a favorable safety profile has been previously established for Vfend for the treatment of fungal infections.

This information has been included in the SPC.

### **5.3 Efficacy**

The bioequivalence of tablets and suspension allows concluding on the efficacy of Vfend for the treatment of fungal infections.

### **5.4 Safety**

The overall safety profile of POS appeared comparable to the tablets. Because the oral tablet is already authorised for children aged 2 to 12 years and the suspension did not contain excipients, which could be harmful for children, the suspension can also be authorised for children aged 2 to 12 years.

### **5.5 Benefit/risk assessment**

Based on the CPMP review of data on quality, safety and efficacy, the CPMP considered that the benefit/risk profile of Vfend 40 mg/ml powder for oral suspension in the treatment of invasive aspergillosis, treatment of fluconazole-resistant serious invasive Candida infections (including *C. krusei*) and treatment of serious fungal infections caused by *Scedosporium* spp. and *Fusarium* spp. was favourable and therefore recommended the granting of the marketing authorisation.