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Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Vfend

Voriconazole

Procedure no: EMEA/H/C/000387/P46/089.1

Note

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

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Administrative information

Invented name of the medicinal product:	Vfend
INN (or common name) of the active substance(s):	Voriconazole
MAH:	Pfizer Ltd.
Currently approved Indication(s)	*Voriconazole, is a broad-spectrum, triazole antifungal agent and is indicated in adults and children aged 2 years and above as follows:* • *Treatment of invasive aspergillosis.* • *Treatment of candidaemia in non-neutropenic patients.* • *Treatment of fluconazole-resistant serious invasive Candida infections (including C. krusei).* • *Treatment of serious fungal infections caused by Scedosporium spp. and Fusarium spp.* *VFEND should be administered primarily to patients with progressive, possibly life-threatening infections.* *Prophylaxis of invasive fungal infections in high risk allogeneic hematopoietic stem cell transplant (HSCT) recipients.*
Pharmaco-therapeutic group (ATC Code):	J02AC03
Pharmaceutical form(s) and strength(s):	Tablets 50/200 mg, Powder for solution for infusion 200 mg, Powder for oral suspension 40 mg/ml
Rapporteur:	**Johann Lodewijk Hillege**

GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

Term	Abbreviation
AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
CI	Confidence Interval
CRF	Case Report Form
CSR	Clinical Study Report
CYP	Cytochrome
DILI	drug induced liver injury
EC	Esophageal Candidiasis
EMA	European Medicines Agency
EORTC	European Organisation for Research and Treatment of Cancer
EOT	End of Treatment
FU	Follow-Up
GCP	Good Clinical Practice
GGT	Gamma-Glutamyl Transferase
IA	Invasive Aspergillosis
ICC	Invasive Candidiasis including Candidemia
IFI	Invasive Fungal Infection
IV	Intravenous
LFT	Liver Function Test
MAH	Marketing Authorisation Holder
MITT	Modified Intent to Treat
PO	Oral
q12h	Every 12 Hours
RMP	Risk Management Plan
SAE	Serious Adverse Event
SCC	Squamous Cell Carcinoma
SMQ	Standardised MedDRA Query

1. Updated Assessment

The current updated report concerns the assessment of the responses as submitted by the applicant. The first round's Rapporteur's AR was circulated and concluded to in the December CHMP. The assessment of the RSI can be found at the end of the current AR under section 6.

2. Introduction

The applicant submitted two paediatric studies A1501080 and A1501085 investigating the safety, tolerability, and efficacy of voriconazole in paediatric patients from 2 to <18 years of age. The present paediatric data is submitted by the MAH in accordance with article 46 of Regulation EC No 1901/2006.

A short critical expert overview has also been provided.

About the product

Voriconazole (Vfend®) is a broad-spectrum, triazole antifungal agent. Its mode of action is inhibition of fungal cytochrome P450 (CYP)-mediated 14α-sterol demethylation, an essential step in ergosterol biosynthesis. Voriconazole is active against a wide range of yeasts and filamentous fungi, including Candida, Aspergillus, Fusarium, and Scedosporium species. The efficacy of voriconazole for the treatment of both invasive aspergillosis and invasive candidiasis in adult patients has been demonstrated in prospective, randomised, controlled studies. Marketing approval has been granted in over 90 countries, including the United States, European Union (EU), and Australia, and a wealth of experience with the product has been accumulated over the past 10 years.

Approved indication(s) and posology

Indication

Voriconazole, is a broad-spectrum, triazole antifungal agent and is indicated in adults and children aged 2 years and above as follows:

- *Treatment of invasive aspergillosis.*
- *Treatment of candidaemia in non-neutropenic patients.*
- *Treatment of fluconazole-resistant serious invasive Candida infections (including C. krusei).*
- *Treatment of serious fungal infections caused by Scedosporium spp. and Fusarium spp.*

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

- *Prophylaxis of invasive fungal infections in high risk allogeneic hematopoietic stem cell transplant (HSCT) recipients.*

Posology

Electrolyte disturbances such as hypokalaemia, hypomagnesaemia and hypocalcaemia should be monitored and corrected, if necessary, prior to initiation and during voriconazole therapy (see section 4.4).

VFEND is also available as 200 mg film-coated tablets, 200 mg powder for solution for infusion, 200 mg powder and solvent for solution for infusion and 40 mg/ml powder for oral suspension.

Treatment

Adults

Therapy must be initiated with the specified loading dose regimen of either intravenous or oral VFEND to achieve plasma concentrations on Day 1 that are close to steady state. On the basis of the high oral bioavailability (96%; see section 5.2), switching between intravenous and oral administration is appropriate when clinically indicated.

Detailed information on dosage recommendations is provided in the following table:

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

* This also applies to patients aged 15 years and older

Treatment duration should be as short as possible depending on the patient's clinical and mycological response. Long term exposure to voriconazole greater than 180 days (6 months) requires careful assessment of the benefit-risk balance (see sections 4.4 and 5.1).

Dosage adjustment (Adults)

If patient response to treatment is inadequate, the maintenance dose may be increased to 300 mg twice daily for oral administration. For patients less than 40 kg the oral dose may be increased to 150 mg twice daily. If patient is unable to tolerate treatment at a higher dose, reduce the oral dose by 50 mg steps to the 200 mg twice daily (or 100 mg twice daily for patients less than 40 kg) maintenance dose.

In case of use as prophylaxis, refer below.

Children (2 to <12 years) and young adolescents with low body weight (12 to 14 years and <50 kg) Voriconazole should be dosed as children as these young adolescents may metabolize voriconazole more similarly to children than to adults

The recommended dosing regimen is as follows:

	Intravenous	Oral
Loading Dose Regimen (first 24 hours)	9 mg/kg every 12 hours	Not recommended
Maintenance Dose (after first 24 hours)	8 mg/kg twice daily	9 mg/kg twice daily (a maximum dose of 350 mg twice daily)

Note: Based on a population pharmacokinetic analysis in 112 immunocompromised paediatric patients aged 2 to <12 years and 26 immunocompromised adolescents aged 12 to <17 years.

It is recommended to initiate the therapy with intravenous regimen, and oral regimen should be considered only after there is a significant clinical improvement. It should be noted that an 8 mg/kg intravenous dose will provide voriconazole exposure approximately 2-fold higher than a 9 mg/kg oral dose.
These oral dose recommendations for children are based on studies in which voriconazole was administered as the powder for oral suspension. Bioequivalence between the powder for oral suspension and tablets has not been investigated in a paediatric population. Considering the assumed limited gastroenteric transit time in paediatric patients, the absorption of tablets may be different in paediatric compared to adult patients. It is therefore recommended to use the oral suspension formulation in children aged 2 to <12.

All other adolescents (12 to 14 years and ≥50 kg; 15 to 17 years regardless of body weight)
Voriconazole should be dosed as adults.

<u>Dosage adjustment (Children [2 to <12 years] and young adolescents with low body weight [12 to 14 years and <50 kg])</u>

If patient response to treatment is inadequate, the dose may be increased by 1 mg/kg steps (or by 50 mg steps if the maximum oral dose of 350 mg was used initially). If patient is unable to tolerate treatment, reduce the dose by 1 mg/kg steps (or by 50 mg steps if the maximum oral dose of 350 mg was used initially).

Use in paediatric patients aged 2 to <12 years with hepatic or renal insufficiency has not been studied (see sections 4.8 and 5.2).

<u>Prophylaxis in Adults and Children</u>

Prophylaxis should be as short as possible depending on the risk for developing invasive fungal infection (IFI) as defined by neutropenia or immunosuppression. It may only be continued up to 180 days after transplantation in case of continuing immunosuppression or graft versus host disease (GvHD) (see section 5.1).

Dosage
The recommended dosing regimen for prophylaxis is the same as for treatment in the respective age groups. Please refer to the treatment tables above.

Duration of prophylaxis
The safety and efficacy of voriconazole use for longer than 180 days has not been adequately studied in clinical trials.
Use of voriconazole in prophylaxis for greater than 180 days (6 months) requires careful assessment of the benefit-risk balance (see sections 4.4 and 5.1).
The following instructions apply to both Treatment and Prophylaxis

Dosage adjustment
For prophylaxis use, dose adjustments are not recommended in the case of lack of efficacy or treatment-related adverse events. In the case of treatment-related adverse events, discontinuation of voriconazole and use of alternative antifungal agents must be considered (see section 4.4 and 4.8)
Dosage adjustments in case of co-administration Phenytoin may be coadministered with voriconazole if

the maintenance dose of voriconazole is increased from 200 mg to 400 mg orally, twice daily (100 mg to 200 mg orally, twice daily in patients less than 40 kg), see sections 4.4 and 4.5.

The combination of voriconazole with rifabutin should, if possible be avoided. However, if the combination is strictly needed, the maintenance dose of voriconazole may be increased from 200 mg to 350 mg orally, twice daily (100 mg to 200 mg orally, twice daily in patients less than 40 kg), see sections 4.4 and 4.5.

Efavirenz may be coadministered with voriconazole if the maintenance dose of voriconazole is increased to 400 mg every 12 hours and the efavirenz dose is reduced by 50%, i.e. to 300 mg once daily. When treatment with voriconazole is stopped, the initial dosage of efavirenz should be restored (see sections 4.4 and 4.5).

Elderly patients
No dose adjustment is necessary for elderly patients (see section 5.2).

Patients with renal impairment
The pharmacokinetics of orally administered voriconazole are not affected by renal impairment. Therefore,no adjustment is necessary for oral dosing for patients with mild to severe renal impairment (see section 5.2).

Voriconazole is haemodialysed with a clearance of 121 ml/min. A 4-hour haemodialysis session does not remove a sufficient amount of voriconazole to warrant dose adjustment.

Patients with hepatic impairment
It is recommended that the standard loading dose regimens be used but that the maintenance dose be halved in patients with mild to moderate hepatic cirrhosis (Child-Pugh A and B) receiving voriconazole (see section 5.2).

Voriconazole has not been studied in patients with severe chronic hepatic cirrhosis (Child-Pugh C).

There is limited data on the safety of VFEND in patients with abnormal liver function tests (aspartate transaminase [AST], alanine transaminase [ALT], alkaline phosphatase [ALP], or total bilirubin >5 times the upper limit of normal).
Voriconazole has been associated with elevations in liver function tests and clinical signs of liver damage,such as jaundice, and must only be used in patients with severe hepatic impairment if the benefit outweighs the potential risk. Patients with severe hepatic impairment must be carefully monitored for drug toxicity (see section 4.8).

Paediatric population
The safety and efficacy of VFEND in children below 2 years has not been established. Currently available data are described in sections 4.8 and 5.1 but no recommendation on a posology can be made.

3. Scientific discussion

3.1. Information on the development program

The MAH stated that studies A1501080 and A1501085 are stand alone studies.

3.2. Information on the pharmaceutical formulation used in the studies

The currently approved paediatric dosing regimens were based on a population pharmacokinetic modeling approach, and are predicted to provide voriconazole exposures comparable to those in adult patients receiving the approved dosing regimens. These 2 paediatric studies were conducted with these regimens to confirm whether these doses are appropriate for paediatric use.

In addition**, Study A1501085** also enrolled 10 paediatric patients with EC. A lower dosing regimen was evaluated, which matched the dosing regimen used in adult patients with EC (200 mg oral (PO) every 12 hours (q12h) without loading doses).

The initial dosing regimens used in Studies A1501080 and A1501085 are summarised by age and indication in Table 1.

At the investigator's discretion a patient could receive dose reduction or escalation based on through samples collected on the 3rd day (or later) of IV/oral therapy in line with the approved SmPC.

Table 1. Voriconazole Dosing Regimens by Age and Indication in Paediatric Patients

Children (2-11 years) & young adolescents (12-14- year-olds weighing <50 kg)[a]	Loading Dose	Maintenance Dose	
	IV	IV	If Switched to Oral Voriconazole[d]
ICC/IA	9 mg/kg IV q12h for the first 24 h[b]	8 mg/kg IV q12h	9 mg/kg PO q12h (maximum initial dose of 350 mg)
EC	No loading dose[c]	4 mg/kg IV q12h	9 mg/kg PO q12h (maximum initial dose of 350 mg)

Adolescents (12-17 years) (excluding 12-14-year-olds weighing <50 kg)[a]	Loading Dose	Maintenance Dose	
	IV	IV	If Switched to Oral Voriconazole[e]
ICC/IA	6 mg/kg IV q12h for the first 24 h[b]	4 mg/kg IV q12h	200 mg PO q12h[f]
EC	No loading dose[c]	3 mg/kg IV q12h	200 mg PO q12h

Abbreviations: IV = intravenous; PO = oral; q12h = every 12 hours; h = hours
[a] Voriconazole dose may be adjusted (dose reduction or escalation) based on clinical response, adverse events, or voriconazole trough concentrations.
[b] Voriconazole IV loading doses should be omitted if the patient has already received the loading doses prior to starting study therapy.
[c] No loading doses were evaluated EC patients.
[d] It should be noted that 9 mg/kg PO q12h in children will provide much lower voriconazole exposure than 8 mg/kg IV q12h, while it will provide exposure comparable to 4 mg/kg IV q12h.
[e] It should be noted that 200 mg PO q12h in adolescents will provide much lower voriconazole exposure than 4 mg/kg IV q12h, while it will provide exposure comparable to 3 mg/kg IV q12h.
[f] For IA treatment, at the investigator's discretion, a dose of 300 mg PO q12h could be used in adolescents.

CHMP comments:
The dosages used with these paediatric studies are in line with the approved SmPC.

Limited voriconazole concentration data were obtained from Studies A1501080 and A1501085. No new clinical pharmacology information is currently available from Studies A1501080 and A1501085. However, analyses to explore the relationship between voriconazole exposure and efficacy and safety endpoints in the paediatric patients in these studies are ongoing. The report will be submitted when available (Target completion date: end September 2014).

The Rapporteur will await the submission of these data.

3.3. Clinical aspects

3.3.1. Introduction

The MAH submitted final reports for:

- **Study A1501080**: A Prospective, Open-Label, Non-Randomised, Multicenter Study to Investigate the Safety and Tolerability of Voriconazole as Primary Therapy for Treatment of Invasive Aspergillosis (IA) and Molds Such As *Scedosporium* or *Fusarium* Species (IFI; invasive fungal infection) in Paediatric Patients.

- **Study A1501085**: A Prospective, Open-Label, Non-Comparative Study to Assess the Safety, Tolerability and Efficacy of Voriconazole for the Primary and Salvage Treatment of Invasive Candidiasis, Candidemia (ICC), and Esophageal Candidiasis (EC) in Paediatric Patients.

3.3.2. Clinical studies

Safety was considered primary end point in both open-label studies. The observed efficacy of both studies will be briefly presented by the Rapporteur as efficacy parameters were considered secondary endpoints.

Data from Studies A1501080 and A1501085, have also been evaluated taking into consideration the events of interest (i.e. important identified and potential risks included in the Risk Management Plan (RMP Version 2.0). Refer to paragraph "*Important Identified and Potential Risks*" for the critical assessment in the paragraph on safety discussion.

Results

Efficacy

Study A1501080

This was a prospective, open label, non-comparative descriptive study conducted to evaluate the safety, tolerability and efficacy of voriconazole in paediatric patients 2 to <18 years of age with invasive fungal infection (IFI) due to *Aspergillus, Scedosporium* or *Fusarium* species. Thirty-one patients were included. Demographics are presented in Table 2 (in the safety section).

Patients who met European Organisation for Research and Treatment of Cancer (EORTC) criteria for proven or probable IA were analysed for efficacy. No patients with infection due to *Scedosporium* or *Fusarium* species were enrolled.

A total of 31 patients received at least 1 dose of voriconazole and were included in the safety population (11 patients were 2 to <12 years old and 20 were 12 to <18 years old). Of these, 14 patients had proven or probable IA (5 patients were 2 to <12 years old and 9 were 12 to <18 years old), and were included in the modified intent to treat (MITT) population.

The overall rate of global response[1] was 64.3% (95% CI: 35.1, 87.2) at the 6-week timepoint, which is similar to that in adult therapeutic studies in IA (53%[1]). Success rates were numerically higher in the 12 to <18 year age-group than in the younger age group (77.8% (95% CI: 40.0, 97.2) and 40.0% (95% CI: 5.3, 85.3), respectively. The rates of successful global response and the number of patients with a successful response remained the same at the EOT timepoint.

[1] A successful global response was defined as either a complete (resolution of all clinical signs and symptoms PLUS resolution of 90 percent or more of the lesions visible on radiological studies and attributed to IA at Baseline) or partial response (clinical improvement PLUS 50 percent to <90 percent resolution of the radiological lesions attributed to IA at Baseline) response.

CHMP comments:

Efficacy was considered secondary. Limited number of paediatric patients (n=31) were enrolled. Of these patients 14/31 had confirmed or probably IA. No patients with infection due to *Scedosporium* or *Fusarium* species were enrolled. Response rate at the 6-weeks timepoint was similar to the observed response rate adult therapeutic studies. The rates of successful global response and the number of patients with a successful response remained the same at the EOT timepoint. Due to the nature of the study and limited number of patients no definite conclusion can be drawn.

Study A1501085

This was an open-label, non-comparative, descriptive study of voriconazole for the treatment of paediatric patients 2 to <18 years of age with ICC and EC. In this study, voriconazole could be initiated either as primary therapy for ICC or EC, or as salvage therapy for ICC or EC with an unsatisfactory response to at least 7 days of treatment with at least 1 other antifungal agent.

A total of 22 patients received at least 1 dose of voriconazole and were included in the safety population (14 patients were 2 to <12 years old and 8 were 12 to <18 years old. A total of 17 patients were included in the MITT population (9 were 2 to <12 years old and 8 were 12 to <18 years old. Demographics are presented in Table 4 (in the safety section)

A total of 7 patients entered the study with a diagnosis of ICC and 10 entered the study with a diagnosis of EC. A total of 5 patients entered the study with a diagnosis of primary ICC, and 8 had the diagnosis of primary EC. A total of 2 patients entered the study with a diagnosis of salvage ICC, and 2 had the diagnosis of salvage EC.

Most patients had baseline *Candida albicans* (12 patients; 2 had isolates from blood only and 10 from other sources[2]) and *Candida tropicalis* (3 patients who had isolates from blood only). Only 2 patients had baseline *Candida glabrata* and *Candida parapsilosis* (1 patient each, both with isolates from blood only.

The overall rate of global response (ICC and EC combined) was 76.5% (95% CI: 50.10, 93.19) at EOT. The rate of response was 88.9% (95% CI: 51.75, 99.72) for 2 to <12 year olds and 62.5% (24.49, 91.48) for 12 to <18 year olds. These rates are comparable with data in therapeutic studies in ICC (65%[2]) and EC (98%[3]).

The global response for patients with EC included success in 7 (70.0%) patients, failure in 1 (10.0%) patient, and indeterminate in 2 (20.0%) patients. The global response for patients with ICC included success in 6 (85.7%) patients and indeterminate in 1 (14.3%) patient.

The global response rate at EOT was success for 4 (80.0%) patients with primary ICC therapy and 2 (100.0%) patients with salvage ICC therapy. The global response rate at EOT was success for 6 (75.0%) patients with primary EC therapy and 1 (50.0%) patients with salvage EC therapy.

Two (2) patients with a diagnosis of esophageal candidiasis and global response of success at the EOT later had recurrence of esophageal candidiasis (14 and 16 days after the last dose of voriconazole, respectively). One (1) patient with a diagnosis of esophageal candidiasis and a global response of

[2] Other specimen type includes culture result from throat/oral mucosa, esophageal mucosa, and perianal site.

success at the EOT (in relation to esophageal candidiasis) developed suspected splenic candidiasis during therapy.

CHMP comments: Efficacy was considered secondary endpoint. Limited number of paediatric patients (n=22) were included. The global response rates at EOT were comparable with data in therapeutic studies in ICC (65%[2]) and EC (98%[3]). The quoted references were submitted by the applicant and are publication of the initial studies.

Due to the nature of the paediatric study and limited number of patients no definite conclusion can be drawn.

In conclusion: Both studies A1501080 and A1501085 were open label with safety as primary endpoint. All Efficacy parameters were considered secondary endpoints. In addition the total number of include patients n=22 and n=23 respectively are limited. Hence no firm conclusion on the efficacy of voriconazole can be drawn.

Safety results

Study A1501080

Patients in the safety population received IV voriconazole for a median of 8.0 days the median length of IV voriconazole treatment was similar in the 2 age groups (8 days and 8.5 days in the 2 to <12 years age-group and 12 to <18 years age/group, respectively). No patient received more than 33 days of IV treatment. The median length of oral voriconazole treatment was also similar in both age groups in the safety population (55 days and 59.5 days in the 2 to <12 years age-group and 12 to <18 years age-group, respectively).

Table 2: Demographic Characteristics of study A1501080 (Safety Population).

	Age Group								
	Age 2 to <12 Years			Age 12 to <18 Years			Overall		
	Male	Female	Total	Male	Female	Total	Male	Female	Total
Number of Subjects	7	4	11	9	11	20	16	15	31
Age (years)									
≥2 to<6	1	0	1	0	0	0	1	0	1
≥6 to<12	6	4	10	0	0	0	6	4	10
≥12 to <18	0	0	0	9	11	20	9	11	20
Mean	7.3	9.0	7.9	14.0	14.1	14.1	11.1	12.7	11.9
SD	2.2	2.4	2.3	1.9	1.6	1.7	4.0	2.9	3.5
Range	3-9	6-11	3-11	12-17	12-17	12-17	3-17	6-17	3-17
Race									
White	3	0	3	4	4	8	7	4	11
Black	0	0	0	0	1	1	0	1	1
Asian	4	4	8	5	5	10	9	9	18
Other	0	0	0	0	1	1	0	1	1
Weight (kg)									
Mean	25.0	29.6	26.7	53.9	46.9	50.1	41.3	42.3	41.7
SD	9.1	11.4	9.7	20.0	10.0	15.3	21.6	12.7	17.6
Range	15.6-42.0	18.8-41.5	15.6-42.0	34.0-94.0	31.5-61.0	31.5-94.0	15.6-94.0	18.8-61.0	15.6-94.0
Height (cm)									
Mean	122.0	131.4	125.4	160.9	158.9	159.8	143.9	151.6	147.6
SD	15.2	15.2	15.1	12.6	9.8	10.9	24.0	16.6	20.8
Range	96.0-147.3	118.0-145.0	96.0-147.3	142.0-179.0	142.0-172.0	142.0-179.0	96.0-179.0	118.0-172.0	96.0-179.0

Cm=centimeter; kg=kilogram; SD=standard deviation.
The number of subjects was the total number of treated subjects.

All-causality treatment-emergent AEs (Table 3) were reported in 30 (96.8%) of the 31 patients (281 events). Similar results were observed across the age groups [11(100%) in age groups 2 to <12 and 19 (95%) in age group 12 to <18].

A total of 15 (48.4%) patients had an SAE; similar rates were observed across the age groups [6 (54.6%) in age group 2 to <12 and 9 (45%) in age group 12 to <18].

The SOCs including the majority of patients that experienced all-causality AEs were Gastrointestinal Disorders (18 patients), Skin and Subcutaneous Tissue Disorders (16 patients), Infections and Infestations (16 patients), Respiratory, Thoracic, and Mediastinal Disorders (14 patients), and General Disorders and Administration Site Conditions (14 patients). No new adverse events of concern were identified when compared to the known safety profile of voriconazole in adults in the therapeutic studies. In general, the safety data from the paediatric patients in this study were consistent with the known safety profile of voriconazole. The safety profile in the 2 age groups was also similar. Where differences in frequencies were observed, they were not assessed as clinically meaningful.

Table 3: Treatment-Emergent Adverse Events (All Causalities) Safety Population.

	Age Group		
	Age 2 to <12 Years	Age 12 to <18 Years	Overall
Subjects evaluable for AEs	11	20	31
Number of AEs	86	195	281
Subjects with AEs	11	19	30
Subjects with SAEs	6	9	15
Subjects with severe AEs	5	8	13
Subjects discontinued due to AEs	1	0	1
Subjects with dose reductions or temporary discontinuation due to AEs	0	4	4

AE=adverse event; SAE=serious adverse event.
The number of subjects evaluable for AEs was the total number of treated subjects. Data up to 7 days after the last dose of study drug was included. Except for number of AEs, subjects were counted only once per treatment in each row. Serious AEs were according to the investigator's assessment. MedDRA (v16.0) coding dictionary was applied.

All SAEs were considered as unrelated to administration of voriconazole by the investigators, except the event of renal failure acute in one Patient and the event of drug induced liver injury (DILI) in another Patient. While the contributory role of voriconazole in developing these 2 SAEs is possible, one Patient was confounded by concomitant use of vancomycin and ganciclovir and another Patient was confounded by concomitant use of paracetamol and concomitant parainfluenza virus infection. This patient had also experienced muscular weakness at the same time,which was considered by in the investigator as steroid induced myopathy.

One (1) patient (3.2%) discontinued the study drug due to sepsis. A total of 4 (12.9%) patients either reduced the dose (3 patients) or temporarily discontinued voriconazole (1 patient) due to an AE; in 3 patients (, all in older age group) the AEs were mild or moderate treatment-related liver enzyme abnormalities and all resolved. In 1 patient the AEs were Thrombocytopenia, Gastrointestinal bleeding, and Acute renal insufficiency, all considered due to the patient's acute lymphoblastic leukemia.

Deaths

Three (3) patients in the 2 to <12 year age-group and 2 patients in the 12 to <18 year age-group died during the study. None of the deaths were related to study treatment. 2 Patients in the 2 to <12 year age-group died from septic shock, and one Patient died of a ruptured mycotic aneurysm. In the 12 to <18 year age-group, one Patient died of septic shock and another Patient died of acute lymphocytic leukemia.

Other findings

No new safety information was identified upon evaluation of laboratory abnormalities, vital signs, electrocardiogram, and physical examination findings.

CHMP comments:

Thirty-one paediatric patients were included in this study. Median IV treatment was 8 days and oral treatment was 55 days in the 2- <12 years group and 59.5 days in 12 - <18 years group.

A total of 15/31 patients had SAE. Rates were similar between age-groups. All the SAE were considered unrelated to voriconazole by the investigators. Two patients experiencing acute renal failure and DILI respectively could be related to voriconazole treatment. However both patients also received concomitant medication (i.e. vancomycin, paracetomol, valganciclovir) which confounds the cases.

Most experienced AEs were gastrointestinal disorders; skin and subcutaneous tissue disorders; infections and infestations; respiratory, thoraric, and mediastinal disorders; and general disorders and administration site disorders. All hepatic-related adverse events occurred in patients in the 12 to <18 age group and resolved.

Three patients in the 2 to <12 year age-group and 2 patients in the 12 to <18 year age-group died during the study. None of the deaths were related to study treatment.

In conclusion, no new adverse events of concern were identified and the safety data from the paediatric patients in this study were consistent with the known safety profile of voriconazole.

Study A1501085

Of the 22 patients who received study drug and are included in the safety population, 9 received IV voriconazole only and 13 received both IV and oral voriconazole. The demographics of the included paediatric patients are presented in Table 4. The median duration of treatment was 7 days (range 2 to 24 days) for IV voriconazole and 9 days (range 2 to 37 days) for oral voriconazole. No patient received more than 24 days of IV treatment or 37 days of oral treatment. The median duration of oral voriconazole treatment was higher in the 2 to <12 year age-group [15 days (range 3 to 37 days)] than the 12 to <18 year age-group [5 days (range 2 to 8 days)]. The median duration of IV voriconazole treatment was similar in the 2 age groups [6.5 days (range 2 to 24) in the 2 to <12 year age-group and 8 (range 5 to 17) in the 12 to <18 year age-group].

All-causality treatment-emergent AEs were reported in 19 (86.4%) of the 22 patients (113 events). No clinically meaningful differences in the frequency of AEs were observed across the age groups [13 (92.9%) in the 2 to <12 age group and 6 (75.0%) in the 12 to <18 age group].

The SOCs including majority of patients that experienced all-causality AEs were Eye Disorders (9 patients) and Blood and Lymphatic Disorders and Gastrointestinal Disorders and Investigations (7 patients each). No new adverse events of concern were identified when compared to the known safety profile in the adult therapeutic studies. In general, the safety data from the paediatric patients in this study were consistent with the known safety profile of voriconazole. The safety profile in the 2 age groups was also similar. Where differences in frequencies were observed, they were not assessed as clinically meaningful.

Table 4: Demographic Characteristics study A1501085(Safety Population).

	Age Group								
	2 to <12 Years			12 to <18 Years			All		
Number of subjects	**Male**	**Female**	**Total**	**Male**	**Female**	**Total**	**Male**	**Female**	**Total**
Age (years)									
≥2 to <6, n	2	3	5	0	0	0	2	3	5
≥6 to <12, n	4	5	9	0	0	0	4	5	9
≥12 to <18, n	0	0	0	2	6	8	2	6	8
Mean	7.2	6.5	6.8	15.0	14.2	14.4	9.1	9.8	9.5
SD	3.4	2.6	2.9	1.4	1.8	1.7	4.7	4.5	4.5
Range	2-11	2-10	2-11	14-16	12-16	12-16	2-16	2-16	2-16
Race									
White, n	2	3	5	1	4	5	3	7	10
Asian, n	3	2	5	1	0	1	4	2	6
Other[a], n	1	3	4	0	2	2	1	5	6
Weight (kg)									
Mean	23.7	24.1	23.9	74.4	48.0	54.6	36.4	34.4	35.1
SD	6.6	14.0	11.1	15.1	17.0	19.7	24.8	19.2	20.8
Range	12.4-31.3	11.0-50.0	11.0-50.0	63.7-85.0	25.0-73.9	25.0-85.0	12.4-85.0	11.0-73.9	11.0-85.0
N	6	8	14	2	6	8	8	14	22
Height (cm)									
Mean	121.1	115.8	118.0	186.3	158.1	165.2	137.4	133.9	135.2
SD	18.4	17.6	17.5	10.9	12.1	17.1	34.2	26.4	28.7
Range	89.8-138.0	87.0-149.0	87.0-149.0	178.6-194.0	141.0-176.0	141.0-194.0	89.9-194.0	87.0-176.0	87.0-194.0
N	6	8	14	2	6	8	8	14	22

Source: Table 14.1.2.1
Abbreviations: N/n=number of subjects; SD=standard deviation
[a] Other includes Hispanic, Gypsy, and Hispanic/Mexican.

Table 5: Treatment-Emergent Adverse Events (All Causalities) Safety Population.

	2 to <12 Years (N=14)	12 to <18 Years (N=8)	Overall (N=22)
Subjects evaluable for adverse events, n	14	8	22
Number of adverse events, n	78	35	113
Subjects with adverse events, n (%)	13 (92.9)	6 (75.0)	19 (86.4)
Subjects with serious adverse events, n (%)	2 (14.3)	1 (12.5)	3 (13.6)
Subjects with severe adverse events, n (%)	4 (28.6)	3 (37.5)	7 (31.8)
Subjects discontinued due to adverse events, n (%)	2 (14.3)	2 (25.0)	4 (18.2)
Subjects with dose reduced or temporary discontinuation due to adverse events, n (%)	3 (21.4)	0	3 (13.6)

Source: Table 14.3.1.1.4.1
Includes data up to 7 days after the last dose of study drug.
Except for the number of adverse events, subjects were counted only once per treatment in each row.
Serious adverse events – according to the investigator's assessment.
MedDRA (v16.0) coding dictionary applied.
Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities; n/N=number of subjects; v=version

A total of 3 patients had an SAE; the occurrence of treatment emergent SAEs in both age groups was similar n=2 in the 12 to <18 age group and n=1 in the 2 to <12 age group). Only 1 patient a 12-year-old White female, experienced treatment related SAE of Severe progression of splenic candidiasis.

A total of 4 patients 2 in each age group discontinued the study drug due to an AE; in 3 patients the AEs were treatment related: Hyperbilirubinaemia (10191002), Mild liver disorders, and Progression of splenic candidiasis.

A total of 3 patients all in the 2 to <12 age group reduced the dose due to an AE (all treatment-related); in 2 patients the AEs were liver enzyme abnormalities; both resolved. The AE involving patient was mentioned above and discontinued study drug after which liver disorder resolved. No temporary discontinuation due to an AE was reported in this study.

Deaths

There were no patient deaths during the study period. One patient died after the safety reporting period (i.e., after the 1-month follow-up visit). The patient, a 3-year old Asian male, died due to progression of underlying disease (anaplastic medulloblastoma), 490 days after the first dose of study drug (455 days after the last dose of study drug).

Other findings

No new safety information was identified upon evaluation of laboratory abnormalities, vital signs, electrocardiogram, and physical examination findings.

CHMP comments:

Twenty-two paediatric patients were included in this study. Median IV treatment was 7 days and oral treatment was 9 days. No patient received more than 24 days of IV treatment or 37 days of oral treatment.

A total of 3/22 patients had SAE. Rates were similar between age-groups. All the SAE were considered unrelated to voriconazole by the investigators. One patient experienced treatment related SAE of severe progression of splenic candidiasis.

Most experienced AEs were eye disorders; blood and lymphatic disorders; and gastrointestinal disorders. Two hepatic-related AE occurred in the 2 to <12 age group.

No deaths occurred during the study. One patient died after the safety reporting period due to anaplastic medulloblastoma.

In conclusion, no new adverse events of concern were identified and the safety data from the paediatric patients in this study were consistent with the known safety profile of voriconazole.

Important Identified and Potential Risks

Data from Studies A1501080 and A1501085, have also been evaluated taking into consideration the events of interest (i.e. important identified and potential risks included in the Risk Management Plan (RMP Version 2.0): Phototoxicity, Squamous cell carcinoma (SCC), Hepatic toxicity, QTc prolongation, Visual Events, Peripheral neuropathy, Skin cancers (non-SCC) and Suicide related disorders), and were also compared to data from adults in the same indication, as shown in Table 6. All combined therapeutic paediatric data (N=105 from Studies 150-303, 304, 305, 307, 309, 602, 603, 604, 608, A1501080 and A1501085) were also compared to adult data from therapeutic studies (N=1603 from Studies 150-303, 304, 305, 307, 309, 602, 603, 604, and 608) as shown in Table 6.

No AEs related to phototoxicity, SCC, skin cancer (non-SCC), or suicide related disorders were observed in either study. Similarly, no AEs related to these risks were observed when safety data from the paediatric population in all combined therapeutic studies was reviewed (N=105, Table 6).

QT prolongation

A search of the clinical database using the QT prolongation (Torsades de Pointes/QT prolongation). Broad and narrow SMQ was conducted to capture all potentially relevant events. No patients were identified in Study A1501085. Two (2) patients (6.5%) were identified in Study A1501080 (1 patient - Loss of consciousness; 1 patient - Cardiac arrest). QT prolongation was not reported in these 2 patients. When safety data from the paediatric population in all therapeutic studies were combined (N=105), the frequency of patients experiencing AEs identified by the wide search criteria (4.8%) was similar to that observed in adults (4.5%) (Table 6).

Visual events

The frequency of patients experiencing visual events in Study A1501085 (36.4%: 8/22) was slightly higher than that in adults in the therapeutic studies (33.0%), whereas in Study A1501080 the frequency of the patients with these events was lower (29%: 9/31). The type, severity and outcome of visual events reported in the 2 studies were similar to those observed in the adult therapeutic studies; the majority of the events were mild or moderate and resolved and none resulted in discontinuation of voriconazole. Visual safety testing results did not show new safety concerns. No clinically meaningful differences in the visual related AEs between the studies and between the age groups in each study were observed. When safety data from the paediatric population in all therapeutic studies were combined (N=105), the frequency of patients with visual events was slightly higher than that in adults, however not statistical significant (35.2% and 33.0% respectively; p=0.6689).

Peripheral neuropathy

The frequency of patients with peripheral neuropathy related events in Study A1501085 (4.5%) was lower than that observed in the adults from therapeutic studies (8.0%). However, in Study A1501080, a numerically higher frequency of patients with peripheral neuropathy related events was observed compared to the adults from therapeutic studies (12.9% and 8.0% respectively). All events in Studies A1501080 and A1501085 were unrelated to treatment with voriconazole except 1. The nature and severity of peripheral neuropathy related AEs in paediatrics from the 2 studies were consistent with the known profile for voriconazole. All except 1 (Muscular weakness) were mild or moderate in severity. The outcome was reported as resolved for all events except 1 (Moderate paraesthesia Study A1501080).). No SAEs or events resulting in permanent discontinuation or dose reduction/interruption were reported. No clinically meaningful differences between the 2 studies and between age groups within each study were observed. The peripheral neuropathy- related events were:

- Study A1501080- Paraesthesia, Skin burning sensation, Muscular weakness, and Arthalgia.
- Study A1501085- Paraesthesia.

When safety data from the paediatric population in all therapeutic studies were combined (N=105), the frequency of patients with peripheral neuropathy related-events (7.6%) was similar to that observed in adults (8.0% [Table 6]).

Hepatic related events

A numerically higher frequency of patients with hepatic- related adverse events was observed in both studies (29% in Study A1501080 and 36.4% in Study A1501085) compared to that reported in the adult therapeutic studies (24.0%). However, the nature and severity of hepatic-related AEs in the 2 studies were consistent with the known safety profile of voriconazole as observed in the adult therapeutic studies. No fatal outcome was reported with any of the hepatic related AEs. No cases of liver failure were reported.

In Studies A1501080 and A1501085, the hepatic-related AEs were primarily liver enzyme abnormalities (mild/moderate)[3] except in 2 patients in Study A1501080 (1 patientreporting severe Drug induced liver injury and 1 patientreporting mild Jaundice cholestatic) and 3 patients in Study A1501085 (1 patientreporting severe Liver disorder, 1 patientwith mild Hepatosplenomegaly and gall bladder disorder, and 1 patientreporting Jaundice cholestatic) and moderate Hyperbilirubinaemia). The outcome of the majority of AEs (all except mild Alanine aminotransferase (ALT) increased in 1 patientand mild Jaundice cholestatic in 1 patient) was reported as resolved.

In the 2 patients reporting severe DILI term Hy's law and severe Liver disorder, a contributory role of voriconazole is possible, however, the cases were confounded by concomitant medications and underlying diseases.

In Study A1501080, none of the hepatic-related AEs resulted in permanent discontinuation from treatment. In 3 patients, the dose was modified or interrupted due to treatment-related mild or moderate liver enzyme abnormalities with resolved outcome.

In Study A1501085, voriconazole was permanently discontinued due to severe Liver disorder in 1 patientand moderate Hyperbilirubinaemia in 1 patient, both resolved after drug discontinuation. Both AEs were reported as treatment related by the investigator but were confounded by concomitant use of chemotherapy and pancreatic cancer, respectively. Dose reductions were reported in 3 patients [1 patient liver disorder with permanently discontinued voriconazole, 1 patient due to moderate Aspartate aminotransferase (AST), ALT and Gamma-glutamyl transferase (GGT) increased and 1 patient due to mild hepatic enzyme increased], all resolved. These AEs were reported as treatment related but were confounded by chemotherapy, veno-occlusive liver disorder (VOLD), and sepsis at baseline, respectively. No temporary dose discontinuations due to AEs were reported in this study.

All hepatic-related adverse events in Study A1501080 occurred in patients in the 12 to <18 age group. Whereas in Study A1501085 all but 2 hepatic-related AE occurred in the 2 to <12 age group. Similar observation was made for clinically significant laboratory abnormalities. A clinically meaningful conclusion from this observation cannot be drawn due to limited sample size in each age group.

When safety data from the paediatric population in all in therapeutic studies were combined (N=105), a similar observation of a higher frequency of patients with hepatic-related events, was observed in the paediatric population when compared to adults in the therapeutic studies. The numerical higher frequency in the combined paediatric population versus adults (28.6% and 24.0% respectively [Table 6]) was mainly associated to an increased incidence of liver function test abnormalities (AEs in the Investigation SOC) in paediatric patients compared to adults (21.90% and 16.09% respectively).

[3] Per the broad search strategy used, 2 AEs (hypoalbuminaemia and prothrombin time prolonged) were reported in two patients but in these two patients the involvement of liver was not confirmed.

The applicant proposes to update Section 4.8 of the SmPC to include this information in the paediatric population subsection.

The frequency of patients who experienced AEs in the Hepatobiliary disorders SOC was similar in the combined paediatric population (7.62% compared to adults (8.05%. In addition, the type and severity of hepatic-related AEs in the paediatric population are similar to adults.

CHMP comments:

The applicant evaluated the data from both studies (A1501080 and A1501085) taking the events of interest (phototoxicity, squamous cell carcinoma (SCC), hepatic toxicity, QTc prolongation, Visual Events, Peripheral neuropathy, skin cancers (non-SCC) and suicide related disorders) as identified in the RMP (V2.0) into account. Data was also compared to the adult data.

No AEs related to phototoxicity, SCC, skin cancer (non-SCC), or suicide related disorders were observed in either study. Similarly, no AEs related to these risks were observed when safety data from the paediatric population in all combined therapeutic studies was reviewed (N=105).

The observed frequencies of QT prolongation and peripheral neuropathy in paediatric patients were similar to adults. The frequency of visual events observed in paediatric patients was slightly higher (non-significant) than the observed frequency in adults.

All hepatic-related adverse events in Study A1501080 occurred in patients in the 12 to <18 age group. Whereas in Study A1501085 all but 2 hepatic-related AE occurred in the 2 to <12 age group. Similar observation was made for clinically significant laboratory abnormalities. A clinically meaningful conclusion from this observation cannot be drawn due to limited sample size in each age group. When taking into account all safety data in paediatric patients in therapeutic studies (n=105) a similar observation of a higher frequency of patients with hepatic-related events, was observed in the paediatric population when compared to adults in the therapeutic studies. The numerical higher frequency in the combined paediatric population versus adults (28.6% and 24.0% respectively) was mainly associated to an increased incidence of liver function test abnormalities (AEs in the Investigation SOC) in paediatric patients compared to adults (21.90% and 16.09% respectively).

The applicant proposes to update Section 4.8 of the SmPC to include this information in the paediatric population subsection. This is agreed upon by the Rapporteur a type II variation is awaited.

Table 6. Summary of Important Identified and Potential Risks for Studies A1501080 and A1501085 and Combined Paediatric Data from the Therapeutic Studies (303, 304, 305, 307, 309, 602, 603, 604, 608, A1501080 and A1501085) Compared with the Adults in the Therapeutic Studies (303, 304, 305, 307, 309, 602, 603, 604, 608).

	Study A1501080			**Study A1501085**			**Adult Patients in Therapeutic Studies***	**Paediatric Patients in Therapeutic Studies****
	All	**2 to <12 Years**	**12 to <18 Years**	**All**	**2 to <12 Years**	**12 to <18 Years**		
No. of patients	**31**	**11**	**20**	**22**	**14**	**8**	**1603**	**105**
Phototoxicity[a], n# (%) [95% CI†]	0	0	0	0	0	0	14 (0.9%) [0.5%, 1.5%]	0
SCC[b], n# (%) [95% CI†]	0	0	0	0	0	0	1 (0.1%) [0.0%, 0.3%]	0
Hepatic toxicity[c] n# (%) [95% CI†]	9 (29.0%)[i] [14.2%, 48.0%]	2 (18.2%) [2.3%, 51.8%]	7 (35.0%) [15.4%, 59.2%]	8 (36.4%) [17.2%, 59.3%]	6 (42.9 %) [17.7%, 71.1%]	2 (25.0%) [3.2%, 65.1%]	384 (24.0%) [21.9%, 26.1%]	30 (28.6%) [20.2%, 38.2%]
QTc prolongation[d], n# (%) [95% CI†]	2 (6.5%)[j] [0.8%, 21.4%]	1 (9.1%) [0.2%, 41.3%]	1 (5.0%) [0.1%, 24.9%]	0	0	0	72 (4.5%) [3.5%, 5.6%]	5 (4.8%) [1.6%, 10.8%]
Visual Events[e] n# (%) [95% CI†]	9 (29.0%) [14.2%, 48.0%]	3 (27.3%) [6.0%, 61.0%]	6 (30.0%) [11.9%, 54.3%]	8 (36.4 %) [17.2%, 59.3%]	5 (35.7 %) [12.8%, 64.9%]	3 (37.5 %) [8.5%, 75.5%]	529 (33.0%) [30.7%, 35.4%]	37 (35.2%) [26.2%, 45.2%]
Peripheral neuropathy[f] n# (%) [95% CI†]	4 (12.9%) [3.6%, 29.8%]	2 (18.2%) [2.3%, 51.8%]	2 (10.0%) [1.2%, 31.7%]	1 (4.5 %) [0.1%, 22.8%]	0	1 (12.5%) [0.3%, 52.7%]	128 (8.0%) [6.7%, 9.4%]	8 (7.6%) [3.3%, 14.5%]
Skin cancers (non-SCC)[g] n# (%) [95% CI†]	0	0	0	0	0	0	6 (0.4%) [0.1%, 0.8%]	0
Suicide related disorders[h] n# (%) [95% CI†]	0	0	0	0	0	0	2 (0.1%) [0.0%, 0.4%]	0

Table 6. Summary of Important Identified and Potential Risks for Studies A1501080 and A1501085 and Combined Paediatric Data from the Therapeutic Studies (303, 304, 305, 307, 309, 602, 603, 604, 608, A1501080 and A1501085) Compared with the Adults in the Therapeutic Studies (303, 304, 305, 307, 309, 602, 603, 604, 608).

	Study A1501080			**Study A1501085**			**Adult Patients in Therapeutic Studies***	**Paediatric Patients in Therapeutic Studies****
	All	**2 to <12 Years**	**12 to <18 Years**	**All**	**2 to <12 Years**	**12 to <18 Years**		
No. of patients	**31**	**11**	**20**	**22**	**14**	**8**	**1603**	**105**

Abbreviations: CI = confidence intervals; n = number of patients reporting at least one event in the risk category; N = total patients in the studies; SCC = Squamous cell carcinoma

* Includes patients meeting the age criteria in Studies 303, 304, 305, 307, 309, 602, 603, 604 and 608

** Includes patients meeting the age criteria in Studies 303, 304, 305, 307, 309, 602, 603, 604, 608, A1501080 and A1501085

Number of patients reporting at least one event in the risk category. Percentages are based out of N.

† Using exact method (Clopper-Pearson) based on F-distribution

MedDRA (v17.0) coding dictionary applied.

a Search criteria= Preferred Terms: Actinic keratosis, Photodermatosis, Photosensitivity allergic reaction, Photosensitivity reaction, Sunburn.

b Search criteria= Preferred Terms: Adenosquamous cell carcinoma, Basosquamous carcinoma, Basosquamous carcinoma of skin, Bowen's disease, Squamous cell carcinoma, Squamous cell carcinoma of skin.

c Search criteria= Standard MedDRA Query (SMQ): Drug related hepatic disorders, comprehensive search [Broad and Narrow search]

d Search criteria= SMQ: Torsade de pointes/QTc prolongation [Broad and Narrow search])

e Search criteria= System Organ Class: Eye disorders; High level Group Terms: Eye disorders congenital, Eye therapeutic procedures, Neurological disorders of the eye, or Ocular neoplasms; High Level Terms: Eye injuries NEC, Eye movement disorders, Ophthalmic function diagnostic procedures, or Ophthalmic histopathology and imaging procedures or Optic nerve disorders NEC; Preferred Terms: Acquired pigmented retinopathy, Floppy iris syndrome, Hepato-lenticular degeneration, Horner's syndrome, IIIrd nerve injury, IVth nerve injury, Intraocular lens dislocation, Intraocular lens opacity, Marfan's syndrome, Millard-Gubler syndrome, Miller Fisher syndrome, Nystagmus, Ophthalmological examination abnormal, Optic nerve injury, Optic pathway injury, Retinal arteriovenous malformation

f Search criteria= SMQ: Peripheral neuropathy [Broad and Narrow search]

g Search criteria= SMQ: Skin neoplasms, malignant, and unspecified [Narrow search] (including PTs Basal cell carcinoma and Malignant melanoma

h Search criteria= SMQ: Suicide/self-injury [Narrow search].

3.3.3. Discussion on clinical aspects

The applicant submitted two paediatric studies (A1501080 and A1501085). Thirty-one and 22 paediatric patients were included respectively. Both studies were open-label with safety as primary endpoint. Due to the nature of the paediatric study and limited number of patients no definite conclusion on efficacy can be drawn**.**

Treatment dosage and duration were in line with the approved SmPC of Vfend. The CHMP observed a probable discrepancy in the total number of paediatric patients stated in SmPC section 5.1 (n=54 aged 2 -15 years) whereas the overview states that n=52 patients were included. Applicant is requested to substantiate the discrepancy.

No new adverse events of concern were identified from both studies and the safety data from the paediatric patients in this study were consistent with the known safety profile of voriconazole.

Three patients died during study A1501080, their deaths were unrelated to the voriconazole treatment. After the safety reporting period of study A1501080 one patient expired due to underlying disease.

Additionally the applicant evaluated the data from both studies (A1501080 and A1501085) taking the events of interest (phototoxicity, squamous cell carcinoma (SCC), hepatic toxicity, QTc prolongation, Visual Events, Peripheral neuropathy, skin cancers (non SCC) and suicide related disorders) as identified in the RMP (V2.0) into account. Data was also compared to the adult data. No AEs related to phototoxicity, SCC, skin cancer (non-SCC), or suicide related disorders were observed in either study. Similarly, no AEs related to these risks were observed when safety data from the paediatric population in all combined therapeutic studies was reviewed (N=105). The observed frequencies of QT prolongation and peripheral neuropathy in paediatric patients were similar to adults. The frequency of visual events observed in paediatric patients was slightly higher (non-significant) than the observed frequency in adults.

All hepatic-related adverse events in Study A1501080 occurred in patients in the 12 to <18 age group. Whereas in Study A1501085 all but 2 hepatic-related AE occurred in the 2 to <12 age group. Similar observation was made for clinically significant laboratory abnormalities. A clinically meaningful conclusion from this observation cannot be drawn due to limited sample size in each age group. When taking into account all safety data in paediatric patients in therapeutic studies (n=105) a similar observation of a higher frequency of patients with hepatic-related events, was observed in the paediatric population when compared to adults in the therapeutic studies. The numerical higher frequency in the combined paediatric population versus adults (28.6% and 24.0% respectively) was mainly associated to an increased incidence of liver function test abnormalities (AEs in the Investigation SOC) in paediatric patients compared to adults (21.90% and 16.09% respectively). The applicant proposes to update Section 4.8 of the SmPC to include this information in the paediatric population subsection. This is agreed upon by the CHMP a type II variation is awaited.

4. CHMP's overall conclusion and recommendation

Overall conclusion

The applicant submitted two paediatric studies (A1501080 and A1501085). Thirty-one and 22 paediatric patients were included respectively. Both studies were open-label with safety as primary endpoint. Although the applicant presented some efficacy data no firm conclusions can be drawn due to the nature of the studies and the limited number of included patients. Treatment dosage and duration were in line with the approved SmPC of Vfend. The CHMP observed a probable discrepancy in the total number of paediatric patients stated in SmPC section 5.1 (n=54 aged 2 -15 years) whereas the overview states that n=52 patients were included. Applicant is requested to substantiate the discrepancy.

No new adverse events of concern were identified from both studies and the safety data from the paediatric patients in this study were consistent with the known safety profile of voriconazole.

The numerical higher frequency in the combined paediatric population *versus* adults was mainly associated to an increased incidence of liver function test abnormalities (AEs in the Investigation SOC) in paediatric patients compared to adults. The applicant proposes to update Section 4.8 of the SmPC to include this information in the paediatric population subsection. This is agreed upon by the CHMP a type II variation is awaited.

The benefit/risk balance of Vfend remains positive in the approved indications.

Recommendation

☐ Fulfilled:

Type II variation to be requested from the MAH to amend the product information as follows:

1. The applicant is requested to submit a type II variation to update SmPC section 4.8 to include the observed increased incidence of liver function test abnormalities in paediatric patients.
2. Limited voriconazole concentration data were obtained from Studies A1501080 and A1501085. No new clinical pharmacology information is currently available from Studies A1501080 and A1501085. However, analyses to explore the relationship between voriconazole exposure and efficacy and safety endpoints in the paediatric patients in these studies are ongoing. The report will be submitted when available (Target completion date: end September 2014). The Rapporteur will await the submission of these data.

☒ Not fulfilled:

Based on the data submitted, the MAH should provide additional clarification requested as part of this procedure. (see section 4 "Additional clarifications requested").

5. Additional clarifications requested

3. The applicant is requested to discuss the observed discrepancy regarding the numbers in paediatric patients treated in the therapeutic studies being n=52 as stated in the overview.

Whereas the SmPC section 5.1 mentions n=61 paediatric patients of whom n=54 were aged 2 -15 years being treated in therapeutic studies.

The timetable is a 30 day response timetable without clock stop.

References

[1] Herbrecht R, Denning DW, Patterson TF, et al. Voriconazole versus amphotericin B or primary therapy of invasive aspergillosis. N Engl J Med n2002;347(6):408-15.

[2] Kullberg B, Sobel J, Ruhnke M, et al. Voriconazole versus a regimen of amphotericin B followed by fluconazole for candidaemia in non-neutropenic patients: a randomised non- inferiority trial. Lancet 2005;9495.

[3] Ally R, Schurmann D, Kreisel W, et al. A randomized, double-blind, double-dummy, multicenter trial of voriconazole and fluconazole in the treatment of esophageal candidiasis in immunocompromised patients. Clin Infect Dis 2001;9(1 Nov):1447-54.

6. Updated Assessment

Assessment of the responses to the CHMP List of Questions - Clinical aspects

Question 1

The MAH is requested to submit within 2 months a type II variation to update SmPC section 4.8 to include the observed increased incidence of liver function test abnormalities in paediatric patients.

Summary of the Applicant's Response

The MAH confirms that a Type II variation to update Section 4.8 of the SmPC will be submitted. The MAH proposes also to include an update to Section 5.1 to reflect the new paediatric patient numbers in the same variation.

CHMP's assessment of the Applicant's Response

The applicant commits to submit a type II variation within 2 months.

Conclusion

Point is solved.

Question 2

Limited voriconazole concentration data were obtained from Studies A1501080 and A1501085. No new clinical pharmacology information is currently available from Studies A1501080 and A1501085. However, analyses to explore the relationship between voriconazole exposure and efficacy and safety endpoints in the paediatric patients in these studies are on-going. The report will be submitted when available (Target completion date: end September 2014). The CHMP awaits the submission of these data.

Summary of the Applicant's Response

The MAH clarifies that the PK-PD report (PMAR-EQDD-A150f-DP4-245: Voriconazole, Pediatric Population PK-PD Analysis Report) was completed in September 2014 and is provided with this response.

The currently approved paediatric dosing regimens were based on a population pharmacokinetic modeling approach. These dosing regimens are predicted to provide voriconazole exposures comparable to those in adult patients. These 2 paediatric studies were conducted with the same regimens and confirm these doses are appropriate for paediatric use. No update to the SmPC is proposed as a result of this analysis.

The objectives of the population pharmacokinetic-pharmacodynamic (PK-PD) analyses were:

- To describe the PK of voriconazole in the target pediatric patient population based on limited sparse PK samples, if data permit
- To predict individual exposure parameters (eg, area under the curve over 12-hour dosing interval [AUC0-12] and trough concentration [Cmin]) based on the final PK parameter estimates, if data permit
- To explore the relationship between voriconazole exposure parameters (AUC0-12 and Cmin) and key efficacy endpoints (survival and global response), if data permit

- To explore the relationship between voriconazole exposure parameters (AUC0-12 and Cmin) and key safety endpoints (hepatic, visual, psychiatric, skin and subcutaneous tissue AEs), if data permit
- To identify and characterize patient factors which influence the variability in the PK and PD of voriconazole (eg, CYP2C19 genotyping status), if data permit
- To evaluate the model performance of voriconazole PK and PD models, if data permit
- To explore the relationship between voriconazole PK/PD index [eg, AUC0-12/minimum inhibitory concentration (MIC)] and efficacy endpoints in a subset of patients, if data permit

Data from two studies were included in the analysis, i.e. study A1501080 and study A1501085 (see table below).

Table S1. Initial Voriconazole Dosing Regimens by Age and Indication

Children (2-11 years) & young adolescents (12-14-year-olds weighing <50 kg)	Loading Dose	Maintenance Dose	
	IV	IV	If switched to oral voriconazole
IA/ICC	9 mg/kg IV q12h for the first 24 h	8 mg/kg IV q12h	9 mg/kg (maximum 350 mg) PO q12h
EC	No loading dose	4 mg/kg IV q12h	9 mg/kg (maximum 350 mg) PO q12h

Adolescents (12-17 years) (excluding 12-14-year-olds weighing <50 kg)	Loading Dose	Maintenance Dose	
	IV	IV	If switched to oral voriconazole[a]
IA/ICC	6 mg/kg IV q12h for the first 24 h	4 mg/kg IV q12h	200 mg PO q12h
EC	No loading dose	3 mg/kg IV q12h	200 mg PO q12h

[a] At the investigator's discretion, a dose of 300 mg PO q12h may be used in adolescents with IA.
Source: A1501080 and A1501085 protocols, Section 5.

In both studies, to facilitate potential dose adjustment, voriconazole trough samples were collected on the 3rd day (or later) of IV or oral therapy or after each dose adjustment. To enable rapid turnaround analysis, the voriconazole samples were shipped to designated non-GLP (Good Laboratory Practice) reference laboratories for assay or analyzed locally. In Study A1501080, the key efficacy endpoints included all-cause mortality at 6 weeks and EOT and global response at 6 weeks and EOT. In Study A1501085, the key efficacy endpoints included global response at EOT and all-cause mortality at 4 weeks (Day 28). Four types of AEs (including hepatic, visual, psychiatric AEs, as well as skin and subcutaneous tissue disorders) were the focus of this analysis. Each type of AE from these two studies was pooled and analyzed separately.

Previously, a two-compartment PK model with first-order absorption and mixed linear and time-dependent nonlinear (Michaelis-Menten) elimination was developed based on voriconazole concentration data from 5 studies (A1501007, A1501037, A1501081, A1501088 and A1501092), including immunocompromised children and adolescents as well as healthy adults (PMAR-00204). All clearance terms [maximum elimination rate (Vmax) at 1 hour after the start of dosing (Vmax,1), linear clearance (CL) and inter-compartmental clearance (Q)] were scaled allometrically, using weight to a power of 0.75; and all volume terms (volume of distribution for the central and peripheral compartments, V2 and V3) were scaled allometrically. Only one parameter, maximum fraction of Vmax inhibition (Vmax,inh), in healthy adults was impacted by the CYP2C19 status, where HEMs and PMs were predicted to have full inhibition (Vmax,inh = 100%, Vmax = 0) of the nonlinear pathway at maintenance dosing. The final model used first-order conditional estimation (FOCE) method on log-transformed concentrations. This PK model was subsequently adopted to fit the voriconazole concentration data from a Phase 3 Study A8851009 (adult patients with IA comparing voriconazole and

anidulafungin combination therapy with voriconazole monotherapy, PMAR-00284) and a Phase 2 PK Study A1501096 (immunocompromised Japanese pediatric subjects, PMAR-00320), respectively.

For PK/PD, Voriconazole doses could vary with time within a patient since dose adjustment was allowed per protocol. Therefore, for PK-PD analysis, individual voriconazole exposures were estimated using individual PK parameters from the final PK model and the actual doses administered to each patient. For the efficacy analysis, average AUC0-12 and Cmin over the treatment period were used. The average AUC0-12 values were also used for the calculation of the PK/PD index (AUC/MIC) for the subset of patients with MIC data available. For the safety analysis, when patients had no hepatic or visual AEs reported, average AUC0-12 and Cmin over the treatment period were used. When patients experienced an AE, the AUC0-12 and Cmin from the onset day of this AE were used. When using the single-panel analysis approach, for patients experiencing multiple AEs, the AUC0-12 and Cmin associated with the first AE occurrence were used. All the efficacy and safety data were evaluated as binary data. For efficacy analysis, only graphical examination was performed given the small sample size and high success rate. Additionally, AUC/MIC was explored as a potential predictor for efficacy. The safety data were evaluated using a logistic regression model in NONMEM with the second order conditional (Laplacian) estimation method. Each safety endpoint was analyzed separately using voriconazole exposure parameters (AUC0-12 and Cmin) as potential predictors. Other covariates (eg, CYP2C19 genotyping status, gender and race) were also examined in each analysis.

This previously developed PK model continued to be adopted to fit the current data from studies A1501080 and A1501085.

The final PK dataset contained 96 voriconazole concentrations from 48 patients. Six concentration records with missing collection time, levels below the limit of quantitation, or inconsistent concentration values were excluded from the PK analysis. The demographics of the patients included in the PK analysis are presented in Table S2.

Table S2. Demographics of Pediatric Patients Included in PK Analysis (N = 48)

Characteristics	Median (Range) or Counts
Age (years)	12 (2 - 17)
Baseline body weight (kg)	37.6 (11 - 94)
Sex (male/female)	22/ 26
Race (white/black/Asian/Other)	18/ 1/ 23/ 6
CYP2C19 genotyping status (EM/HEM/PM/Unknown[a])	17/ 12/ 3/ 16

EM = homozygous extensive metabolizers, HEM = heterozygous extensive metabolizers, PM = poor metabolizers.
[a] = The genotyping status for patients who didn't provide a sample or whose sample had insufficient volume for analysis was defined as unknown.

There were 30 mITT patients with exposure and efficacy data pairs. Among them, 14 patients were diagnosed with proven or probable IA, 6 patients with ICC and 10 patients with EC. The MIC data for Aspergillus (ranged from 0.125 to 0.5 µg/ml) are available in 5 IA patients only, and the MIC data for Candida (0.03 µg/ml are available in 14 patients.

In both studies, only a few concentration data were collected from the absorption phase and the concentration data were quite variable, which posed a challenge in the model fitting. The simplified model with first-order absorption and linear elimination was selected as the final PK model to describe the pediatric data. Compared to the previous PK model, the removal of the nonlinear clearance from the PK model did not show any degradation of model performance. Based on the parameter estimates and the diagnostic plots, two runs (Run 6 and Run 13) showed better performance than other runs (ie, lower OFV, improved diagnostic plots, improved precision of parameter estimates, and successful convergence). These two runs represent two different model structures. Run 6 is a two-compartment

model with first-order absorption and mixed linear and time-dependent nonlinear elimination, which is similar to the previous PK model. Run 13 is a simplified model with less parameters for the elimination phase: a two-compartment model with first-order absorption and linear elimination only. These two runs had similar results, and Run 13 had slightly better performance than Run 6. The simplified model (Run 13) was selected as the final PK model. No new covariates were identified in the current analysis. The comparison of the model parameter estimates is shown in the table below.

Table 11. Comparison of Voriconazole Parameter Estimates from the Population PK Models for the Current Data with Previous Analyses

Parameter	Typical value (%RSE[a])					Interindividual variability[c] / SD[b] (%RSE[a])					
	Original Ped Data (N = 112)	Adult Data (N = 305)	Japanese Ped Data (N = 21)	Current Run 6 (N = 48)	Current Run 13 (N = 48)		Original Ped Data (N = 112)	Adult Data (N = 305)	Japanese Ped Data (N = 21)	Current Run 6 (N = 48)	Current Run 13 (N = 48)
k_m (µg/mL)						$k_{m,i} = k_m * \exp(\eta_{km\text{-}Vmax,1})$					
θ_{km}	1.15 (28)	1.15 (10)	0.922 (30)	9.52 (55)	-	$\omega_{km\text{-}Vmax,1}$	1.36 (21)	1.91 (28)	1.36 (11)	NS	-
$V_{max,1}$ (mg/h/70kg[d])						$V_{max,1,i} = V_{max,1} * \exp(\eta 1 * \theta_{Vmax,scale})$					
$\theta_{Vmax,1}$	114 (16)	0.113 (10)	118 (14)	117 (8.5)	-	$\omega_{km\text{-}Vmax,1}$	1.36 (21)	1.91 (28)	1.36 (11)	NS	-
						$\theta_{Vmax,scale}$	0.584 (10)	0.583 (10)	1.25 (12)		
$V_{max,inh}$*											
$\theta_{Vmax,inh}$	1.50 (9.3)	1.50 (9.3)	2.61 (19)	2.03 (80)	-		NS	NS		NS	-
$\theta_{AGE<12}$	-0.39 (39)										
T_{50} (h)											
θ_{T50}	2.41 (6.6)	2.42 (5.7)	2.45 (6.3)	8.60 (72)	-		NS	NS		NS	-
CL (L/h/70kg[d])											
θ_{CL}	6.16 (13)	5.30 (4.2)	6.02 (11)	5.31 (33)	7.79 (14)	ω_{CL}	0.435 (18)	0.634 (11)	0.696 (10)	0.686 (29)	0.675 (23)
V_2 (L/70kg)											
θ_{V2}	79.0 (3.1)	77.6 (2.9)	75.0 (32)	72.7 (14)	72.3 (14)	ω_{V2}	0.136 (21)	0.139 (25)	0.142 (11)	NS	NS
V_3 (L/70kg)											
θ_{V3}	103 (6.0)	89.5 (5.4)	101 (6.1)	101 (10)	100 (10)	ω_{V3}	0.769 (15)	0.831 (26)	0.784 (11)	NS	NS
Q (L/h/70kg[d])											
θ_{Q}	25.4 (6.8)	15.9 (5.7)	24.6 (4.4)	24.7 (37)	23.3 (43)	ω_{Q}	0.424 (22)	0.459 (27)	0.434 (11)	NS	NS
F1						$logit(F1,i) = logit(F1) + ETATR,i$; $ETATR,i = (\exp(\eta_{F1} * \theta_{BC\text{-}F}) - 1) / \theta_{BC\text{-}F}$					
θ_{F1}	0.585 (13)	0.595 (13)	0.597 (13)	0.805 (93)	1.77 (69)	ω_{F1}	1.67 (19)	0.713 (24)	1.69 (11)	NS	NS
						$\theta_{BC\text{-}F}$	0.367 (42)	0.411 (34)	0.330 (23)		
k_a (h^{-1})											
θ_{ka}	1.19 (20)	1.2 (FIX)	1.38 (14)	5.12 (118)	0.08 (69)		0.898 (35)		0.894 (11)	NS	NS
Alag (h)											
θ_{Alag}	0.12 (0.4)	1 (0.52)	0.121(2.8)	0.12(8333)	-		NS	NS	NS	NS	-

Table 11. Comparison of Voriconazole Parameter Estimates from the Population PK Models for the Current Data with Previous Analyses

Rate (mg/h)											
θ_{rate}	-	12.8 (9.1)	-	25.7 (29)	28.4 (48)	ω_{R2}	-	0.910 (20)	-	NS	NS
Residual Error Parameter											
Original Ped Data		**Adult Data**		**Japanese Ped Data**			**Current Data**		**Run 6**	**Run 13**	
$W = SQRT(\theta^2)$	0.365(4.3)	σ_{IV}^2 (%)	53 (6.7)	$W = SQRT(\theta^2)$	0.239 (5.8)		σ_{IV}^2 (%)		82 (24)	72 (26)	
		σ_{oral}^2 (%)	61 (28)				σ_{oral}^2 (%)		69 (30)	64 (28)	

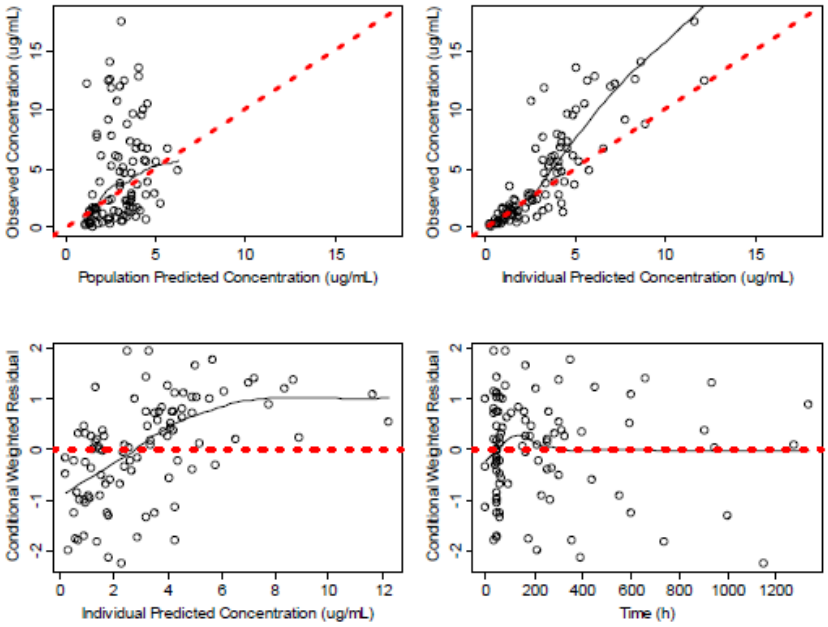
Abbreviations: N = number of patients, k_m = Michaelis-Menten constant, $V_{max,1}$ = maximum elimination rate at 1 hour after start of dosing, $V_{max,inh}$ = maximum fraction of V_{max} inhibition, T_{50} = time in hours at which half of the maximum inhibition occurs, CL = linear clearance, V_2 = central volume of distribution, V_3 = peripheral volume of distribution, Q = inter-compartmental clearance, k_a = first order absorption rate constant, F1 = oral bioavailability (calculation: $F1 = 1/(1+\exp(-\theta_{F1}))$), ALAG = absorption lag-time, W = SD of residual error (on log-scale), NS = not supported in the model, WT = weight (kg). The asterisk (*) indicates that Vmax,inh is 100% if the patient is a CYP2C19 HEM or PM in the analysis of data from studies A8851009 and A1501096.

a. %RSE: percent relative standard error of the estimate = SE/parameter estimate * 100. SE in the model using original data was computed based on a limited non-parametric bootstrap (n=10), and SE in subsequent analyses was obtained from $COVARIANCE reported by NONMEM.
b. Standard deviation of random effects (ω).
c. The inter-individual variability was estimated using exponential random effects unless otherwise specified (eg, $CL,i = CL*\exp(\eta_{CL})$).
d. Note that a power function of 0.75 was applied for clearance terms, ie, the relationship to weight is not linear.

Source of the previous parameter estimates: original pediatric data (PMAR-00204), adult data (PMAR-00284) and Japanese pediatric data (PMAR-00320)[7,8,9]
Source of the current parameter estimates: artifact IDs 8064378 and 8087931

It indicated that the current sparse data did not support the time-dependent nonlinear clearance in the model fitting. Given the limited concentration data, the interindividual random effect could be estimated for linear clearance only with acceptable shrinkage. It is acknowledged that this final PK model was still not ideal since voriconazole concentrations with high values were underestimated (see figures below).

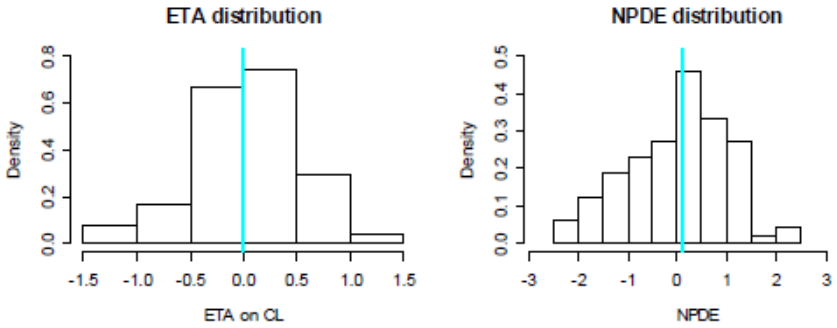
Figure 2. Basic Goodness of Fit Plots (Run 13 – Linear Elimination)



Key – open symbols are observed data, dashed line is the line of identity or unity, solid line is the loess smooth.

ePharm location: /A150 UK109496 Voriconazole/A1501080 & A1501085/Pop PK Model/PK Model Development/Run 13 analysis step ID 513911 (artifact ID = 8348532)

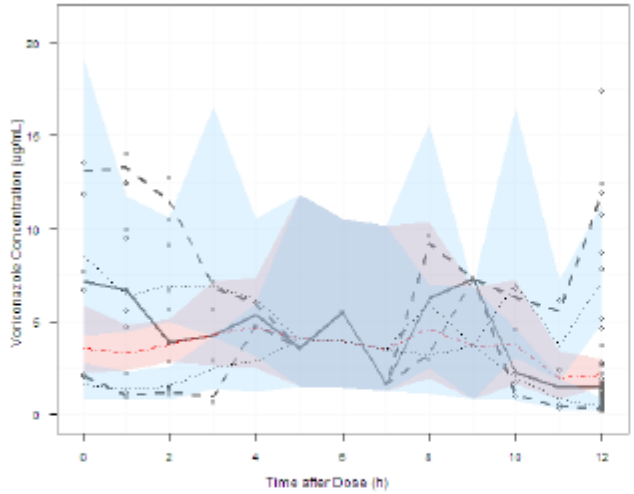
Figure 4. Frequency Histograms of ETA on Clearance and NPDE – Run 13



Key – solid vertical line is zero for ETA distribution or the median NPDE value for NPDE distribution.

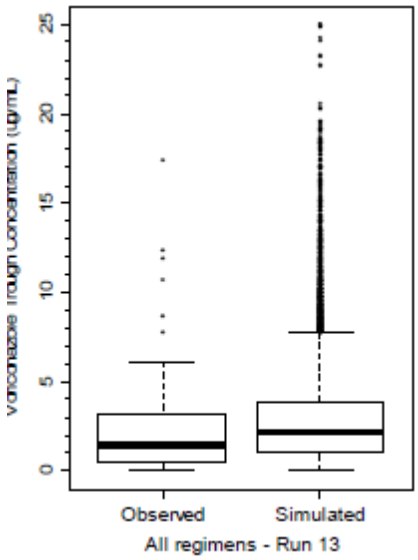
ePharm location: /A150 UK109496 Voriconazole/A1501080 & A1501085/Pop PK Model/PK Model Development/Run 13 analysis step ID 513911 (artifact ID = 8348532)

Figure 5. Visual Predictive Check: Observed and Simulated Median, 5th and 95th Percentile Voriconazole Concentrations, 90% Prediction Interval for Run 13.



Key – open symbols are observed data. Black solid and dashed lines represent the median, 5th and the 95th percentile of the observed concentrations, and red dash-dotted and black dotted lines represent the median, 5th and the 95th percentile of the simulated concentrations. The band around the simulated percentiles represents the 90% confidence intervals. 500 replicates were simulated.

Figure 6. Visual Predictive Check – Observed and Simulated Voriconazole Trough Concentrations – Run 13.



Key – The horizontal line at the center of the box is the median; the box represents the inter-quartile distance; whiskers represent ≤1.5 times the inter-quartile range and outliers are represented by points outside of the whiskers. 500 replicates were simulated. Note that the simulated outliers represent 500 replicates of the observed outliers, which is reflected as many points above the whisker bar in the simulation arm.

Trough samples here were defined as those between ≥11 hours and <12.5 hours post-dose.

Twenty-three (23) patients provided 30 trough samples at IV doses and observed median (range) C_{min} was 1.2 (0.11-17.4) µg/mL; 10 patients provided 10 trough samples at oral doses and observed median (range) C_{min} was 1.75 (0.25-11.9) µg/mL (source: artifact ID 8388154).

Nonetheless, this model appeared to be able to reasonably describe the voriconazole trough concentrations although the absorption phase was not estimated well. Overall, based on the totality of the model performance metrics, this simplified model was deemed acceptable to provide individual voriconazole exposure estimates (AUC0-12 and Cmin), which would allow subsequent exploratory exposure-response analysis.

Based on individual PK parameters from the final PK model, voriconazole exposure parameters in these pediatric patients (N = 48) at recommended IV and oral dosing regimens for IA, ICC and EC infections were estimated, and are summarized by age and weight group in Table 12, Table 13 and Table 14, respectively. At the matching doses, the voriconazole exposures in children and young adolescents with low body weight were comparable to those in all other adolescents (heavier or older) given the large inter-individual variability. For instance, the geometric mean AUC0-12 at 8 mg/kg IV q12h (or 4 mg/kg IV q12h in heavier or older adolescents) were 49.63, 54.91, and 37.28 µg·h/mL, respectively, and there was a substantial overlap of AUC0-12 distributions across these 3 age-weight groups.

Table 12. Summary of Estimated Voriconazole Exposure Parameters in Children (2 to <12 years) at Recommended Loading and Maintenance Doses based on the Final PK Model (Run 13)

Children (2 to <12 years old)				
Voriconazole Dosing Regimen	9 mg/kg IV LD	8 mg/kg IV q12h	9 mg/kg (max 350 mg) PO q12h	4 mg/kg IV q12h
	AUC_{0-12} (µg·h/mL)			
n	21	21	21	21
Geometric Mean (CV%)	28.35 (18)	49.63 (57)	46.86 (60)	24.99 (63)
Arithmetic Mean (SD)	28.84 (5.27)	55.78 (31.61)	52.96 (31.68)	28.46 (17.92)
Median (Range)	29.77 (18.38 - 40.27)	51.54 (20.67 - 171.08)	45.66 (19.84 - 170.76)	25.78 (10.33-96.79)
5^{th} – 95^{th} Percentile	20.66 - 33.80	24.85 - 80.2	23.86 - 77.04	12.43 - 40.33
No (%) of Patients				
AUC_{0-12} <30 µg•h/mL	11 (52)	4 (19)	4 (19)	15 (71)
AUC_{0-12} >100 µg•h/mL	0 (0)	1 (5)	1 (5)	0 (0)
	C_{min} (µg/mL)			
n	21	21	21	21
Geometric Mean (CV%)	1.43 (35)	2.65 (77)	3.56 (64)	1.28 (86)
Arithmetic Mean (SD)	1.53 (0.54)	3.29 (2.52)	4.1 (2.62)	1.64 (1.41)
Median (Range)	1.63 (0.58 - 2.82)	2.95 (0.69 - 12.67)	3.48 (1.39 - 13.86)	1.42 (0.32 - 7.1)
5^{th} – 95^{th} Percentile	0.77 - 2.13	0.97 - 5.22	1.71 - 6.08	0.45 - 2.57
No (%) of Patients				
C_{min} <1 µg/mL	4 (19)	2 (10)	0 (0)	7 (33)
C_{min} >6 µg/mL	0 (0)	1 (5)	2 (10)	1 (5)

IV= intravenous, LD = loading dose, q12h = every 12 hours, PO = oral, CV% = percent coefficient of variation, SD = standard deviation, AUC_{0-12} = area under the curve over a 12-hour dosing interval, C_{min} = tough concentration.
ePharm location:/A150 UK109496 Voriconazole/A1501080 & A1501085/Pop PK Model/Exposure estimation/Run 4 analysis step ID 529219 (artifact ID 8631437)

Table 13. Summary of Estimated Voriconazole Exposure Parameters in Young Adolescents (12 to 14 Years) Weighing Less than 50 kg at Recommended Loading and Maintenance Doses based on the Final PK Model (Run 13)

Young adolescents aged 12 to 14 years weighing <50 kg				
Voriconazole Dosing Regimen	9 mg/kg IV LD	8 mg/kg IV q12h	9 mg/kg (max 350 mg) PO q12h	4 mg/kg IV q12h
	AUC_{0-12} (µg·h/mL)			
n	10	10	10	10
Geometric Mean (CV%)	29.59 (19)	54.91 (40)	50.57 (43)	27.55 (40)
Arithmetic Mean (SD)	30.17 (5.76)	60.45 (24.29)	56.24 (24.35)	30.37 (12.28)
Median (Range)	32.85 (18.19 - 35.04)	68.24 (20.35 - 85.79)	62.02 (19.54 - 82.44)	34.22 (10.17 - 43.27)
5^{th} – 95^{th} Percentile	20.53 - 34.87	24.89 - 84.58	23.90 - 81.27	12.44 - 42.64
No (%) of Patients				
AUC_{0-12} <30 µg•h/mL	4 (40)	1 (10)	2 (20)	4 (40)
AUC_{0-12} >100 µg•h/mL	0 (0)	0 (0)	0 (0)	0 (0)
	C_{min} (µg/mL)			
n	10	10	10	10
Geometric Mean (CV%)	1.51 (35)	3.0 (52)	3.86 (46)	1.46 (53)
Arithmetic Mean (SD)	1.63 (0.57)	3.62 (1.87)	4.36 (1.99)	1.77 (0.93)
Median (Range)	1.88 (0.55 - 2.15)	4.19 (0.66 - 5.61)	4.84 (1.36 - 6.51)	2.04 (0.31 - 2.77)
5^{th} – 95^{th} Percentile	0.72 - 2.14	0.95 - 5.52	1.71 - 6.42	0.45 - 2.72
No (%) of Patients				
C_{min} <1 µg/mL	2 (20)	1 (10)	0 (0)	2 (20)
C_{min} >6 µg/mL	0 (0)	0 (0)	4 (40)	0 (0)

IV= intravenous, LD = loading dose, q12h = every 12 hours, PO = oral, CV% = percent coefficient of variation, SD = standard deviation, AUC_{0-12} = area under the curve over a 12-hour dosing interval, C_{min} = tough concentration.
Note: 8 out of 10 patients were from Study A1501080.
ePharm location:/A150 UK109496 Voriconazole/A1501080 & A1501085/Pop PK Model/Exposure estimation/Run 4 analysis step ID 529219 (artifact ID 8631435)

Table 14. Summary of Estimated Voriconazole Exposure Parameters in All Other Adolescents at Recommended Loading and Maintenance Doses based on the Final PK Model (Run 13)

All Other Adolescents (12 to 14 years old weighing ≥50 kg & 15 to 17 years old regardless of weight)					
Voriconazole Dosing Regimen	6 mg/kg IV LD	4 mg/kg IV q12h	200 mg PO q12h	3 mg/kg IV q12h	300 mg PO q12h
	AUC_{0-12} (µg·h/mL)				
n	17	17	17	17	17
Geometric Mean (CV%)	22.72 (16)	37.28 (59)	27.72 (65)	28.54 (65)	41.33 (63)
Arithmetic Mean (SD)	22.99 (3.59)	43.04 (25.56)	33.51 (21.65)	33.68 (22.05)	49.64 (31.24)
Median (Range)	22.79 (17.41 - 29.40)	33.78 (17.7 - 110.05)	25.07 (8.89 - 79.36)	25.36 (13.28 - 95.39)	37.6 (13.33 - 110.82)
5th – 95th Percentile	17.94 - 27.82	18.88 - 82.95	12.06 - 72.48	14.17 - 68.14	18.09 - 106.46
No (%) of Patients					
AUC_{0-12} <30 µg•h/mL	17 (100)	7 (41)	9 (53)	10 (59)	7 (41)
AUC_{0-12} >100 µg•h/mL	0 (0)	1 (6)	0 (0)	0 (0)	2 (12)
	C_{min} (µg/mL)				
n	17	17	17	17	17
Geometric Mean (CV%)	1.19 (32)	2.18 (75)	2.15 (67)	1.66 (82)	3.21 (66)
Arithmetic Mean (SD)	1.25 (0.4)	2.76 (2.07)	2.65 (1.79)	2.17 (1.78)	3.93 (2.58)
Median (Range)	1.18 (0.66 - 1.98)	1.97 (0.76 - 8.27)	1.94 (0.65 - 6.46)	1.47 (0.56 - 7.18)	2.91 (0.98 - 9.06)
5th – 95th Percentile	0.72 - 1.82	0.85 - 6.01	0.89 - 5.87	0.63 - 4.95	1.34 - 8.63
No (%) of Patients					
C_{min} <1 µg/mL	5 (29)	2 (12)	2 (12)	5 (50)	1 (6)
C_{min} >6 µg/mL	0 (0)	1 (6)	1 (6)	0 (0)	4 (24)

IV= intravenous, LD = loading dose, q12h = every 12 hours, PO = oral, CV% = percent coefficient of variation, SD = standard deviation, AUC_{0-12} = area under the curve over a 12-hour dosing interval, C_{min} = tough concentration.
Note: There were 6 patients who were 12 to 14 years old weighing ≥50 kg (4 of them from Study A1501080).
ePharm location:/A150 UK109496 Voriconazole/A1501080 & A1501085/Pop PK Model/Exposure estimation/Run 4 analysis step ID 529219 (artifact ID 8631436)

In adult patients with IA from Study A8851009, the estimated voriconazole geometric mean (CV%) AUC0-12 and Cmin at 4 mg/kg IV q12h were 51.0 (43%) µg·h/ml and 3.10 (52%) µg/ml, respectively; those at 300 mg oral q12h were 32.9 (45%) µg·h/ml and 2.04 (54%) µg/ml, respectively; and those at 200 mg oral q12h were 22.0 (46%) µg·h/ml and 1.37 (54%) µg/ml, respectively (see table 17). Similarly, there was a concomitant use of omeprazole or esomeprazole in approximately 30% of these adult IA patients. At matching IV doses, the average exposure values and exposure distributions in pediatric patients were comparable to those in adult IA patients. At matching oral doses, the average oral exposures in pediatric patients were higher than those in adult IA patients; however, there was a substantial overlap of exposure distributions between these two groups. Considering that treatment is being provided for potentially life-threatening infections, it is preferred to start with a relatively high dose and reduce to lower doses if needed to ensure sufficient exposure coverage. Therefore, the proposed dosing regimens as the initial recommendation for pediatric patients are deemed acceptable.

Table 17. Estimated voriconazole exposure parameters in Adult Patients with IA (Study A8851009)

Voriconazole Dose	3 mg/kg IV q12h	4 mg/kg IV q12h	200 mg PO q12h	300 mg PO q12h
	AUC_{0-12} (µg·h/mL)			
n	283	283	149	149
Geometric Mean (CV%)	38.5 (43)	51.0 (43)	22.0 (46)	32.9 (45)
Median (Range)	43.1 (2.9 - 102.8)	57.3 (3.90 - 135)	24.5 (2.1 - 60)	36.7 (3.21 - 87.8)
5th – 95th Percentile	13.7 - 77.1	18.3 - 101	7.06 - 45.0	10.6 - 67.3
	C_{min} (µg/mL)			
n	283	283	149	149
Geometric Mean (CV%)	2.33 (53)	3.10 (52)	1.37 (54)	2.04 (54)
Median (Range)	2.83 (0.02 - 7.61)	3.78 (0.02 - 10.0)	1.64 (0.02 - 4.58)	2.46 (0.03 - 6.71)
5th – 95th Percentile	0.55 - 5.69	0.75 - 7.44	0.29 - 3.29	0.44 - 4.85

IV= intravenous, LD = loading dose, q12h = every 12 hours, PO = oral, CV% = percent coefficient of variation, AUC_{0-12} = area under the curve over a 12-hour dosing interval, C_{min} = tough concentration.
Source data: PMAR-00284 (artifact IDs 7474036 and 8761524)[9]

Although CYP2C19 genotyping status was not identified as being predictive of voriconazole PK in this analysis, a slight trend was observed that the average voriconazole exposure tended to be higher in HEM group (CYP2C19 heterozygous extensive metabolizers) than that in EM group (CYP2C19 homozygous extensive metabolizers). Nonetheless, there was a substantial overlap of the exposure distributions across these groups due to large inter-individual variability.

Although race was not identified as being predictive of voriconazole PK in this analysis, a slight trend was observed that the average voriconazole exposure tended to be higher in Asian patients than in non-Asian patients. There was a substantial overlap of the exposure distributions between Asian and non-Asian groups due to large inter-individual variability.

Population PK-PD analysis:

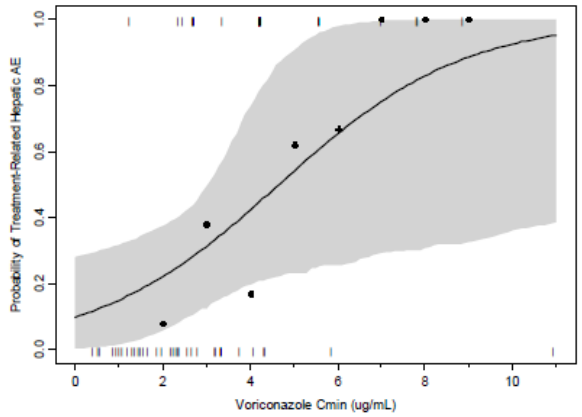
Efficacy

Since there were very few failure cases, only graphic examination was performed. For the failure, indeterminate or missing cases, the corresponding voriconazole exposures were above or close to the average values in patients who had success except for one EC patient. It indicated that failure was not due to low exposure to voriconazole. This EC patient with global response failure had the lowest average voriconazole AUC0-12 and his corresponding Cmin was also in the lower end (although not the lowest), who was neutropenic at baseline. In the 10 EC patients, there were 7 global success, one failure and 2 indeterminate at EOT. Given only one failure case, no definitive conclusions can be drawn for the correlation between voriconazole exposure and global response in EC patients. All the 6 ICC patients had global success at EOT. In the 14 IA patients, 11 patients were alive, 2 were expired and one was lost to follow up at EOT. The 3 IA patients who were expired or lost to follow up had relatively high concentrations. Additionally, in the 14 IA patients, there were 9 global success, one failure, one indeterminate and 3 missing at EOT. This failure case had relatively high concentration. In addition, due to limited MIC data and failure cases, the correlation between the PK-PD index and the efficacy data could not be assessed adequately. The success rate was high for all indications, suggesting the dosing regimens evaluated in studies A1501080 and A1501085 are appropriate for pediatric use although the sample size was limited.

Safety

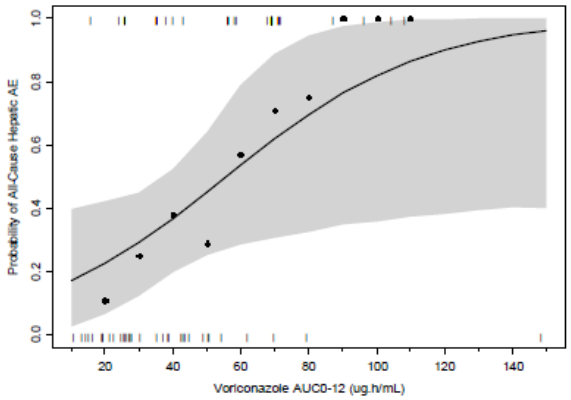
Among all the safety endpoints evaluated, a positive association with voriconazole exposure was established for hepatic AEs only. It should be noted that this positive association was shown only when the multiple-panel data were analyzed. When the single-panel data were analyzed, this positive association diminished. It is noted that multiple-panel data analysis approach may have a slight over-estimation on AE probability prediction since a patient with multiple AEs would be counted multiple times, which may introduce bias. Furthermore, for the all-cause hepatic AEs, the positive association was only related with voriconazole AUC0-12 (voriconazole Cmin marginally missed the inclusion criterion). Thus, the observed positive association between voriconazole exposure and the occurrence of a hepatic AE is weak which is further evidenced by the wide 95% CI around the population prediction of probability of hepatic AE occurrence (Figure 18 and Figure 19).

Figure 18. Observed and Model Predicted Probability of Treatment-Related Hepatic AE Occurrence vs. Voriconazole C_{min} (MP)



Key – '|'symbols are observed individual data (AE present = 1, AE absent = 0), solid circles are observed probability of AE at each concentration level (note: individual concentration values were rounded up to the next integral value for summary purpose). The line and the corresponding band represent the population predicted probability and its 95% confidence interval (computed with 1000 bootstrap).

Figure 19. Observed and Model Predicted Probability of All-Cause Hepatic AE Occurrence vs. Voriconazole AUC_{0-12} (MP)



Key – '|'symbols are observed individual data (AE present = 1, AE absent = 0), solid circles are observed probability of AE at each exposure level (note: individual exposure values were rounded up to the next increment value for summary purpose). The line and the corresponding band represent the population predicted probability and its 95% confidence interval (computed with 1000 bootstrap).

With the limited sample size, it is difficult to establish definitive exposure-response relationships for voriconazole in this analysis given the complex clinical situation for subjects with serious fungal infections. Thus, management of voriconazole treatment (eg, dose adjustment) remains at the discretion of the physician taking into consideration the individual patient's clinical response, tolerability profile and voriconazole concentration (if available).

CHMP's assessment of the Applicant's Response

As indicated, limited data are available from studies A1501080 and A1501085. This hampered the development of a robust model. Despite the limitations of the model, with some underestimation of high plasma concentrations, the data indicate that at matching doses, voriconazole exposures in children and young adolescents with low body weight were comparable to those in all other adolescents (heavier or older). With regard to adults, there is an indication of higher exposure in paediatrics, however, a large variability is observed, the data are limited and there is a large overlap in values.

As already concluded based upon the provided results of both studies, no new adverse events of concern were identified from both studies and the safety data from the paediatric patients in this study are consistent with the known safety profile of voriconazole.

With regard to efficacy, both studies A1501080 and A1501085 were open label with safety as primary endpoint. All efficacy parameters were considered secondary endpoints. In addition the total number of included patients is limited. Hence no firm conclusion on the efficacy of voriconazole can be drawn.

Taken together, the data is in line with the known safety profile in the paediatric population and no firm conclusion on efficacy can be drawn.

Conclusion

Point resolved.

Question 3

The MAH is requested to discuss the observed discrepancy regarding the numbers in paediatric patients treated in the therapeutic studies being n=52 as stated in the overview. Whereas the SmPC section 5.1 mentions n=61 paediatric patients of whom n=54 were aged 2 -15 years being treated in therapeutic studies.

CHMP's assessment of the Applicant's Response

The MAH clarifies that the 52 paediatric subjects quoted in the Clinical Overview from the recent Article 46 submission represent those subjects enrolled in the original therapeutic studies who were <18 years old. Section 5.1 of the current SmPC includes information that was approved at the time of the original MAA submission in 2000, and refers to a different subset of paediatric subjects. The MAH clarifies that the 54 subjects quoted in the current SmPC were from compassionate use studies as well as the therapeutic studies. This together with the different age range presented in the current SmPC, explains the apparent discrepancy in numbers.
A Type II variation will be submitted to update Sections 4.8 and 5.1 of the SmPC with regards to the safety and clinical information on paediatric patients based on the analysis of all paediatric data following completion of the 2 paediatric therapeutic studies (A1501080 and A1501085).

Assessment of the Applicant's Response

The MAH's substantiation is clear and seems to be enough for the assessment of the awaited update of section 5.1.

Conclusion

Point is solved.

7. OVERALL SUMMARY AND CONCLUSIONS ON THE APPLICANT'S RESPONSES

The applicant submitted two paediatric studies (A1501080 and A1501085). Thirty-one and twenty-two paediatric patients were included respectively. Both studies were open-label with safety as primary endpoint. Although the applicant presented some efficacy data no firm conclusions can be drawn due

to the nature of the studies and the limited number of included patients. Treatment dosage and duration were in line with the approved SmPC of Vfend.

With regard to the developed population pharmacokinetic model, only limited data were available from studies A1501080 and A1501085. This hampered the development of a robust model. Although the limitations of the model, with some underestimation of high plasma concentrations, the data indicate that at the matching doses, the voriconazole exposures in children and young adolescents with low body weight were comparable to those in all other adolescents (heavier or older) given the large inter-individual variability. With regard to adults, there is an indication of higher exposure in paediatrics, however, a large variability is observed, the data are limited and there is a large overlap in values.

No new adverse events of concern were identified from both studies and the safety data from the paediatric patients in this study were consistent with the known safety profile of voriconazole.

Three patients died during study A1501080, their deaths were unrelated to the voriconazole treatment. After the safety reporting period of study A1501080 one patient expired due to underlying disease.

Additionally the applicant evaluated the data from both studies (A1501080 and A1501085) taking the events of interest (phototoxicity, squamous cell carcinoma (SCC), hepatic toxicity, QTc prolongation, Visual Events, Peripheral neuropathy, skin cancers (non SCC) and suicide related disorders) as identified in the RMP (V2.0) into account. Data was also compared to the adult data. No AEs related to phototoxicity, SCC, skin cancer (non-SCC), or suicide related disorders were observed in either study. Similarly, no AEs related to these risks were observed when safety data from the paediatric population in all combined therapeutic studies was reviewed (N=105). The observed frequencies of QT prolongation and peripheral neuropathy in paediatric patients were similar to adults. The frequency of visual events observed in paediatric patients was slightly higher (non-significant) than the observed frequency in adults.

All hepatic-related adverse events in Study A1501080 occurred in patients in the 12 to <18 age group. Whereas in Study A1501085 all but 2 hepatic-related AE occurred in the 2 to <12 age group. Similar observation was made for clinically significant laboratory abnormalities. A clinically meaningful conclusion from this observation cannot be drawn due to limited sample size in each age group. When taking into account all safety data in paediatric patients in therapeutic studies (n=105) a similar observation of a higher frequency of patients with hepatic-related events, was observed in the paediatric population when compared to adults in the therapeutic studies. The numerical higher frequency in the combined paediatric population versus adults (28.6% and 24.0% respectively) was mainly associated to an increased incidence of liver function test abnormalities (AEs in the Investigation SOC) in paediatric patients compared to adults (21.90% and 16.09% respectively).

The applicant proposes to update Section 4.8 and section 5.1 of the SmPC to include this information in the paediatric population subsection. This is agreed upon by the CHMP and a type II variation is awaited.

The benefit/risk balance of Vfend remains positive in the approved indications.

The MAH should submit within 2 months an update of Sections 4.8 and 5.1 of the SmPC to include the information related to P46 89.1.

7.1. Unresolved Issues

None.