



Australian Government

Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Voriconazole

Proprietary Product Name: Vfend

Sponsor: Pfizer Australia Pty Ltd

May 2013

TGA Health Safety
Regulation

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Contents

I. Introduction to product submission	4
Submission details	4
Product background	4
Regulatory status	5
Product Information	5
II. Quality findings	5
III. Nonclinical findings	5
IV. Clinical findings	5
Introduction	5
Pharmacokinetics	6
Pharmacodynamics	6
Efficacy	6
Safety	11
List of questions and evaluation of responses	12
Clinical summary and conclusions	25
Recommendation regarding authorisation	25
V. Pharmacovigilance findings	26
Risk management plan	26
VI. Overall conclusion and risk/benefit assessment	27
Quality	27
Nonclinical	27
Clinical	27
Risk management plan	31
Risk-benefit analysis	31
Outcome	35
Attachment 1. Product Information	36
Attachment 2. Extract from the Clinical Evaluation Report	36

I. Introduction to product submission

Submission details

<i>Type of Submission:</i>	Extension of indications
<i>Decision:</i>	Approved
<i>Date of Decision:</i>	11 January 2012
<i>Active ingredient:</i>	Voriconazole
<i>Product Name:</i>	Vfend
<i>Sponsor's Name and Address:</i>	Pfizer Australia Pty Ltd 38-42 Wharf Road West Ryde NSW 2114
<i>Dose form:</i>	Tablets, powder for injection, powder for suspension
<i>Strengths:</i>	Tablets: 50 mg and 200 mg; powder for injection: 200 mg/vial; powder for suspension: 40 mg/mL
<i>Container:</i>	Tablets: blister pack; powder for injection: vial; powder for suspension: bottle.
<i>Pack sizes:</i>	2, 10, 14, 20, 28, 30, 50, 56, 100 (tablets); 1 (vial); 1 x 70 mL (when reconstituted; bottle)
<i>Approved Therapeutic use:</i>	Prophylaxis in patients who are at high risk of developing invasive fungal infections. The indication is based on studies including patients undergoing haematopoietic stem cell transplantation.
<i>Route of administration:</i>	Oral (tablets and powder for suspension), intravenous infusion (powder for injection)
<i>Dosage:</i>	Intravenous formulation: Loading dose: 6 mg/kg every 12 h for first 24 h; maintenance dose after first 24 h: 4 mg/kg every 12 h. Oral formulations: maintenance dose after the first 24 h: 200 mg every 12 h (for those \geq 40 kg) or 100 mg every 12 h (for those \leq 40 kg).
<i>ARTG Numbers:</i>	82507, 82505, 82503, 99016

Product background

Voriconazole (voriconazole) is a broad-spectrum, triazole antifungal agent approved in Australia since 2002 for the treatment of fungal infections, as follows:

VFEND is indicated for treatment of the following fungal infections:

- *Invasive aspergillosis.*

- *Serious Candida infections (including C. krusei), including oesophageal and systemic Candida infections (hepatosplenic candidiasis, disseminated candidiasis, candidaemia).*
- *Serious fungal infections caused by Scedosporium species and Fusarium species.*
- *Other serious fungal infections, in patients intolerant of, or refractory to, other therapy.*

This AusPAR describes the application by Pfizer Australia Pty Ltd (the sponsor) to extend the indications for Vfend to include prophylaxis. The proposed additional indication is:

prophylaxis against development of invasive fungal infections (IFI) in high risk patients such as haematopoietic stem cell transplant (HSCT) recipients.

Regulatory status

Vfend tablets and powder for intravenous (IV) infusion received initial registration in the Australian Register of Therapeutic Goods (ARTG) in September 2002; the oral suspension was registered in January 2004.

At the time of the current submission, voriconazole was registered in approximately 100 countries; however, applications to extend the indications for this medicine, as proposed in the current application, had not been lodged elsewhere in the world.

Product Information

The approved Product Information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

II. Quality findings

There was no requirement for a quality evaluation in a submission of this type.

III. Nonclinical findings

There was no requirement for a nonclinical evaluation in a submission of this type.

IV. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

Introduction

Background and rationale

This submission seeks to add the additional indication of: *Use for prophylaxis against the development of serious invasive fungal infections (IFI) in high-risk patients, such as hematopoietic stem cell transplant (HSCT) recipients.*

1. Vfend (voriconazole) is registered in Australia for the treatment of severe IFI.
2. IFI are major causes of morbidity and mortality in allogeneic HSCT recipients.
3. IFI caused by Candida species were more frequent during the pre-engraftment period, but are now reduced by the use of fluconazole as prophylaxis. However, there is a

need for a well-tolerated antifungal agent that can be used to prevent both *Aspergillus* and *Candida* infections during both phases after allogeneic HSCT.

4. The following antifungal drugs have been approved with prophylaxis indications, although approvals have not been granted in all countries worldwide: micafungin, fluconazole, itraconazole and posaconazole. Micafungin and fluconazole are primarily used for prevention of IFI from *Candida* species, and in Australia, posaconazole is indicated for the prophylaxis of IFI among patients 13 years of age and older who are at high risk of developing these infections, such as patients with prolonged neutropenia or HSCT recipients. Itraconazole is approved for prophylaxis throughout Europe and in Australia.
5. A pivotal multi-centre study has been conducted to demonstrate non-inferiority of voriconazole versus itraconazole in regards of primary prophylaxis of IFI among recipients of allogeneic HSCT.

Scope of the clinical dossier

The pivotal study is termed "A1501073". It was designed and conducted as a prospective, open-label, multi-centre study, comparing voriconazole to itraconazole for the primary prophylaxis of IFI in subjects with allogeneic HSCT. Supportive data is provided by Study A1501038, a prospective, open-label, non-comparative, multi-centre study for the secondary prophylaxis of IFI with voriconazole in patients with allogeneic stem cell transplants.

Paediatric data

No data were provided.

Good clinical practice

Studies A1501073 and A1501038 were conducted in compliance with the ethical principles originating in or derived from the Declaration of Helsinki, and in compliance with all relevant International Conference on Harmonization (ICH) Good Clinical Practice (GCP) Guidelines.

Pharmacokinetics

No data were provided

Pharmacodynamics

No data were provided

Efficacy

Evaluator's summary and conclusions on clinical efficacy

Study A1501073

This was a multicentre, randomised, open label, non-inferiority trial. The primary objective was to compare the success of antifungal prophylaxis with voriconazole versus itraconazole at 180 days post HSCT (Visit 9). A summary of the study population is shown in Table 1.

Table 1. Study A1501073 - Study population

	Number (%) of Subjects	
	Voriconazole	Itraconazole
Screened	534	
Randomized to study treatment	503	
Randomized	243	260
Treated	234	255
Completed ^a	176 (75.2)	175 (68.6)
Discontinued before Day 180 Visit ^b	58 (24.8)	80 (31.4)
Died ^c	35 (15.0)	38 (14.9)
Adverse event – related to treatment	8 (3.4)	7 (2.7)
Adverse event – unrelated to treatment	7 (3.0)	6 (2.4)
Failure of prophylaxis	1 (0.4)	1 (0.4)
Fungal breakthrough infection	0	1 (0.4)
Lost to follow-up	0	1 (0.4)
Other reasons ^d	5 (2.1)	14 (5.5)
Subject no longer willing to participate in study	2 (0.9)	12 (4.7)
Analyzed for efficacy ^e		
Intent-to-Treat	224 (95.7)	241 (94.5)
Modified Intent-to-Treat	224 (95.7)	241 (94.5)
Per Protocol	185 (79.1)	199 (78.0)
Analyzed for adverse events (Safety Population)	234 (100.0)	255 (100.0)
Analyzed for clinical laboratory results ^f	221 (94.4)	236 (92.5)

Source: Tables 13.1.1, 13.1.1x, 13.1.2, 13.1.2x, and 13.1.3; Appendix B1.2

^aIncludes subjects from Site 1028 (7 who completed in the voriconazole group and 9 who completed in the itraconazole group) who were evaluated for safety only.

^bIncludes subjects from Site 1028 (including 1 subject in the itraconazole group who discontinued from the study due to death) who were evaluated for safety only.

^cAdditional deaths were recorded among subjects who discontinued for reasons other than death and then died before Day 180.

^dOther reasons for discontinuation included: participation in another clinical trial, allogeneic transplant relapse, received more than 14 days of an empirical antifungal treatment, received a new transplant, suspected fungal infection, failure to complete visits, and investigator decision.

^eA total of 24 treated subjects from Site 1028 (10 from voriconazole and 14 from itraconazole) were evaluated for safety only. Percentages for the Intent-to-Treat, modified Intent-to-Treat, and Per Protocol populations in this table were derived from the Safety population.

^fIn order to be analyzed for laboratory results, subjects had to have a baseline value and at least 1 posttreatment value for a laboratory parameter.

The primary endpoint was the success of antifungal prophylaxis at Visit 9. To be a success at Visit 9, the subject had to meet all 3 of the following conditions:

- Be alive at Visit 9,
- Have no breakthrough proven or probable IFI by Visit 9, and
- Be considered a success at 100 days post-transplant (Visit 7), defined as follows:
 - Be alive at Visit 7
 - Have no breakthrough proven or probably IFI by Visit 7
 - Meet both of the following conditions:
 - Have no discontinuation of study drug for more than 14 days by Visit 7 for any reason (including empiric therapy, alternative prophylaxis and no prophylaxis)
 - For patients randomised to itraconazole, no more than 14 days of itraconazole capsules could have been taken by Visit 7.

Success in these terms was reported for 48.7% in the voriconazole group and 33.2% in the itraconazole group. The comparison between voriconazole versus itraconazole as primary prophylaxis for IFI in HSCT recipients showed non-inferiority and, subsequently, superiority for voriconazole in respect of the primary outcome measure. The difference held when stratifying for conditioning regimen as outlined in the study protocol. The computed odds ratio (OR) from a logistic regression model, which adjusts the provided prophylaxis for conditioning, relatedness of donor, and country, computed to 2, in favour of voriconazole (95% confidence interval (CI): 1.35, 2.95).

The difference in success of prophylaxis at Day 100 was 14.2%. The main driving factor for the observed success was the 14.6% difference between the two groups in insufficient prophylaxis (not taking prophylaxis for at least 86 days, itraconazole capsules for > 14 days, other antifungal treatment for > 14 days).

The number of observed IFI at Day 180 (3 subjects (1.3%) in the voriconazole group, 4 subjects (1.7%) in the itraconazole group) or deaths (40 subjects (17.9%) in the voriconazole group, 44 subjects (18.3%) in the itraconazole) did not differ statistically significantly between groups.

The duration until prophylaxis was discontinued varied significantly between the two groups, being 89 days in the voriconazole group versus 72 days in the itraconazole group. Most frequently adverse events (AEs) were reported as the reason for discontinuation in a greater proportion of patients discontinuing voriconazole.

Subjects in both groups (almost 40% in the voriconazole and 49% in the itraconazole group) were treated empirically with other antifungal treatments, ultimately without proven or probable IFI.

The mean duration of hospital stay did not differ significantly between groups. Mean scores for the effectiveness, convenience, and global satisfaction domains from the Treatment Satisfaction Questionnaire for Medication (TSQM) were higher at Visit 4 (Day 14) for voriconazole compared with itraconazole. There were no differences in respect of death at one year or 400 days post HSCT.

Discussion

For patients undergoing HSCT, fungal prophylaxis is an accepted component of treatment protocols and the decision to use an active comparator in the study is considered justified. Itraconazole is registered in Australia for prophylactic use in such patients. The TGA requested the sponsor justify the use of itraconazole as a comparator, as opposed to other agents. Based on the sponsor's response (see response to Question 9 under List of Questions, below), its use as a comparator for Study A150103 is accepted.

The two study groups appear to be well randomised with respect to their demographics and baseline characteristics. Statistical requirements for non-inferiority trials, as outlined in the European Medicines Agency (EMA) Committee for Medicinal Products for Human use (CHMP) Guideline: *Note For Guidance On Statistical Principles For Clinical Trials* (CPMP/ICH/363/96, March 1998) appear to be satisfied, except for the non-blinded design.

Breakthrough IFI happened very rarely (1.3% and 1.7%, respectively, for voriconazole and itraconazole) in either group. Other authors consistently reported higher numbers (Trifilio *et al.*¹ reports 18%; studies included in the meta-analysis by Vardakas *et al.*² report a range from 0.3% to 25%; Marr *et al.*³ report between 4 and 10% in allograft recipients).

The need for a composite outcome to reduce study numbers to manageable proportions is considered understandable. With respect to the components of the primary outcome:

- It is biologically plausible that the low infection rate for both groups may be due to prophylaxis. This component of the composite endpoint was potentially subject to confounding due to use of empirical therapy and use of High Efficiency Particulate Air (HEPA) filtered airflow equipped facilities.
- Survival may be influenced by prevention of IFI, and thus, it is considered an acceptable component of a composite primary endpoint. However, the underlying disease conditions included in Study A1501073 and the transplant treatment would be

¹ Trifilio S, Singhal S, Williams S *et al.* Breakthrough fungal infections after allogeneic stem cell transplantation in patients on prophylactic voriconazole. *Bone Marrow Transplant* 2007;40:451–456.

² Vardakas KZ, Michalopoulos A, Falagas ME. Fluconazole versus itraconazole for antifungal prophylaxis in neutropenic patients with haematological malignancies: a meta-analysis of randomised-controlled trials. *BJ Haematol* 2005;131:22-28.

³ Marr KA, Carter RA, Crippa F *et al.* Epidemiology and outcome of mould infections in hematopoietic stem cell transplant recipients. *Clinical Infectious Diseases* 2002;34:909–917.

anticipated to have made a considerable independent contribution to survival or otherwise.

- The third component of the outcome, having no discontinuation greater than 14 days, including, for the itraconazole group, no use of capsules for more than 14 days, is considered to have ultimately determined the finding of superiority of voriconazole compared to itraconazole. While probable or proven IFI and the need to use substitute treatment would not be subject to bias, other reasons for discontinuation are considered contentious in an unblinded study:
 - Discontinuation due to possible IFI may be influenced by differing interpretation of clinical signs and differing opinions as to the need for, or the duration of, interruption of prophylaxis and substitution of alternative treatment.
 - Lack of tolerability of the treatment or unwillingness to continue in the study are considered not to be related to biological plausibility of efficacy and could have reasonably been anticipated *a priori* to bias against itraconazole solution, which is known to be unpalatable. Indeed, the applicant's reason for not including a double-dummy group was the burden of subjecting the voriconazole group to 'a placebo containing cyclodextrin which has a recognised tolerability profile'.

Although superiority of voriconazole is claimed in the clinical study report (CSR), it is not claimed in the PI and, based on the above, this is considered appropriate.

Regarding the primary objective, it is recommended that the following definition is included in the PI:

The primary endpoint was the success of antifungal prophylaxis at 180 days post-transplant (Visit 9). To be a success at this time point, the participant had to meet all 3 of the following conditions:

- *Be alive at Visit 9,*
- *Have no breakthrough proven or probable IFI by Visit 9,*
- *Be considered a success at 100 days post-transplant (Visit 7), defined as follows:*
 - *Be alive at Visit 7*
 - *Have no breakthrough proven or probably IFI by Visit 7*
 - *Meet both of the following conditions:*
 - *Have no discontinuation of study drug for more than 14 days by Visit 7 for any reason (including empiric therapy, alternative prophylaxis and no prophylaxis)*
 - *For patients randomised to itraconazole, no more than 14 days of itraconazole capsules could have been taken by Visit 7.*

The information in the PI includes a p-value indicating a significant difference between the two study drugs in terms of the primary outcome. It is noted that the proposed p-value was not exact, that is, reported as < 0.01 . Inclusion of the exact figure is recommended.

The proposed PI also includes a result for 'The proportion of patients who were able to continue voriconazole prophylaxis for 100 days after HSCT... $p < 0.01$ '. This is not considered the appropriate outcome for inclusion. The relevant outcome, and that recommended for inclusion in the PI, is: 'The proportion of subjects with insufficient prophylaxis, that is, those who missed > 14 days of prophylaxis before Visit 7, took less than 86 days of prophylaxis before Visit 7, or, if randomised to itraconazole, took more than 14 days of itraconazole capsules before Visit 7. The result was 104 (46.4%) in the voriconazole group and 147 (61.0%) in the itraconazole group, resulting in a treatment difference of -14.6% (95% CI:

23.5, -5.6; $p = 0.0015$). This is the outcome which determined the significant difference in the primary outcome analysis and it is important that this is clear to the reader of the PI. Thus, although this is a secondary outcome analysis, it is recommended that the exact p -value result is included.

Study A1501038

Study A1501038 was a non-comparative, open-label, multi-centre study aiming to evaluate the administration of voriconazole for secondary prophylaxis of IFI (patients had either proven or probable IFI in their history). The majority of patients were male (62%), with a mean age of 48 years. The majority of subjects (84%) received STC from peripheral blood stem cells and unrelated donors (47%). Of the patients that had an unrelated donor, 58% experienced Graft versus Host Disease (GvHD). The most common diagnosis of previous IFI was probable aspergillosis (59%). A summary of the study population is shown in Table 2.

Table 2. Study A1501038 – Study population

Disposition	Voriconazole Number of Subjects
Screened	46 ^a
Assigned to treatment	45
Treated	45
Completed study (up to Visit/Month 12) ^{b, c}	29
Discontinued (before Visit/Month 12) from Safety Population	16
Subject died	11
Adverse event	2
Lost to follow-up ^d	1
Other	1
No longer willing to participate	1
Analysis Sets	
Safety	45
ITT ^e	43
MITT ^e	40
PP ^e	32

Source: Tables 13.1.1, 13.1.1x and 13.1.3 and Appendices B1.1, B1.2, and B13.10.2

^a Note that this is the number of subjects with data at screening in the study database. It is possible that other subjects were screened; sometimes screen failures do not get added into the database.

^b Includes 2 subjects from Site 1024 who were evaluated for safety but not for efficacy.

^c Subject [redacted information] completed the study and died after Month 12.

^d Subject [redacted information] was discontinued (lost to follow-up) and then died prior to Month 12.

^e See Appendix B4.1 for a list of the subjects excluded from this population. In addition, a total of 2 subjects from Site 1024 were omitted from the efficacy analyses.

Abbreviations: ITT = intent-to-treat; MITT = modified intent-to-treat; PP = per protocol.

Visit 12 is the 12-Month Follow-Up Visit.

The primary efficacy analysis was based on the Modified Intent-to-Treat (MITT) population. The primary endpoint was the proportion of subjects developing a proven or probable IFI between the start of prophylaxis and the 12 month follow-up visit.

A total of 3/28 (10.7% [95% CI: 2, 28]) patients developed proven or probably IFI over the 12 month study period, compared to 30% expected from previous therapies.

Discussion

The sample size was small and the 95% CI stretch from 2% to 28%; the upper boundary of close to 30% compares with that expected (30%) from previous therapies. However, there seems to be no generally recommended regimen for secondary prophylaxis of IFI in HSCT recipients.

In Study A1501038, the major problems related to unblinded study treatment and observational study design, small numbers of participants, and the use of non-study antifungal agents by some 40% of patients for between 9 and 85 days, which may have confounded the results.

It is recommended that this primary analysis result is included in the PI and that the CI is also included. It is further recommended that the proportion of patients receiving empirical antifungal treatment is included.

Safety

Studies providing evaluable safety data

Safety data was submitted in Study A1501073, Study A1501038 and the periodic safety update report (PSUR) covering the period 1 March 2010 to 28 February 2011.

Evaluator's overall summary and conclusion on clinical safety

Study A1501073

Nearly all subjects in Study A1501073 experienced AEs, more than 99% in both groups. More than half (53% in the voriconazole and 55% in the itraconazole group) of the AEs were treatment related. Severe AEs were reported in approximately half of the subjects (53% in the voriconazole group and 53% in the itraconazole group), but were infrequently attributed to treatment (14% and 12%, respectively). From the sponsor's point of view, AEs reported most frequently were associated with leukaemia and its treatment. Adverse events associated with hepatobiliary disorders occurred more frequently in the voriconazole group (20.1% versus 11% in the itraconazole group), as did eye disorders (12% versus 2.7%). There were more serious AEs (SAEs) in the voriconazole group (47% versus 37% for all-causality SAEs; 8% versus 5% for treatment related SAEs). Increases in liver function test parameters were greater in the voriconazole group.

A high proportion of subjects discontinued study treatment (at least temporarily) in both groups due to AEs. Discontinuations due to AEs all-causality was 39% in both groups; the proportion was higher in the voriconazole group for treatment related AEs leading to discontinuations (26%, versus 22% in the itraconazole group).

There was no statistically significant difference in respect of deaths; although it seemed to differ between groups by primary diagnosis (20% of deaths in the voriconazole group had an acute lymphocytic leukaemia, versus 6.4% in the itraconazole group, whilst the relationship was 40% versus 51.1% of deaths with acute myeloid leukaemia as underlying disease).

Study A1501038

A total of 26 subjects experienced 59 AEs considered to be treatment related; 9 subjects experienced 45 serious treatment related AEs. Thirteen subjects died, but no death was causally attributed to study treatment. Fourteen of 45 subjects (31%) discontinued treatment due to treatment related AEs. This result confirms the high proportion of subjects who discontinued treatment due to related AEs in study A1501073 (about one quarter of subjects).

Adverse events were similar to those observed in Study A1501073; the most common organ class for treatment related AEs being the hepatobiliary system. Three subjects experienced hallucinations and 3 experienced eye disorders.

Laboratory abnormalities were mainly in haematology and liver function test parameters. Apparently, approximately 20% of subjects with normal renal function experienced blood urea nitrogen (BUN) elevations.

PSUR

No new safety concerns have been identified in the PSUR covering the period from 1 March 2010 to 28 February 2011. Worldwide exposure in this period has been estimated at approximately 207 thousand patients in the USA and 380 thousand in other countries. Additionally, several studies were newly analysed in this time period, which confirmed the known safety profile of voriconazole. Four studies have been published in this timeframe: one of them did not find evidence of an effect of voriconazole on long-term visual function in patients with paracoccidioidomycosis.

One study reported that both cytochrome P450 (CYP) 2C19 genotypes and the CYP3A4 inhibitor erythromycin can influence the plasma concentration of voriconazole, and erythromycin increases plasma concentration of voriconazole in a CYP2C19 genotype-dependent manner. Pfizer stated that this was a single dose study, and that Pfizer's own study with multiple dosing did not find an influence on plasma concentrations to a clinically significant degree. In the absence of details of both studies, it is not possible for the evaluator to make a judgement.

The safety topic *hepatobiliary events* revealed no new safety concern; however, the University of Wisconsin Hepatic Education Programme, which has been introduced in 2009 to raise awareness among physicians for this safety concern, seems to have little impact on reporting and will be re-evaluated in the near future.

A search for *skin cancer* and *squamous cell cancer (SCC)* revealed just 16 cases in total. The fact that, for instance, all 8 cases from the USA were reported by the same physician might be indicative of underreporting.

The reported 32 cases with long term use, defined as more than 90 days, revealed no new safety concern.

List of questions and evaluation of responses

Efficacy

Study A1501073

1. What is the potential impact of empirical antifungal therapy administered concomitantly to the study medication? Apparently, the higher proportion receiving empirical therapy in the itraconazole arm is supposed to underline the higher need for other anti-fungal treatment in this group. However, the protocols for empirical therapy might vary between centres/countries, as might have the duration (number of days on empirical therapy) between the groups. Is it possible that empirical therapy prevented the development of IFI differently between the two groups, hence introduced confounding?

Pfizer response:

The investigators did not collect information regarding the protocols for empirical therapy. Some of the non-study drug antifungal agents were given as continued prophylaxis after randomised study drug was discontinued and others were more likely used for empirical therapy and/or treatment of suspected IFI. Review of the non-study systemic antifungals is summarised in Table 3. The most likely of these to be given as empirical therapy for treatment of suspected IRIs were caspofungin and amphotericin (liposomal or conventional).

Evaluator comment

While conceding the difficulty faced in management of highly immune compromised patients and the necessity to treat each case on its merits, in the absence of recorded information or protocol mandated management strategy, confounding could not be ruled out.

Table 3. Comparison of non-study systemic antifungals

Systemic antifungal agent	Voriconazole (n=224)	Itraconazole (n=241)
Caspofungin	24 (10.7%)	48 (19.9%)
Liposomal amphotericin	14 (6.3%)	17 (7.1%)
Conventional amphotericin B	4 (1.8%)	7 (2.9%)
Fluconazole	21 (9.4%)	37 (15.4%)
Itraconazole	5 (2.2%)	8 (3.3%)
Voriconazole	9 (4.0%)	34 (14.1%)
Posaconazole	5 (2.2%)	11 (4.6%)

2. Despite the fact that many other publications applied a similar concept in respect of allowing for empirical therapy, Cornely *et al.*⁴ defined failure as ‘*receipt of any other systemic antifungal agent for 4 days or more*’, an approach that appears to be more conservative. How would you assess the impact of empirical therapy in light of these factors?

Pfizer response

If patients who received any other systemic antifungal agent for 4 days or more were considered to be failures, the success rate at day 180 would be 37.5% (84/224) for voriconazole and 24.9% (60/241) for itraconazole, with difference 12.6% [95% CI: 4.2% to 21.0%] still considered significant. (Though not accounting for multiplicity).

3. Please clarify the definition of insufficient prophylaxis and discontinuation:
- The numbers for success of prophylaxis at day 100 are reported with 121 (54.0%) in the voriconazole and 96 (39.8%) in the itraconazole group; whereas the numbers for insufficient prophylaxis are 104 (46.4%) in the voriconazole group and 147 (61.0%) in the itraconazole group. Should the sum be 100%, respectively 224 and 241, for the two groups?
 - Table 5 (in the CSR) shows the disposition of subjects. The numbers of subjects who discontinued from the study before day 180 are divided into different (and relevant) categories.
 - What is the meaning of failure of prophylaxis in contrast to IFI?
 - The category “Other reasons” contains the proportion of subjects who took empirical therapy for more than 14 days. Please provide a similar table for insufficient prophylaxis at day 100 (the report states: *Insufficient prophylaxis “that is, who missed more than 14 days of prophylaxis before Visit 7, took less than 86 days of prophylaxis before Visit 7, or, if randomised to itraconazole, took more than 14 days of itraconazole capsules before Visit 7”*). Does this statement include insufficient prophylaxis due to, for example, AEs, death and empirical therapy? Please provide a stratification by reasons that led to discontinuation of prophylaxis until day 100.

⁴ Cornely OA, Maertens J, Winston DJ *et al.* Posaconazole vs. fluconazole or itraconazole prophylaxis in patients with neutropenia. *N Engl J Med* 2007;356:348-59.

- Another conclusion drawn from Table 5 is potential for the presence of bias. The proportion of subjects not willing to continue the study seems higher (significantly?) in the itraconazole group. Considering the non-blinded design, is this an indicator for bias?

Pfizer response

Two patients in each group were considered successes at day 100 but were categorised as receiving “insufficient prophylaxis” for receiving less than 86 days of study drug before Day 100. One patient was considered a failure at Day 100 because voriconazole was discontinued for hepatic toxicity. There were two cases that were permanently discontinued from the study because of “failure of prophylaxis” according to the investigator: One patient prematurely discontinued voriconazole after 26 days because of “intolerance of study medication”, and one patient discontinued itraconazole after 16 days because of a possible IFI that was not confirmed to be proven or probable.

Twelve patients in the itraconazole group and 2 patients in the voriconazole group withdrew for reported reason “subject no longer willing to participate in study”. One patient in the itraconazole group discontinued during the post-study treatment phase. The remaining patients discontinued the study at the time they discontinued study drug. In the voriconazole group, 1 patient discontinued study drug because of “ongoing nausea”, and the other withdrew consent. In the itraconazole group, 3 patients discontinued because of intolerance of study medication, 2 because of AEs, and the remaining 5 withdrew consent. The sponsor does not believe that these findings indicate potential bias.

The investigator-assessed reasons for discontinuation of study drug prophylaxis prior to day 100 are listed in Table 4:

Table 4. Investigator-assessed reasons for discontinuation of study drug prophylaxis prior to Day 100

Reason	Voriconazole n=224	Itraconazole n=241
Breakthrough fungal infection	1	4
Non-compliance	3	1
Intolerance of study medication	15	52
Adverse event	67	56
Death	4	2
Subject completed at least 100 days but < 180 days of prophylaxis	1	2
Other	11	26

Evaluator comment

Table 4 includes “Subject completed at least 100 days but < 180 days of prophylaxis”, which is out of place in a list of reasons for discontinuation before Day 100. The Table highlights the discrepancies between groups in reasons for discontinuation, with many more patients in the itraconazole group discontinuing for intolerance of study medication and “other” than in the voriconazole. The large numbers of discontinuations are considered to have the potential to bias results.

4. Is it possible, or how likely is it, that the non-blinded design is a potential source for bias, especially when the main finding is based on a difference in duration of taking the study medication (which could be influenced by the non-blinded design rather easily)?

Pfizer response

If blinding were to be undertaken, patients would have an added burden of treatment and would have included a placebo containing cyclodextrin, which has a recognised tolerability profile. A placebo containing cyclodextrin would have impaired the ability to compare long-term tolerability, which is an important consideration given the prolonged period of risk for IFI.

Evaluator comment

Regarding questions 3 and 4 and with respect to participants' willingness to continue, and also the duration of taking the medicine, in an unblinded study, the possibility of bias due to an unpalatable treatment in one arm could not be ruled out.

5. Characteristics of subjects in the two study groups don't differ significantly, however there are more men and the prevailing ethnicity is White. Are these results generalisable to other/general HSCT populations?

Pfizer response

The distribution of gender and race was similar to that of other studies.^{5,6} The belief is that there were adequate numbers of females and non-Whites to allow generalisation to other/general HSCT populations.

6. What is the explanation for the low IFI rates in this study? Does this low rate pose a limitation to the estimation of an IFI-preventing effect of voriconazole versus itraconazole?

Pfizer response

One reason for the low IFI rate could be that both study drugs are active against *Aspergillus*. The majority of the IFIs in the other studies were cases of invasive *aspergillosis* that developed in patients receiving fluconazole as prophylaxis.

Another reason for the low rate of IFIs is that the 2002 European Organization for Research and Treatment of Cancer-Mycoses Study Group (EORTC-MSG) definitions were used, which include proven or probable IFI. In fact, the use of these definitions for antifungal prophylaxis trials has recently been questioned (Wingard *et al.*, 2010). The reason is that in a patient with a suspected IFI, investigators are likely to discontinue study drug prophylaxis before a proven or probable diagnosis of IFI can be confirmed.

A second Data Review Committee (DRC) was organised to re-examine the reasons for study drug discontinuation in this study. This DRC reviewed patient data blinded to study drug and assigned a primary reason for study drug discontinuation to each case. In this review, the definitions for IFI were broadened to include proven, probable and possible IFI according to the 2008 EORTC-MSG definitions:

- Proven IFI – clinical signs and symptoms, radiological finding consistent with IFI, and mycological or histopathological confirmation of IFI from a biopsy
- Probable IFI – clinical signs and symptoms, radiological finding consistent with IFI, and one microbiological criterion (either mycology or serology)
- Possible IFI – clinical signs and symptoms, radiological finding consistent with *aspergillosis*, without a microbiological criterion (either mycology or serology)

⁵ Wingard JR, Carter SL, Walsh TJ *et al.* Randomized, double-blind trial of fluconazole versus voriconazole for prevention of invasive fungal infection after allogeneic hematopoietic cell transplantation. *Blood*. 2010;116:5222–5118.

⁶ Ulmann AJ, Lipton JH, Vesole DH *et al.* Posaconazole or fluconazole for prophylaxis in severe graft-versus-host-disease. *NEJM*. 2007;356:335-347.

- Suspected IFI – clinical signs and symptoms, with report of pulmonary disease consistent with IFI, but without report of a radiological finding and without a microbiological criterion
- Persistent fever with no evidence of IFI – persistent fever, typically in the context of prolonged neutropenia, without report of pulmonary disease

The data for all remaining patients who prematurely discontinued study drug were also reviewed by the DRC and assigned a primary reason for study drug discontinuation using the following categories: gastrointestinal intolerance, liver function test abnormality, visual toxicity, other drug toxicity, progression of underlying disease, other medical condition and other reason not specified above.

The DRC-assessed reasons for study drug discontinuation are listed in Table 5. The sponsor believes that these data provide a better estimation of the IFI-preventing effect of voriconazole compared to itraconazole. These data were recently presented at an international medical conference.⁷

Table 5. Number (%) of patients who discontinued study drug, by primary reason

Reason	Voriconazole n (%)	Itraconazole n (%)	p value
	n=104*	n=147*	
Probable IFI	1 (1.0)	4 (2.7)	NS
Possible IFI	1 (1.0)	14 (9.5)	<0.01
Probable or Possible IFI	2 (1.9)	18 (12.2)	<0.01
Suspected IFI	3 (2.9)	0 (0.0)	NS
Persistent fever w/o evidence IFI	5 (4.8)	11 (7.5)	NS
Any IFI-related reason	10 (9.6)	29 (19.7)	<0.05
Gastrointestinal intolerance	4 (3.8)	45 (30.6)	<0.001
LFT abnormality	45 (43.3)	15 (10.2)	<0.001
Visual toxicity	6 (5.8)	0 (0.0)	<0.01
Other drug toxicity	3 (2.9)	1 (0.7)	NS
Progression of underlying disease	5 (4.8)	2 (1.4)	NS
Other medical condition	20 (19.2)	26 (17.7)	NS
Other reason / unable to assess	11 (10.6)	29 (19.7)	NS

Abbreviations: IFI = invasive fungal infection; LFT = liver function test; NS = not significant.

* Number of patients who discontinued study.

Evaluator comment

With respect to “probable or possible IFI”, the p-value for the latter is heavily weighted by the results for “possible IFI” and in neither case is multiplicity considered. Thus these results are considered hypothesis generating.

7. Another factor recommended for the prevention of IFI is the attempt to reduce the exposure to molds. Tomblyn *et al.*⁸ suggest that recipients at risk should stay in HEPA filtered airflow equipped facilities. Has exposure in the participating centres been assessed?

Pfizer response

This information was not collected.

⁷ Bow EJ, Cornely OA, Slavin M *et al.* Recategorisation of reasons for premature discontinuation of antifungal prophylaxis in the IMPROVIT study – focus on IFI-related reasons. Poster presented at the 22nd European Congress of Clinical Microbiology and Infectious Diseases (ECCMID), London, UK, 31 March–3 April 2012

⁸ Tomblyn M, Chiller T, Einsele H *et al.* Guidelines for preventing infectious complications among hematopoietic cell transplant recipients: a global perspective. *Bone Marrow Transplant* 2009; 44:453–455.

8. An Appendix in the CSR introduces an interesting question: the size of the observed effect seems to be quite heterogeneously between different countries. For instance, the coefficient for Spain is -0.61 (approximate OR = 0.25) whereas the coefficient for the Czech Republic is 0.98 (OR = 9.5). Is it correct to present pooled data; and does 'country' act as an effect-modifier?

Pfizer response

The sponsor regenerated the logistic model by including an interaction term of "treatment by country". The interaction was not significant ($p = 0.61$). In the absence of effect modification, an estimate of treatment effect by pooling across countries is generally valid.

9. Why was itraconazole considered as the most suitable comparator instead of other medications, such as posaconazole?
- Cornely *et al.* 2007 compared posaconazole versus fluconazole or itraconazole (admittedly not in the same patient population) and found that '*posaconazole prevented invasive fungal infections more effectively than did either fluconazole or itraconazole and improved overall survival.*' These results have been supported by a recently published study (which came admittedly too late for the sponsor's trial) by Sánchez-Ortega *et al.*⁹ (although the sample size was small). The authors conclude: '*Our single-centre experience suggests that antifungal prophylaxis with posaconazole may lead to a better outcome than itraconazole for patients in the early high-risk neutropenic period after allogeneic bone marrow transplant.*'
 - If the age-limitation of posaconazole (to patients >13 years) was a concern, it is noted that the number of subjects below the age of 13 years who were included in Study A1501073 is almost negligible.

Pfizer response

At the time the study was designed, posaconazole was still investigational and fluconazole was the only oral agent approved for prophylaxis in all HSCT recipients. Itraconazole is a broad-spectrum antifungal with activity against a wide range of yeasts and filamentous fungi, including *Candida* and *Aspergillus* species and has proven efficacy in the treatment of invasive infections with these organisms.

There was strong data to support the efficacy of itraconazole compared to fluconazole as prophylaxis against this infection in allogeneic HSCT patients:

- In a meta-analysis of 13 randomised clinical trials, itraconazole prophylaxis significantly reduced incidence of IFI, and the oral solution was superior to the capsule in reducing IFI incidence and mortality.¹⁰
- Subsequent studies also showed a reduction in the incidence of *aspergillosis* with itraconazole prophylaxis in allogeneic HSCT recipients.^{11,12}
- In a prospective randomized clinical trial, itraconazole was demonstrated to be superior to fluconazole in preventing IFI in allogeneic HSCTs.¹³

⁹ Sánchez-Ortega I, Patiño B, Arnán M *et al.* Clinical efficacy and safety of primary antifungal prophylaxis with posaconazole vs itraconazole in allogeneic blood and marrow transplantation. *Bone Marrow Transplant* 2011;**46**:733-739.

¹⁰ Glasmacher A, Prentice A, Gorschlüter M *et al.* Itraconazole prevents invasive fungal infections in neutropenic patients treated for hematologic malignancies: Evidence from a meta-analysis of 3,597 patients. *J Clin Oncol.* 2003;**21**:4615-4626.

¹¹ Grigg AP, Brown M, Roberts AW *et al.* A pilot study of targeted itraconazole prophylaxis in patients with graft-versus-host disease at high risk of invasive mould infections following allogeneic stem cell transplantation. *Bone Marrow Transplant* 2004;**34**:447-453.

¹² Marr KA, Crippa F, Leisenring W *et al.* Itraconazole versus fluconazole for prevention of fungal infections in patients receiving allogeneic stem cell transplants. *Blood* 2004;**103**:1527-1533.

At the time the study was conducted, itraconazole was approved for prophylaxis in most European countries, and was one of the drugs of choice for this indication.

Itraconazole was available in three formulations: oral solution, capsules, and IV. The oral solution of itraconazole was chosen as the main comparator for this study because it is more reliably absorbed than the capsule formulation. Although the oral solution of itraconazole is associated with nausea, unpleasant taste and diarrhoea, the protocol included strategies to maximize the chance that patients could complete the planned duration of prophylaxis:

- Patients with mucositis could be switched to the IV formulation of itraconazole at any time during the study. Clinical supplies of the IV formulation of itraconazole were provided for sites in countries where it was not commercially available.
 - Patients who were unwilling to continue the oral solution were permitted to take itraconazole capsules for a maximum of 14 days without being considered to be failures.
10. The study population was limited to a few indications for HSCT (acute leukaemia or myelodysplastic syndrome, failure of therapy for lymphoma, or transformation of chronic myeloid leukaemia). Are the results transferrable to patients who receive HSCT due to other underlying diseases, such as aplastic anaemia and others?

Pfizer response

The sponsor believes that the results of the study apply only to the patient population studied.

11. Are these results transferrable to other populations at risk for IFI, which are neither explicitly included nor excluded by the proposed PI, such as solid organ recipients?

Pfizer response

The sponsor does not believe that the results of this study are applicable to recipients of other types of transplants.

12. Is there a significant difference between the two treatment groups in respect of:

- the proportion of subjects
- the combination of drugs taken by individuals
- the duration of intake

as immunosuppression definitely increases the risk for IFI?

Pfizer response

There was no significant difference in the proportion of patients who received at least one immunosuppressive agent while receiving study drug prophylaxis: 98.2% (220/224) for voriconazole, 97.9% (236/241) for itraconazole. The proportion who received combinations of these agents was not compared. The median duration of use was 87.08 days for voriconazole and 70.08 days for itraconazole. Concomitant medications were only captured during the time that patients were receiving study drug, and the duration of study drug was longer for voriconazole patients.

13. Would the administration of voriconazole for a longer period, or as primary prophylaxis in a later stage following HSCT, result in major differences to the described outcomes? The median time of diagnosis of breakthrough IFI in patients

¹³ Winston D, Mariarz R, Chandrasekar P *et al.* Intravenous and oral itraconazole versus intravenous and oral fluconazole for long-term antifungal prophylaxis in allogeneic hematopoietic stem-cell transplant recipients. *Ann Intern Med* 2003;138:705-713.

receiving voriconazole has been cited as 180 days after STC (Imhof *et al.*¹⁴); Fukuda *et al.*¹⁵ reported 107 days as the median duration for the occurrence of mold infections after STC. To reframe the question: what would be the maximum duration of recommended use of voriconazole for prophylaxis of IFI, or is this up to the physicians' discretion?

Pfizer response

The sponsor believes that the study results support the use of voriconazole as primary prophylaxis for at least the first 100 days after allogeneic HSCT and for up to an additional 80 days if immunosuppression persists.

14. For which age groups is an extension of indication sought? The youngest participant in Study A1501073 was 11 years of age (being almost 12 according to the report), with age ranging from 11 to 70 years and an average of 43 years.

Pfizer response

The sponsor is seeking an indication for primary prophylaxis in allogeneic HSCT recipients in adults and in adolescents who are at least 12 years old. The sponsor is not seeking an indication in the remaining paediatric population.

15. Clinical relevance of plasma levels is not known for many fungal species. However, the range of voriconazole plasma concentrations measured at Day 14 seems rather wide, ranging from < 10 ng/mL to 10,000 ng/mL. Is this of clinical relevance in respect of IFI prevention in HSCT patients? Would plasma level monitoring be necessary?

Pfizer response

The samples were collected at random times after drug administration. The sponsor identified 34 patients (15.2%) with trough levels measured; the median concentration was 0.85 µg/mL (range: 0-4.53 µg/mL), and concentrations were > 0.5 and > 1 µg/mL in 22 (64.7%) and 13 (38.2%) of these patients, respectively. The trough concentration range was not different from that observed in healthy subjects receiving the same dosing regimen. For example, in the pharmacokinetic study A1501092, 34 healthy subjects received the 200 mg oral twice daily regimen and the results showed that the median trough concentration in these subjects was 0.46 µg/mL with a range of 0.14–4.27 µg/mL.

Considering that there were relatively few cases of breakthrough IFI in the voriconazole group (3 subjects), the sponsor deemed that the exposure associated with the 200 mg oral twice daily dose would be adequate to prevent IFIs, with no requirement for routine plasma level monitoring.

16. Taking prophylaxis beyond Day 100 has apparently only positive effects on the defined efficacy outcomes. Subjects don't count as failure anymore after Day 100, but prophylaxis might (if study medication is not detrimental to life) have a beneficial impact on survival and IFI. On the other hand, longer administration of prophylaxis might point to the presence of certain indications (as outlined in the study protocol, and better AE profile). What is the proportion of subjects in each group taking prophylaxis for 100-180 days?

Pfizer response

The proportion of patients continuing study drug prophylaxis for more than 100 days was 96/224 (42.9%) for voriconazole and 68/241 (28.2%) for itraconazole. In the itraconazole group, 34/241 (14.1%) patients received voriconazole and 11/241 (4.6%) patients

¹⁴ Imhof A, Balajee SA, Fredricks DN *et al.* Breakthrough fungal infections in stem cell transplant recipients receiving voriconazole. *Clinical Infectious Diseases* 2004;39:743-746.

¹⁵ Fukuda T, Boeckh M, Carter RA *et al.* Risks and outcomes of invasive fungal infections in recipients of allogeneic hematopoietic stem cell transplants after nonmyeloablative conditioning. *Blood* 2003;102:827-833.

received posaconazole prior to Day 180, which may have prevented the development of IFIs on the itraconazole arm of the study.

17. Another risk factor that is repeatedly linked with risk for IFI after HSCT (for instance by Fukuda *et al.* 2003) is cytomegalovirus (CMV). Has this risk factor been assessed, or what is the rationale for not doing so?

Pfizer response

Cytomegalovirus infection was reported as an adverse event in 31/234 (13.2%) patients who received voriconazole and 26/255 (10.2%) patients who received itraconazole. Based on the adjudication of the second DRC, 2 patients with CMV infection developed probable/possible IFI in the study; both had received itraconazole prophylaxis.

18. Categories, as stated in the proposed PI, for the number of patients taking voriconazole for more than 12 weeks and 6 months differ from those reported in the clinical data, which prevents verification of these figures. It appears as 31 patients (28 without those from study site 1028) took prophylaxis for more than 181 days (6 months) in Study A1501073, which would result in a bigger sum than the one reported. Please provide clarification.

Pfizer response

In the A1501073 study (MITT without site 1028), 123 subjects received voriconazole for > 84 days and 28 subjects received voriconazole for >180 days. In the A1501038 study, 23 subjects received voriconazole for > 84 days, whereas none received it for > 180 days. The categories as stated in the proposed PI for the number of patients taking voriconazole for more than 12 weeks and 6 months has been amended accordingly.

19. How important is the lack of efficacy of voriconazole against mucormycosis given that breakthrough mucormycosis '*in patients with haematological diseases or HSCT recipients receiving voriconazole for prophylaxis against fungal infection, empirical therapy of febrile neutropenia, or both*' occurs in up to 9% of post HSCT IFI (according to Sun and Singh, 2011¹⁶).

Pfizer response

Physicians need to be aware that breakthrough mucormycosis can develop in allogeneic HSCT patients and that this infection should be one of the considerations in a patient who develops fever and sino-pulmonary infection while receiving voriconazole prophylaxis.

Study A1501038

1. Information about demographics and baseline characteristics of subjects is rather scarce (no information about, for example, conditioning regimen, ethnicity, and CMV). The population participating in the trial might be quite heterogeneous, and failure/success of prophylaxis might happen disproportionately often in particular groups of HSCT recipients. Please comment.

Pfizer response

Additional information regarding the baseline characteristics of patients was included in the publication (Cordonnier *et al.*, 2010¹⁷). The primary diagnosis was acute myelocytic leukaemia in 31 patients, acute lymphocytic leukaemia in 7, unspecified acute leukaemia in 1, and mycosis fungoides in 1. The conditioning regimen was myeloablative in 27 patients (60%), including 14 patients who received total body irradiation, and non-myeloablative in 18 (40%), including seven given total body irradiation. The most

¹⁶ Sun H-Y, Singh N. Mucormycosis: its contemporary face and management strategies. *Lancet* 2011;4:301-311.

¹⁷ Cordonnier C, Rovira M, Maertens J *et al.* Voriconazole for secondary prophylaxis of invasive fungal infections in allogeneic stem cell transplant recipients: results of the VOSIFI study. *Haematologica* 2010;95:1762-1768.

common source of stem cells for HSCT was the peripheral blood (n = 38; 84%), followed by bone marrow (n = 6; 13%) and cord blood (n = 1; 2%). Twenty-four patients (53%) were transplanted from a family donor, including HLA-identical siblings (18 patients), HLA mismatched relatives (5 patients) and an identical twin (1 patient); 21 patients (47%) were transplanted from an unrelated donor.

2. The case definition of probable cases in study A1501038 is a modification (by the MSG) of the EORTC criteria of probable fungal infection. It allows the inclusion of cases with a halo sign in imaging (computed tomography (CT) scan) without any microbiological evidence, which is, in contrast, an integral part of the diagnosis as suggested by the EORTC. A reference is made to the papers by Herbrecht *et al.*¹⁸ and Cornely *et al.*¹⁹, who applied the same case definition previously. The first writes, however, that *'The largest discrepancy between the diagnoses of investigators and the determinations of the data-review committee resulted not from misinterpretation of the diagnostic criteria but from the lack of confirmation by the radiologists on the data-review committee of the presence of a halo or air-crescent sign on a CT scan of the lungs in 60 cases.'* The second refers to an expert panel that suggested this approach (De Pauw and Patterson²⁰). This expert panel further highlights that *'However, it is important that patients with mycological evidence of fungal disease remain the backbone of the populations intended for epidemiological surveys and trials of therapy.'* Indeed, in 2008 the diagnostic criteria for invasive fungal disease were modified (De Pauw *et al.*²¹), yet the requirement of microbiological evidence for the category "probable" has not been dropped; quite in contrast *'Cases that meet the criteria for a host factor and a clinical criterion but for which mycological criteria are absent are considered possible IFD'*. In light of this development (which happened after conducting Study A1501038), how likely is the misclassification of possible cases as "probable IFI"?

Pfizer response

There were 31 patients with previous *aspergillosis*, of whom 6 were categorised as proven and 25 were categorised as probable, using the 2002 EORTC criteria. Had the unmodified EORTC-MSG definitions for probable invasive fungal infection been applied, five patients in the group with probable infections would have been classified as possible cases. There were no breakthrough aspergillosis infections reported in this study.

3. The change in the EORTC-MSG criteria in 2002 led to a study amendment (number 3). Where in the submitted dossier are the respective changes listed?

Pfizer response

Amendment No. 3 included a change in the definition of IFI based on the recently published EORTC-MSG criteria.²² The definition of IFI was modified to accept a halo sign on imaging, plus appropriate host and clinical criteria.

¹⁸ Herbrecht R, Denning DW, Patterson TF *et al.* Voriconazole versus amphotericin B for primary therapy of invasive aspergillosis. *N Engl J Med* 2002;347:408-415.

¹⁹ Cornely OA, Maertens J, Winston DJ *et al.* Posaconazole vs. fluconazole or itraconazole prophylaxis in patients with neutropenia. *N Engl J Med* 2007;356:348-59.

²⁰ Pauw B and Patterson T. Should the consensus guidelines' specific criteria for the diagnosis of invasive fungal infection be changed? *Clinical Infectious Diseases* 2005;41:S377-S380.

²¹ Pauw B, Walsh T, Donnelly JP *et al.* Revised definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group. *Clinical Infectious Diseases* 2008;46:1813-1821.

²² Ascioğlu S, Rex JH, de Pauw B *et al.* Defining opportunistic invasive fungal infections in immunocompromised patients with cancer and hematopoietic stem cell transplants: an international consensus. *Clinical Infect Dis* 2002;34:7-14.

4. Why does the proposed PI contain results from the MITT population, which features more favourable outcomes in respect of IFI (7.5%) than the complete case analysis (10.3%); especially considering that the complete case analysis is the more conservative approach? Also, data in respect of survival stems from an analysis based on the MITT population, which raises the same question.

Pfizer response

A “complete” case was defined as a patient in whom the outcome (breakthrough IFI) was observed and/or the subject was evaluable for the entire study period. There were 14 subjects in the MITT that were not evaluable for the entire study period: 11 subjects died, 1 subject was lost to follow-up, 1 subject withdrew and 1 withdrew due to an AE. In 2 of these cases, the outcome was observed (breakthrough IFI) so they were included in the complete case analysis. The remaining patients were not considered complete cases because they died and as a result were technically not evaluable for the entire study period. However, these patients did not develop a breakthrough IFI before they died, and should be included in the primary analysis.

Evaluator comment

It is accepted that, according to the Statistical Analysis Plan, the primary analysis was based on the MITT population with a supporting analysis based on the per protocol (PP) population, and that the result of the primary analysis is appropriate for inclusion in the PI.

5. Please provide further information in respect of concomitantly administered empirical antifungal therapy. According to the list of concomitant medications, for instance, 12 out of 45 subjects received amphotericine, 7 subjects received fluconazole, and so forth. How has a successful secondary prophylaxis been differentiated from the influence of concomitant empirical antifungal treatment? How long (how many days) did subjects receive empirical therapy, and what was the proportion overall?

Pfizer response

Allogeneic HSCT patients receiving prophylaxis can develop fever unresponsive to antibiotics that could potentially be caused by an IFI. The protocol specified that in patients with fever unresponsive to antibiotics, systemic empiric antifungal therapy must be initiated, pending the results of a diagnostic procedure. If an IFI was ultimately confirmed, the patient would be considered to be a failure in the study. Otherwise, the use of several days of empirical antifungal treatment without confirmation of an IFI was not considered to be a failure.

There were 3 patients who received non-study antifungal agents for an identified breakthrough IFI. The 6 remaining patients received an antifungal agent for another reason; in none of these was a breakthrough IFI confirmed. The details of these cases are as follows:

- One received ambisome for 23 days for pneumonia
- One received voriconazole for 32 days for pericarditis
- One received caspofungin for 9 days for presumed infection
- One received ambisome for 85 days for “antifungal” (likely)
- One received amphotericin B for 11 days for oral candidiasis
- One received voriconazole for 13 days for pneumonia

Evaluator comment

Use of non-study antifungal agents for between 9 and 85 days may have confounded results.

6. Is there an oral loading dose suggested? The proposed PI contains neither separate dosage advice for secondary prophylaxis, nor an oral loading dose regimen for primary prophylaxis.

Pfizer response

Although an oral loading dose was allowed in study A1501038, the sponsor does not plan to recommend an oral loading dose for this indication because most allogeneic HSCT patients may have impaired oral absorption at the initiation of prophylaxis. Therefore, the sponsor recommends that prophylaxis with voriconazole be initiated with the IV loading dose only.

Safety

1. It is noted that in Study A1501073, the proportion of the event 'death' differed between the two groups in respect of the primary diagnosis. Twenty percent of patients who died in the voriconazole group were diagnosed with acute lymphocytic leukaemia, whilst the respective figure was 6.4% in the itraconazole group. Forty percent of patients who died in the voriconazole group were diagnosed with acute myeloid leukaemia, versus 51.1% in the itraconazole group. Is this difference attributable to a differential impact of prophylaxis on death rates according to the underlying diagnosis, or is this observation just due to chance?

Pfizer response

The sponsor compared mortality rates in patients with acute leukaemia prior to allogeneic HSCT: in patients with acute myelogenous leukaemia, 26/102 (25.5%) died in the voriconazole group, compared to 43/119 (36.1%) in the itraconazole group. In patients with acute lymphocytic leukaemia prior to allogeneic HSCT, 9/43 (20.9%) died in the voriconazole group, compared to 13/44 (29.5%) in the itraconazole group. A review of the causes of death indicated that the majority were caused by progression of leukaemia.

2. Table 13.7.1.1 in the CSR suggests that the change of BUN from baseline values was greater in the voriconazole group; approximately 20% of subjects in Study A1501038 with normal baseline renal function experienced abnormal values later during the study. Is this observation due to an impairment of renal function by voriconazole?

Pfizer response

The IV formulation of voriconazole contains sulfobutylether-beta-cyclodextrin (SBECD), which has the potential to have an effect on renal function, particularly in patients with moderate or severe renal impairment (creatinine clearance < 50 mL/min), where accumulation of SBECD may occur. The oral formulation of voriconazole does not contain SBECD and does not have this risk. Considering that the majority of voriconazole given in these studies was the oral formulation, it is unlikely that these changes in renal function were caused by voriconazole.

3. The protocol of Study A1501073 defines the recording period for non-serious AEs as "from the time the subject has taken at least one dose of trial treatment through to 14 days after the last dose of study drug" and for SAEs "from the time the subject has taken at least one dose of trial treatment through to 28 days after the last dose of study drug". However, many tables show figures for a shorter period, namely for the period of 7 days after the last dose taken. Please provide AEs in adherence to the above classification.

Pfizer response

The CSR tables for treatment-emergent AEs that previously included data up to 7 days after last dose of study drug have been regenerated, with data up to 14 days after last dose of study drug.

4. The submitted PSUR for the period March 2010 to February 2011 did not reveal any new safety risk in respect of skin cancer, including SCC. However, this risk is of particular interest in Australia given it is the country with the highest incidence of non melanoma skin cancer (NMSC) worldwide. It seems quite likely that underreporting is present. The study by Vadnerkar *et al.*,²³ which is part of the risk management plan, “*suggested that prolonged use of voriconazole is a risk factor for SCC after lung transplantation, particularly among older patients residing in areas with high sun exposure*”. What is the risk-benefit estimation from this point of view? With which certainty can an elevated risk for NMSC linked with voriconazole be excluded for Australia, particularly among patients of Caucasian origin; or, what rate of new NMSC would result from use of voriconazole for the proposed indications in Australia?

Pfizer response

It is recognised that there have been reports of NMSC in patients who have received voriconazole prophylaxis for relatively long periods of time. However, these reports of NMSC have been predominantly in lung transplant patients, who are recognized to be at risk for NMSC. In contrast, SCC is rare in allogeneic HSCT patients. There were no reports of NMSC in either of the two voriconazole prophylaxis studies in this submission.

Physicians who prescribe voriconazole prophylaxis should be aware that development of SCC of the skin and melanoma have been reported in transplant patients during long-term therapy. Patients should avoid intense or prolonged exposure to direct sunlight during voriconazole treatment, and if a patient develops a skin lesion consistent with SCC or melanoma, voriconazole should be discontinued.

5. The published article *Effects of erythromycin on voriconazole pharmacokinetics and association with CYP2C19 polymorphism*²⁴ comes to the conclusion that CYP2C19 genotypes and CYP3A4 inhibitor erythromycin can influence the plasma concentration of voriconazole, and erythromycin increases plasma concentration of voriconazole in a CYP2C19 genotype-dependent manner. However, the proposed PI states that macrolide antibiotics had no significant effect on voriconazole maximum plasma concentration (C_{max}) and area under the concentration-time curve (AUC). Please clarify this issue.

Pfizer response

The drug interaction study referenced in this article (Shi *et al.*, 2010) tested only a single dose regimen of voriconazole, which does not mirror clinical practice. In contrast, all of the sponsor’s drug interaction studies were designed as multiple-dose studies. Specifically, the drug interaction study with erythromycin evaluated the effect of 7 day regimen (1 g every 12 h) of erythromycin on the pharmacokinetics of voriconazole (200 mg oral every 12 h for 10 days²⁵). This study demonstrated no clinically significant effect of erythromycin on the pharmacokinetics of voriconazole.

Other questions

The evaluator also requested revisions to the PI and Consumer Medicine Information (CMI); details of these are beyond the scope of this AusPAR.

²³ Vadnerkar A, Nguyen MH, Mitsani D *et al.* Voriconazole exposure and geographic location are independent risk factors for squamous cell carcinoma of the skin among lung transplant recipients. *J Heart Lung Transplant* 2010;29:1240-1244.

²⁴ Shi HY, Yan J, Zhu W *et al.* Effects of erythromycin on voriconazole pharmacokinetics and association with CYP2C19 polymorphism. *Eur J Clin Pharmacol* 2010; 66: 1131-1136.

²⁵ Purkins L *et al.* No clinically significant effect of erythromycin or azithromycin on the pharmacokinetics of voriconazole in healthy male volunteers. *Br J Clin Pharmacol* 2003;56(Suppl 1):30-36.

Clinical summary and conclusions

Benefit-risk assessment

Assessment of benefits

Invasive fungal infection as a complication in recipients of HSCT is associated with significant morbidity and mortality. *Aspergillus* and *Candida* are the organisms most commonly associated with such infections in this setting, and both are generally sensitive to voriconazole. The incidence of probable or proven IFI in the two studies, including patients with and without prior fungal infection, demonstrated low level of probable or proven IFI.

Voriconazole in film coated tablet form is likely to be accepted by patients as palatable. Voriconazole in IV form allows flexibility in mode of delivery, an important consideration when oral intake is not possible.

Assessment of risks

Study A1501073 of patients without prior fungal infection did not include sufficient numbers of patients to prove non-inferiority solely in terms of incidence of IFI. Study A1501038, examining treatment of patients with prior fungal infection, included small numbers of participants and there was no control group. There were possible confounding factors in both studies, relating to the decision about use of empirical treatment, and there was potential for bias in these unblinded studies.

Prolonged exposure to an antifungal treatment has the potential to result in development of resistance and to result in a shift in the epidemiology of fungal infection. However, this risk is not limited to use of voriconazole.

Cross resistance to azoles may occur among *Candida* species, potentially limiting use of other azole antifungal treatments.

Voriconazole has a significant AEs profile, including hepatobiliary disorders, renal disorders, visual disturbances and haematological disorders.

CYP3A4, CYP2C19 and CYP2C9 inhibition or induction results in a considerable potential for drug interactions, which may be problematic in a population of patients often requiring multiple medications over the long course of treatment required for prophylaxis.

Assessment of benefit-risk balance

The balance of risks and benefits is considered to lie on the side of benefit.

Recommendation regarding authorisation

Extension of the indication to include prophylaxis of fungal infection is recommended; however, it is recommended that the wording is changed to include the basis for the indication, that is, that *'the indication is based on studies including patients undergoing HSCT'*. The reason for this addition is included in the sponsor's response to Question 10 (see *List of Questions*, above) regarding transferability of results to other patient populations, in which case the sponsor states: *'the results of the study apply only to the patient population studied.'*

The evaluator also recommended that issues raised with respect to the proposed PI and CMI be addressed; details of these recommendations are beyond the scope of this AusPAR.

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a Risk Management Plan (RMP), version 1.1 (Date 7 August 2011), which was reviewed by the TGA's Office of Product Review (OPR).

Safety specification

The summary of the Ongoing Safety Concerns, as specified by the sponsor, is as follows:

Table 6. Summary of the Ongoing Safety Concerns

Important identified risks	<ul style="list-style-type: none"> • Hepatic toxicity • QTc prolongation • Visual events (including optic neuritis, papilloedema and other visual concerns) • Phototoxicity • Peripheral Neuropathy
Important potential risks	<ul style="list-style-type: none"> • Skin Cancer • Suicide-related events
Important missing information	<ul style="list-style-type: none"> • Effects in pregnancy • Effects in pediatrics

Potential for resistance is mentioned in the RMP.

Routine pharmacovigilance, as well as plans to monitor potential for resistance, would appear to be sufficient to manage these safety concerns.

Pharmacovigilance plan

Routine pharmacovigilance activities are proposed for all ongoing safety concerns. Routine pharmacovigilance activities are proposed to monitor all important identified risks, important potential risks and important missing information. Designated Medical Event (DME) and Targeted Medical Event (TME) review, and use of data capture tools are components of the routine pharmacovigilance activities described by the sponsor.

There are two ongoing studies to address the important missing information '*effects in paediatrics*'. No other additional pharmacovigilance activity is proposed.

Use of routine pharmacovigilance for all ongoing safety concerns is considered acceptable, as voriconazole has been on the market for some time and the evaluator is not aware of any new safety signals.

The routine pharmacovigilance activities described are considered generally consistent with Section 3.1.2 *Routine pharmacovigilance practices*, in the *Note for Guidance on Planning Pharmacovigilance Activities* (CPMP/ICH/5716/03, June 2005), and this is acceptable.

Risk minimisation activities

The sponsor has concluded that routine risk minimisation activities (that is, product labelling) is sufficient for all ongoing safety concerns. No additional risk minimisation activities are proposed. Use of routine risk minimisation is considered acceptable to manage the risks associated with voriconazole. Use of product labelling as routine risk minimisation is considered sufficient to mitigate the ongoing safety concerns.

Summary of recommendations

The OPR provides these recommendations in the context that the submitted RMP is supportive to the application; the implementation of a RMP satisfactory to the TGA is imposed as a condition of registration; and the submitted EU-RMP is applicable without modification in Australia unless so qualified:

- Potential for resistance is mentioned in the RMP, along with plans to monitor this. The evaluator has no objection with how the sponsor plans to monitor resistance; however it is recommended that the sponsor add “*development of resistant strains*” as an important potential risk.
- The RMP should be updated to reflect the fact that routine pharmacovigilance is proposed for the important missing information.
- The ‘dermatological adverse event’ precaution is considered to be under-representative of the risk of skin cancer, particularly in Australia where patients are already at an increased risk. This is especially important given the proposed indication is likely to substantially expand the patient group. Consideration should also be made to distributing a ‘Dear Healthcare Professional Letter’ advising Australian prescribers of the important potential risk of skin cancer.

The evaluator also recommended revisions to the proposed PI and CMI with regards to statements on peripheral neuropathy and skin cancer. Details of these recommendations are beyond the scope of this AusPAR.

VI. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate’s overview and recommendations:

Quality

There were no quality data.

Nonclinical

There were no nonclinical data.

Clinical

Supporting data

The clinical data consist of one non-inferiority comparison with itraconazole (Study A1501073) to assess primary prophylaxis against IFI, and one uncontrolled study (Study A1501038) documenting secondary prophylaxis.

Clinical efficacy

Study A1501073

This was a randomised, open-label, multinational study in patients (≥ 12 years age) with allogeneic HSCT to compare antifungal prophylaxis with voriconazole compared to itraconazole at Day 180 post-HSCT transplant in a non-inferiority comparison (predefined treatment difference no worse than 10%).

The patients started on IV therapy (voriconazole or itraconazole) for 2 days (Days 0 and 1) before switching to oral therapy on Day 2.

The voriconazole dosing regimen was as follows (patients could be switched to IV therapy in case of mucositis or gut GvHD):

Table 7. Study A1501073 dosing regimen

	Intravenous	Oral	
		<u>Tablet or Powder for Oral Suspension for Subjects 40 kg and above</u>	<u>Tablet or Powder for Oral Suspension for Subjects less than 40 kg</u>
Loading Dose Regimen (first 24 hours)	6 mg/Kg every 12 hours	N/A	N/A
Maintenance Dose (after first 24 hours)	4 mg/Kg twice daily	200 mg twice daily	100 mg twice daily

The itraconazole dosing regimen was 200 mg twice daily IV on Days 0 and 1, followed by 200 mg twice daily as an oral solution (oral capsules < 5 days were allowed up to a maximum of 14 days). The IV formulation could be given (200 mg once daily) if patients had mucositis or gut GvHD.

The primary efficacy endpoint was a composite. An assessment of success for the primary endpoint was made if a patient met the following conditions:

1. Survived to Day 180 post-transplant (Visit 9) with no breakthrough IFI (proven or probable), and
2. No discontinuation of study drug for more than 14 days for any reason during the scheduled 100 days of prophylactic treatment (Visit 7).

There were a number of secondary efficacy outcomes.

A total of 503 patients were randomised (243 and 260 in voriconazole and itraconazole groups, respectively). Randomisation was blocked by center and stratified by the following factors:

- Conditioning regimen: myeloablative or non-myeloablative
- Relatedness of donor: matched-related or mismatched/unrelated

The mean age of patients was 43.3 ± 14.4 years (range 11-70 years) and 42.7 ± 14.6 years (range 13-70 years) in voriconazole and itraconazole groups, respectively.

The study drugs were started on the day of the HSCT, at least 48 h after completion of conditioning therapy. Both study drugs were administered for at least 100 days or until breakthrough IFI, death or premature discontinuation. For patients with certain risks, the study drugs could be given up to 180 days. All patients were followed to 180 days post transplant.

Results

The median duration of treatment was 97 days (range 1-258 days) in the voriconazole group, compared to 68 days (range 3-223 days) in the itraconazole group. The primary analysis was based on a MITT population, that is, patients who received at least one dose of study drug. A total of 24 patients from a single site (10 and 14 from voriconazole and itraconazole groups, respectively) were excluded due to violations of GCP.

The results for the primary outcome indicated superiority of voriconazole prophylaxis (48.7%) over itraconazole prophylaxis (33.2%), as shown in Table 8 below:

Table 8. Summary of success of prophylaxis at Visit 9 (Day 180) – unadjusted responder rates – MITT population

	Voriconazole N=224	Itraconazole N=241	Difference in Proportions ^a Voriconazole - Itraconazole
Visit 9 (Day 180)			
Number (%) of Responders	109 (48.7%)	80 (33.2%)	15.5%
95% CI ^b			(6.6%, 24.3%)

N is the number of subjects in the Modified ITT(MITT) population for the given treatment. All percentages are calculated using N in the denominator

a Proportions are expressed as percentages

b Approximate 2 sided 95% CI for the difference in proportions

The conclusion from the primary analysis was corroborated with analysis adjusted for the randomisation strata, analysis using the PP population and in logistic regression analysis.

The results for some of the secondary efficacy outcomes were as follows:

Table 9. Summary of secondary outcomes – Study A1501073

Study A1501073	voriconazole (N = 224)	itraconazole (N = 241)	Treatment difference (95% CI)
Success rate (primary variable)	109 (48.7%)	80 (33.2%)	15.5% (6.6%, 24.3%)
Deaths (Day 180)	40 (17.9%)	44 (18.3%)	-0.4% (-7.4%, 6.6%)
Breakthrough IFI (Day 180)	3 (1.3%)	4 (1.7%)	-0.3% (-2.5%, 1.9%)
Insufficient prophylaxis (Day 100)	104 (46.4%)	147 (61.0%)	-14.6% (-23.5%, -5.6%)
Success rate (Day 100)	121 (54.0%)	96 (39.8%)	14.2% (5.2%, 23.2%)
Deaths (Day365)	58 (25.9%)	75 (31.1%)	-5.2% (-13.4%, 3.0%)
Deaths (Day 400)	59 (26.3%)	76 (31.5%)	-5.2% (-13.5%, 3.1%)

A total of 102 patients (43.6%) in the voriconazole group, compared to 106 patients (41.6%) in the itraconazole group, experienced GvHD.

Study A1501038

This was an uncontrolled study of treatment of 45 patients (mean age 48.4 ± 14.1 years; range 22-72 years) with voriconazole for secondary prevention of IFI in allogeneic HSCT patients with underlying haematological disease who had previous proven or probable IFI. The patients treated in this study had a 10.7% IFI rate, evaluated using a complete case analysis, or a crude incidence rate of 7.5% using a MITT population. All 3 incident cases of IFI occurred during the first 6 months of treatment. Secondary efficacy results, based on other populations and at other time points, and all using a complete case analysis, provided an overall IFI incidence rate ranging from 9.4% to 13.0%.

Graft versus Host Disease was reported in 13 patients.

Safety

The clinical safety data in support of this application consists primarily of the above two clinical trials. In addition, post marketing safety data, including from sponsored clinical trials, has been provided.

Study 1501073

The number of AEs per 30 days of treatment was 10.8 (95% CI: 8.7, 12.8) in the voriconazole group, compared to 12.1 (95% CI: 10.1, 14.1) in the itraconazole group.

The number of treatment related AEs per 30 days of treatment was 1.6 (95% CI: 1.1, 2.2) in the voriconazole group, compared to 1.9 (95%CI: 1.3, 2.5) in the itraconazole group.

Table 10. Summary of safety data - Study A1501073

	voriconazole	itraconazole
N (safety)	234	255
AEs	232 (99.1%)	254 (99.6%)
Discontinuations due to AE	92 (39.3%)	101 (39.6%)
Treatment related AEs	123 (52.6%)	139 (54.5%)
SAEs	111 (47.4%)	95 (37.3%)
Deaths	40 (17.1%)	47 (18.4%)

Treatment related AEs by organ system reported at relatively different rates in the two groups (voriconazole versus itraconazole) were: eye disorders (12% versus 2.7%), gastrointestinal disorders (12.4% versus 32.2%), hepatobiliary disorders (20.1% versus 11%), and psychiatric disorders (7.3% versus 1.6%).

The most frequently reported treatment related AEs with higher occurrence in the voriconazole group compared to the itraconazole group were: visual impairment (14 patients (6%) versus zero), cytolytic hepatitis (11 patients (4.7%) versus 5 patients (2%)), hepatotoxicity (17 patients (7.3%) versus 6 patients (2.4%)), and abnormal liver function test (12 patients (5.1%) versus 6 patients (2.4%)). All cases of visual impairment occurred in the voriconazole group, but were reported to have resolved without sequelae.

Treatment related SAEs were reported in 8.1% and 5.1% patients in the voriconazole and itraconazole groups, respectively. Fourteen patients had hepatobiliary SAEs: (6.0%) in the voriconazole group, compared to 4 patients (1.6%) in the itraconazole group. Treatment related hepatobiliary SAEs were reported in 9 patients in the voriconazole group (3.8%), compared with 2 patients (0.8%) in the itraconazole group.

Study A1501038

A total of 45 patients were exposed to voriconazole in this study. AEs were reported in all. A total of 26/45 (58%) experienced treatment related AE, whereas SAEs were reported in 23/45 (51%) patients.

The most frequent treatment related AEs were: hepatotoxicity (4), hallucination (3), headache (3), and eye disorders (2).

Two patients discontinued the study due to AEs (hepatotoxicity and abnormal liver function test), both of which were serious and considered to be treatment related.

A total of 12 patients died prior to the 12 month follow up visit, including one patient who died after withdrawal from the study. An additional death was reported after month 12.

Clinical evaluator's recommendation

The clinical evaluator recommends approval for prophylaxis of fungal infection; however, it is recommended that the wording is changed to include the basis for the indication, that is, that *'the indication is based on studies including patients undergoing HSCT'*.

Risk management plan

The RMP reviewers agree with the proposed routine pharmacovigilance activities and the PI document with respect to the known risk associated with voriconazole therapy, such as hepatotoxicity. Further listing of risks, such as peripheral neuropathy and skin cancer, has been identified. Some of these recommendations have either been adopted previously *via* a safety related change to the PI, or have now been agreed by the sponsor.

Risk-benefit analysis

Delegate considerations

The clinical evaluator has noted that the 'third' component in the composite primary efficacy endpoint (not more than 14 days missed on study drug (voriconazole)/formulation (itraconazole) during the scheduled 100 days of treatment, that is, insufficient prophylaxis) has determined the superior efficacy of voriconazole over itraconazole.

However, the Delegate noted this was constructed as a compound outcome and would have served to make the outcome conservative. Its components, including all-cause mortality, are accepted outcomes in this context and are considered appropriate.

Proposed action

The indication proposed for approval is:

prophylaxis in patients who are at high risk of invasive fungal infections. The indication is based on studies including patients undergoing haematopoietic stem cell transplantation

The proposed dose for prophylaxis is as follows, consistent with that used in the controlled clinical trial:

Table 11. Proposed dosing regimen

	Intravenous	Oral Tablets or Suspension	
		≥ 40 kg	< 40 kg
Loading Dose Regimen (first 24 hrs)	6 mg/kg every 12 hours (for the first 24 hrs)		
Maintenance Dose (after first 24 hrs)	4 mg/kg every 12 hrs	200 mg or 5 mL every 12 hrs	100 mg or 2.5 mL every 12 hrs

This dosing is the same as currently approved in adults for the treatment of IFI, other than oesophageal candidiasis. New dose finding studies were not done for prophylactic use. This is considered acceptable.

Advice requested from ACPM

The Delegate sought general advice on this application from the ACPM, and requested the committee address the following in particular:

1. Appropriateness of the composite primary efficacy endpoint.

Does the committee consider the components and construction of the composite efficacy endpoint valid for the purpose of assessing prophylaxis against IFI? Are the overall results and the results for the individual components consistent with the conclusion that voriconazole is effective prophylaxis against IFI under the conditions of the pivotal trial in this submission?

2. Appropriateness of itraconazole as a comparator to voriconazole.

The Delegate noted that the sponsor had addressed this in their response to question 9 from the TGA (see List of Questions, above). The Delegate accepted that posaconazole was not approved for this use when the sponsor's studies were set up; however, posaconazole would now be considered a more appropriate comparator for asserting non-inferiority given its approved indication and its efficacy relative to itraconazole. The current clinical guidelines also support use of posaconazole in this setting.

The committee is requested to provide advice regarding lack of direct comparison between voriconazole and posaconazole, and whether this needs to be reflected in the PI and attention drawn to the relevant clinical guideline. It is reassuring that the pivotal Study A1501073 was able to demonstrate clinical superiority of voriconazole over itraconazole and was not limited to a show of non-inferiority only.

3. Dosing recommendations.

The mean age of patients in the pivotal Study A1501073 was 43.3 ± 14.4 years (range 11-70 years) in the voriconazole group and 42.7 ± 14.6 years (range 13-70 years) in the itraconazole group. A total of nine patients < 18 years of age were treated with voriconazole in this study. Only adults were treated in the accompanying uncontrolled trial. The current Australian PI for voriconazole includes pharmacokinetic data in children; does not recommend treatment in the < 2 years age groups; has dosing guidelines for the 2 to < 12 years age group; and allows dose equivalence between adolescents and adults. The proposed dosing itself is based on body weight (≥ 40 kg and < 40 kg). In view of these considerations, will it be reasonable to allow these recommendations to apply to the proposed prophylaxis indication?

Response from Sponsor**Introduction**

In this response, the sponsor addressed the issues raised in the Delegate's overview for which ACPM advice was sought.

1. Appropriateness of the composite primary efficacy endpoint.*Sponsor's response:*

At the time the pivotal trial in this submission was designed, the lack of significant differences in IFI incidence or survival during previous prospective clinical trials prompted Pfizer to choose a composite measure as the primary endpoint, in order to facilitate the detection of relevant clinical differences between the two study drugs. The primary efficacy endpoint incorporated ability to tolerate study drug for ≥ 100 days after HSCT with survival to Day 180 with no breakthrough IFI. This was based on the hypothesis that to be suitable for use as prophylaxis after HSCT, an antifungal agent must be effective and tolerated for relatively long periods.

According to the Guideline: *Points to Consider on the Clinical Evaluation of New Agents for Invasive Fungal Infections* (CHMP/EWP/1343/01)²⁶ the primary efficacy variable in a prophylaxis study would be the incidence of proven or probable IFI. However, the *Points to Consider* document recognizes that the projected size of adequately controlled trials may make them unfeasible and allows for the use of other study designs.

Pfizer did not compare the incidence of IFI as the primary analysis in the pivotal prophylaxis study for the following reason:

- Both voriconazole and itraconazole are active against *Aspergillus* and *Candida*, which cause the majority of IFI after allogeneic HSCT. As a result, it would be unlikely to find a difference in rates of breakthrough IFI in this study. Although the EMA guideline allows sponsors to “exclude inferiority” in the primary efficacy analysis, the investigators agreed that a study which simply concludes that voriconazole is “not inferior” to itraconazole in the prevention of breakthrough IFI would not generate useful clinical information.

The *Points to Consider* document allows for alternative statistical designs. Pfizer developed an alternative “composite” endpoint for the prophylaxis study, which incorporated the rate of breakthrough IFI with survival and tolerability. According to the study investigators, this was an appropriate endpoint for the following reasons:

- Another study of prophylaxis after allogeneic HSCT (the Blood and Marrow Transplant (BMT) Clinical Trials Network (CTN) “BMT-CTN Study”²⁷) incorporated a comparison of “fungal-free” survival to 180 days as the primary analysis. This endpoint was designed to capture breakthrough IFI as well as deaths which may have been caused by an undiagnosed fungal infection or by a complication of drug toxicity. Pfizer modelled the primary endpoint on the BMT-CTN study endpoint.
- Because both study drugs used in the trial have the potential to prevent IFI, including *Aspergillus* infections, the ability to tolerate study drug for relatively long durations becomes an important consideration. Current transplant regimens are associated with prolonged periods of immunosuppression, and IFIs (particularly invasive *aspergillosis*) may develop for up to 6 months after allogeneic HSCT.²⁸
- The oral solution of itraconazole contains cyclodextrin and may not be tolerated for the long durations needed for effective antifungal prophylaxis after allogeneic HSCT. Based on the better tolerated oral formulation, Pfizer anticipated that oral voriconazole would be better tolerated than itraconazole as long-term prophylaxis after allogeneic HSCT, but this hypothesis needed to be investigated in a prospective clinical trial. This is the reason why Pfizer incorporated the ability to tolerate study drug into the composite endpoint.

2. Appropriateness of itraconazole as a comparator to voriconazole.

Sponsor’s response:

The current clinical guidelines that recommend the use of posaconazole for the prophylaxis in higher risk allogeneic HSCT, pre-engraftment, also recommend itraconazole and fluconazole as alternative agents in this setting. The paper describing the process for

²⁶ Available at <http://www.tga.gov.au/pdf/euguide/ewp134301enfin.pdf>

²⁷ Wingard JR, Carter SL, Walsh TJ *et al.* Randomised, double-blind trial of fluconazole versus voriconazole for prevention of invasive fungal infection after allogeneic hematopoietic cell transplantation. *Blood* 2010;116:5111-5118.

²⁸ Garcia-Vidal C, Upton A, Kirby KA *et al.* Epidemiology of invasive mold infections in allogeneic stem cell transplant recipients: biological risk factors for infection according to time after transplantation. *Clinical Infectious Diseases* 2008;47:1041-1050.

the development of these guidelines provides a summary of clinical pathways.²⁹ In the pathway for higher risk allogeneic SCT, pre-engraftment, voriconazole, itraconazole and lipid formulation amphotericin are listed as options to posaconazole, illustrating the general consensus that voriconazole can be used as an alternative to posaconazole in this setting despite the absence of a head-to-head comparison. Similarly, both voriconazole and posaconazole are recommended as prophylaxis during both pre-engraftment and post-engraftment phases after allogeneic HSCT in published clinical guidelines globally.^{30,31,32} If approval of the proposed prophylaxis indication is granted in Australia, Pfizer anticipates that voriconazole will be added to the evidence-based recommendations for antifungal prophylaxis at the next update of the Australian and New Zealand clinical guideline.

3. Dosing recommendations.

Sponsor's response:

Pfizer believes that the dosing recommendations detailed in the application can be applied to the proposed prophylaxis indication for the following reasons.

It is of note that body weight has been identified as a covariate with respect to voriconazole clearance, the IV dose was designed as weight-based (for example, 3 or 4 mg/kg), which can be managed. Since oral therapy is typically given as tablet formulation, it is convenient to use a fixed dose for administration purposes. Based on the typical body weight in adults (60-70 kg), the 200 mg oral dose was selected to match the 3 mg/kg IV dose with comparable total exposure. To avoid any potential over-exposure in subjects with low body weight, a weight cut-off (40 kg) was implemented for dose reduction (for example, the voriconazole exposure achieved in a 35 kg subject receiving 100 mg oral twice daily dose would still be comparable to that at 3 mg/kg IV twice daily).

The pharmacokinetics of voriconazole in patients treated for prophylaxis are not expected to be different from those in other patient populations (for example, with invasive *aspergillosis* or *Candida* infection). Due to this rationale, the same dosing regimens (for other indications) were implemented in the pivotal Study A1501073: the loading dose of voriconazole was 6 mg/kg IV administered every 12 h for 2 doses. Maintenance with voriconazole was given as either IV therapy with 4 mg/kg twice daily or as oral doses of 200 mg twice daily if the subject weighed ≥ 40 kg and 100 mg twice daily if the subject weighed < 40 kg. Results from Study A1501073 confirmed that these regimens were effective in preventing fungal infections. Although only nine patients < 18 years of age were treated with voriconazole in this study, no marked differences were seen compared to adult patients. Therefore, the proposed dosing recommendations can be applied to both adults and adolescents for prophylaxis indication.

The current paediatric doses were derived to match adult dosing regimens by achieving comparable voriconazole total exposures: 4 mg/kg IV twice daily in paediatrics matches 3 mg/kg IV twice daily in adults, 6-7 mg/kg IV twice daily in paediatrics to match 4 mg/kg

²⁹ Slavin MA. Introduction to the updated Australian and New Zealand consensus guidelines for the use of antifungal agents in the haematology/oncology setting. *Intern Med J* 2008;38:457-467.

³⁰ Centers for Disease Control and Prevention; Infectious Disease Society of America; American Society of Blood and Marrow Transplantation. Guidelines for preventing opportunistic infections among hematopoietic stem cell transplant recipients. *MMWR Recomm Rep.* 2000;49(RR-10):1-125.

³¹ Tomblyn M, Chiller T, Einsele H *et al.* Guidelines for preventing infectious complications among hematopoietic cell transplant recipients: a global perspective. Recommendations of the Center for International Blood and Marrow Transplant Research (CIBMTR®), the National Marrow Donor Program (NMDP), the European Blood and Marrow Transplant Group (EBMT), the American Society of Blood and Marrow Transplantation (ASBMT), the Canadian Blood and Marrow Transplant Group (CBMTG), the Infectious Disease Society of America (IDSA), the Society for Healthcare Epidemiology of America (SHEA), the Association of Medical Microbiology and Infectious Diseases Canada (AMMI), and the Centers for Disease Control and Prevention (CDC). *Bone Marrow Transplant* 2009;44:453-558.

³² Marr KA, Bow E, Chiller T *et al.* Fungal infection prevention after hematopoietic stem cell transplantation. *Bone Marrow Transplant* 2009;44:483-487.

IV twice daily in adults. Therefore, although no paediatric patients between the 2 to < 12 years age groups were included in Study A1501073, the current dosing guidelines for this age group in the Australian PI are also applicable for treating paediatric patients for prophylaxis.

Conclusion

Invasive fungal infections continue to be reported as major complications after allogeneic HSCT. There is a need for a well-tolerated broad spectrum antifungal agent that can be given as prophylaxis for extended periods after allogeneic HSCT. Voriconazole is active against a wide range of yeasts and filamentous fungi, including *Aspergillus*, *Fusarium*, and *Scedosporium* species. Voriconazole is available as an IV and oral formulation, which allows continuation of therapy in patients who have difficulty in swallowing (for example, due to severe mucositis), and can therefore cover the entire risk period of IFI in HSCT patients, unlike other azoles that are only available as oral formulations.

The clinical data presented in this submission support the use of voriconazole for antifungal prophylaxis in high risk patients such as allogeneic HSCT recipients. Accordingly, Pfizer supports the clinical evaluator's recommendation to approve the application to extend the indications for voriconazole (Vfend) to '*prophylaxis in patients who are at high risk of invasive fungal infections. The indication is based on studies including patients undergoing haematopoietic stem cell transplantation.*'

Advisory committee considerations

The ACPM, having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, considered these products to have an overall positive benefit-risk profile for the indication;

For prophylaxis against development of invasive fungal infections (IFI) in high risk patients such as haematopoietic stem cell transplant (HSCT) recipients.

The ACPM agreed with the Delegate to the proposed amendments to the PI and CMI and recommended:

- Inclusion in the *Clinical Trials* section of the PI clear reference to details of the trial population, specifically the inclusion and exclusion criteria.
- Review of the CMI to ensure alignment with the new indication.

The ACPM advised that the implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of these products.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Vfend tablets, powder for intravenous infusion, and powder for oral suspension, containing voriconazole, for the following new indication:

Prophylaxis in patients who are at high risk of developing invasive fungal infections. The indication is based on studies including patients undergoing haematopoietic stem cell transplantation.

The full indications are now:

Vfend is indicated:

- *For treatment of the following fungal infections:*
- *Invasive aspergillosis.*
- *Serious Candida infections (including C. krusei), including oesophageal and systemic Candida infections (hepatosplenic candidiasis, disseminated candidiasis, candidaemia).*
- *Serious fungal infections caused by Scedosporium spp and Fusarium spp.*
- *Other serious fungal infections, in patients intolerant of, or refractory to, other therapy.*
- *Prophylaxis in patients who are at high risk of developing invasive fungal infections. The indication is based on studies including patients undergoing haematopoietic stem cell transplantation.*

Specific conditions of registration applying to these goods

The implementation in Australia of the voriconazole RMP, dated 7 August 2011 version 1.1, included with submission and any subsequent revisions, as agreed with the TGA and its OPR.

Attachment 1. Product Information

The Product Information approved at the time this AusPAR was published is at Attachment 1. For the most recent Product Information please refer to the TGA website at <<http://www.tga.gov.au/hp/information-medicines-pi.htm>>.

Attachment 2. Extract from the Clinical Evaluation Report

Therapeutic Goods Administration

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