Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Voriconazole

Proprietary Product Name: Vorcon

Sponsor: Aspen Pharma Pty Ltd

June 2017

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance) when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

Common abbreviations

Abbreviation	Meaning
AAN	Australian approved name
ACPM	Advisory Committee for Prescription Medicines
ADEC	Australian Drug Evaluation Committee (now ACPM)
ALT	alanine aminotransferase
ARGPM	The Australian regulatory guidelines for prescription medicines
AST	aspartate aminotransferase
$AUC_{(0-t)}$	Area under the Concentration time curve from time 0 to tau
BD	Twice daily
BSA	Body surface area
CBER	Center for Biologics Evaluation and Research (FDA)
CDER	Center for Drug Evaluation and Research (FDA)
C_{max}	maximum serum concentration
EMA	European Medicines Agency
EURD	European reference dates (maintained by EMA)
FDA	Food and Drugs Administration (USA)
GFR	glomerular filtration rate
HP-β-CD	hydroxypropyl-β-cyclodextrin (AAN: hydroxypropylbetadex)
IV	intravenous
NOAEL	no observable adverse effect level
PDE	Permitted Daily Exposure
PK	pharmacokinetic
PND	Post natal day
PSC	Pharmaceutical Subcommittee (of ACPM)
PSUR	Periodic Safety Update Report
RMP	Risk Management Plan

Abbreviation	Meaning
SBE-β-CD	sulfobutyl ether beta-cyclodextrin sodium
SC	subcutaneous
SmPC	Summary of Product Characteristics (EU)
t½	Half life

I. Introduction to product submission

Submission details

Type of submission:	New generic medicine
Decision:	Approved
Date of decision:	24 June 2016
Date of entry onto ARTG	27 July 2016
Active ingredient:	Voriconazole
Product name:	Vorcon
Sponsor's name and address:	Aspen Pharma Pty Ltd[1]
Dose forms:	Tablet and powder for injection
Strengths:	50 mg and 200 mg (tablet) and 200 mg powder for injection
Containers:	Blister pack (tablet) and vial (powder for injection)
Pack sizes:	1 vial (injection), 56 tablets
Approved therapeutic use:	*Voriconazole 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.*
Routes of administration:	Oral (tablet); intravenous (powder for injection)
Dosage:	For details of dosage and administration please see the Product Information (PI).
ARTG numbers:	235934, 235933, 235932

[1] Post registration the sponsor has changed to Southern Cross Pharma Pty Ltd, Suite 5, 118 Church St, Hawthorn, VIC 3122

Product background

This AusPAR describes the application by Aspen Pharma (the sponsor) seeking registration of Vorcon as a generic voriconazole 50 mg and 200 mg (tablet) and 200 mg powder for injection for the following indication (the same as the innovator):

> *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.*

The innovator product is Vfend (voriconazole 50 mg and 200 mg tablets and 200 mg lyophilized powder for injection) from Pfizer Australia, which was approved in 2002 for use in serious, deep fungal infections in patients from 2 years of age and above, including a prophylaxis indication.

This submission is being referred to the Advisory Committee for Prescription Medicines (ACPM) for advice because Vorcon voriconazole 200 mg powder for injection contains a new excipient.

Regulatory status

At the time the TGA considered this application, a similar application had been approved in the European Union through the decentralised procedure (approved 19 May 2015 for the tablet form and the intravenous (IV) version was approved 18 March 2016)) and was under consideration in New Zealand (submitted 3 May 2016).

Product Information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

II. Quality findings

Introduction

The proposed presentations for Vorcon are presented in Table 1.

Table 1: Proposed presentations for Vorcon

Trade name	Strength	Dosage form	Presentation
Vorcon	200 mg	Powder for injection	Vial
Vorcon	50 mg	Film-coated tablet	Blister pack
Vorcon	200 mg	Film-coated tablet	Blister pack

As discussed below, the proposed generic injection product includes a different solubilising excipient (that is, hydroxypropyl-β-cyclodextrin (HP-β-CD)) than that used in the innovator's product Vfend (that is sulfobutyl ether beta-cyclodextrin sodium; SBE-β-CD). *Advice is sought regarding the potential risk of the substitution of SBE-β-CD in the innovator product with HP-β-CD in this generic product, particularly for juvenile patients (2 to 12 years).*

The same pack presentation is proposed for the generic powder for injection as that registered for Vfend (that is, 200 mg powder in a glass vial).

Voriconazole powder for injection is reconstituted with water for injections to give a concentrated solution that is compatible with the following infusion fluids:

- 0.9% sodium chloride intravenous infusion, compound sodium lactate intravenous infusion
- 5% glucose and compound sodium lactate intravenous infusion
- 5% glucose and 0.45% sodium chloride intravenous infusion
- 5% glucose intravenous infusion
- 5% glucose in 20 mEq potassium chloride infusion
- 0.45% sodium chloride intravenous infusion
- 5% glucose and 0.9% sodium chloride intravenous infusion.

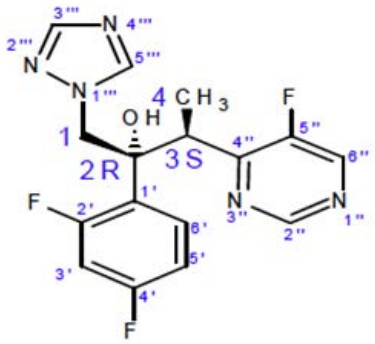
Voriconazole infusion must not be diluted with 4.2% sodium bicarbonate infusion. Compatibility with other concentrations is unknown.

The maximum daily dose for oral administration is 800 mg (loading dose of 400 mg every 12 hours.

The maximum daily dose for intravenous administration is 5 mg/kg every 12 hours.

Drug substance (active ingredient)

Figure 1: Voriconazole



Voriconazole is a white or almost white powder which is very slightly soluble in water, freely soluble in methylene chloride and sparingly soluble in methanol. The structure contains 2 chiral centres and the required enantiomer has the 2R,3S configuration, shown in Figure 1.

Voriconazole API is manufactured in 3 chemical steps at [Information redacted], using the starting materials 'CEFP' (4-chloro-6-ethyl-5-fluoropyrimidine) and DFEAT (1-(2,4-difluorophenyl)-2-(1H-1,2,4-triazol-1-yl)ethanone with two isolated intermediates. The desired 2R, 3S diastereomer is selected by crystallisation as the chiral salt with 1R-(-)-10-camphor sulfonic acid. Final purification is by re-crystallisation from isopropanol.

Specifications applied to the starting materials and the isolated intermediates have been adequately justified and are considered satisfactory.

Voriconazole is the subject of both a harmonised Ph Eur/ BP monograph and a USP monograph. The company includes discussion of 10 potential related substances including the 5 specified in the BP/EP monograph, and acceptable controls are applied to all in the drug substance specifications. Levels of the enantiomeric impurity (BP/EP Impurity D) are adequately controlled to NMT 0.2% by a chiral HPLC test method. Discussion and control of potentially genotoxic impurities is acceptable.

Controls applied to the drug substance are based on the BP/EP monograph with additional in-house tests for identification by X-ray diffraction (XRD) (to control polymorphic form), impurity E by ion chromatography, particle size by laser diffraction, residual solvents by GC and palladium content by ICP-MS.

The drug substance specifications are considered acceptable, after some tightening of related substance limits and inclusion of an appropriate test and limit for particle size distribution.

Drug product; powder for injection

Voriconazole powder for injection/infusion is presented as a white to off white lyophilised powder packaged in glass vial type I, sealed with rubber stopper and aluminium cap with plastic flip-off seal.

Formulation details are provided in Table 2.

Table 2: Formulation details for the powder for injection presentation of Vorcon

Ingredient	Quality standard	Function
Voriconazole	Ph. Eur.	Active ingredient
Hydroxy propyl β cyclodextrin	Ph. Eur.	Complexing agent/ solubilising agent
Sodium chloride	Ph. Eur.	Tonicity agent
Hydrochloric acid	Ph. Eur.	pH adjustment
Solvents used and removed in process:		
Water for Injection	Ph. Eur.	Solvent

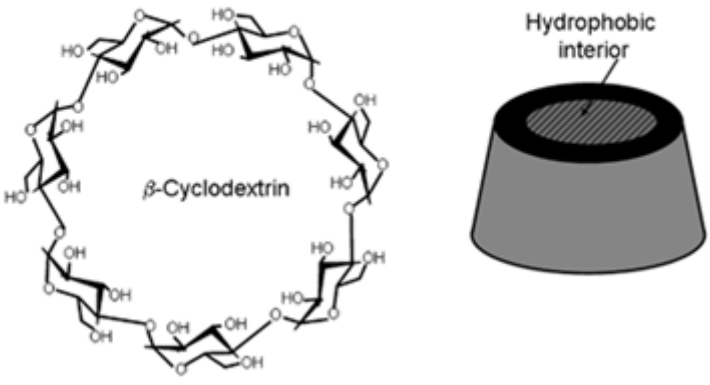
The drug substance specification includes tests and limits for bacterial endotoxins and microbiological quality to ensure that the drug product will meet the required microbiological acceptance criteria. The proposed drug product does not contain any preservatives, antioxidants or other antimicrobial agents.

When reconstituted with 19 mL water for injection, the proposed drug product has an osmolality of 530 mosmol/kg ± 10% and a pH between 5.0 and 7.0. The resultant clear concentrate must be further diluted prior to administration as an intravenous infusion. Compatibility with the proposed infusion fluids has been adequately demonstrated.

The excipients used in the manufacture of the finished product all comply with the Ph. Eur. pharmacopoeial standards. With the exception of HP-β-CD, they are conventionally used in the manufacture of parenteral finished products and are therefore acceptable.

Voriconazole is poorly soluble in water, thus use of a solubilising /complexing agent is required to achieve a solution suitable for injection. Voriconazole exhibits pH dependent solubility. Accordingly, the active ingredient is dissolved in an acidic medium to which the solubilising agent is added followed by adjustment to the desired pH and volume. The sponsor investigated several agents [information redacted]. The glucose chains of cyclodextrines form a cone like hydrophobic cavity into which compounds may enter and form a water soluble complex (molecular encapsulation) (Figure 2).

Figure 2: Structure of β-cyclodextrins

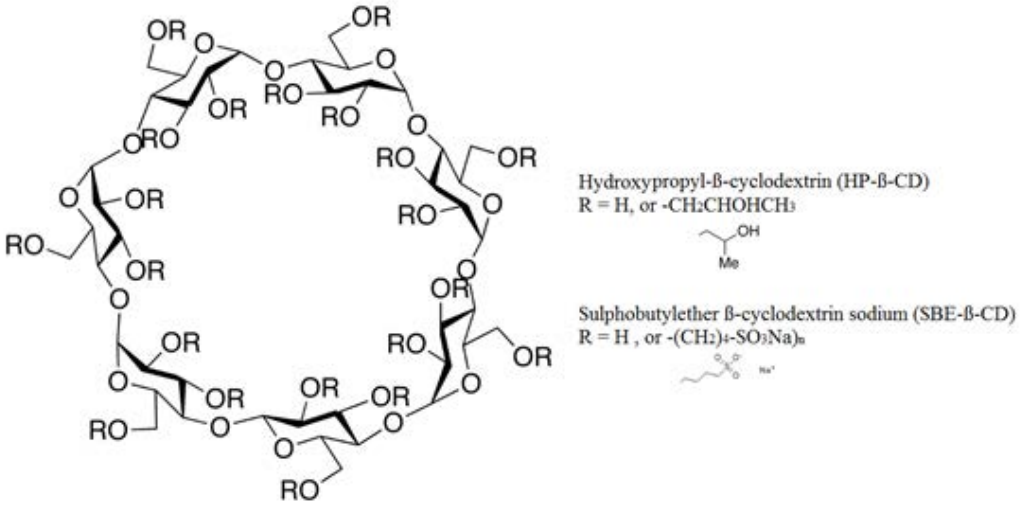


β-cyclodextrin itself (7 glucose units) is nephrotoxic and not suitable for parenteral formulations and hence was not investigated. None of the agents listed above were found to form a complex with the desired solubility and were not considered further.

The use of substituted β-cyclodextrins can result in improved solubility of the encapsulation complex and potentially lower toxicity. Accordingly, the drug product manufacturer investigated the use of modified β-cyclodextrin containing hydroxylpropyl substituents. A grade of hydroxypropyl β-cyclodextrin (see structure below in Figure 3) containing 0.65 hydroxylpropyl units per glucose unit was chosen to achieve the desired solubility.

The innovator's powder for injection product contains the related modified cyclodextrin 'sulphobutylether β-cyclodextrin sodium' (SBE-β-CD; Australian approved name (AAN) 'sulfobutyl betadex sodium'; see structure below in Figure 3) to increase solubility. The sponsor has not provided an explanation for choosing a different solubilising agent to that of the innovator.

Figure 3: Structure of hydroxypropyl β-cyclodextrin and sulphobutylether β-cyclodextrin sodium



A comparative summary of the Australian and UK innovator's products and the proposed formulation is tabulated in Table 3.

Table 3: A comparative summary of the Australian and UK innovators product and the proposed generic product

Ingredient	Vfend (AU)	Vfend (EU)	Proposed product
Voriconazole	200 mg/vial (10 mg/mL)	200 mg/vial (10 mg/mL)	200 mg/vial
Sulphobutylether β-cyclodextrin sodium (SBE-β-CD)	3200 mg/vial (160 mg/mL)	3200 mg/vial (160 mg/mL)	Not present
Hydroxypropyl β-cyclodextrin (HP-β-CD)	Not present	Not present	2400 mg/vial
Sodium chloride	Not present	Not present	225.60 mg/vial

Hydroxypropyl-β-cyclodextrin (HP-β-CD) has not been used in a product currently listed on the ARTG that has an intravenous route of administration, although it is an ingredient in registered tablets, eye drops and an oral liquid. It is noted that HP-β-CD can be found in EU marketed parenteral formulations with intravenous dosing of up to 16 g HP-β-CD daily. Maximum daily dose is approximately 14.4 g HP-β-CD for a 100 kg individual[2].

It is noted that a maximum level of 0.4 % of HP-β-CD (Unique Ingredient Identifier No. 1I96OHX6EK) for an injection is published on FDA's Inactive Ingredient Guide.[3] The background review for cyclodextrins used as excipients[4] gives the safe exposure for HP-β-CD as 250 mg/kg/day over 21 days for parenteral exposure in humans older than 2 years.[5] This document further notes that HP-β-CD is not indicated for newborn babies and infants under 2 years old, and for patients with renal impairment, because of insufficient toxicological knowledge in juveniles, and accumulation of cyclodextrins in the kidney at renal impairment. The proposed PI states that the proposed drug product is not recommended for children less than 2 years of age and suggests oral voriconazole for patients with moderate to severe renal dysfunction.

The safety of the proposed levels of HP-β-CD has been assessed by the TGA drug toxicology evaluation section (nonclinical evaluation report, dated 29 April 2016).

This report concluded that '*There are no nonclinical objections to registration of generic voriconazole (Vorcon) containing HP-β-CD excipient in adults. There are no nonclinical data for the HP-β-CD excipient in young animals. Clinical data for HP-β-CD excipient in children and adolescents are very limited in terms of subject numbers and duration of treatment, and it is recommended that clinical advice is sought regarding use in those age groups.*' Accordingly, clinical advice has been sought with respect to the potential risk of the substitution of SBE-β-CD in the innovator product with HP-β-CD in this generic product, for juvenile patients (2 to 12 years).

Due to the difference in solubilising agent used in the proposed injection product with respect to the innovator's injection product, the sponsor conducted a bioequivalence study (study number VRL-P3-502) comparing the proposed generic drug product to the innovator's Vfend sourced from the EU.

The 90% CI for AUC_{0-t} and C_{max} for the generic versus the EU innovator's product for voriconazole were within the acceptance criteria (that is, 80.00 to 125.00%) required to conclude bioequivalence. An acceptable justification for the use of an overseas comparator was also submitted.

The manufacturing process consists of dissolution of the HP-β-CD in 70% of the required volume of water for injection. The active ingredient is added and dissolved followed by sodium chloride. The bulk solution is made to volume with water for injection, followed by adjustment of pH using 0.1N hydrochloric to pH 5.4 to 5.8. The solution is not buffered. Voriconazole in solution is thermally labile and so terminal sterilisation by autoclave was not suitable. Aseptic filtration was therefore chosen as the method of sterilisation. After dissolution, the solution is filtered through a 0.2 µm filter to reduce the bacterial count.

[2] EMA/CHMP/333892/2013 - Background review for cyclodextrins used as excipients <http://www.ema.europa.eu/docs/en_GB/document_library/Report/2014/12/WC500177936.pdf>
[3] Inactive Ingredient Search for Approved Drug Products <http://www.accessdata.fda.gov/scripts/cder/iig/getiigWEB.cfm>
[4] EMA/CHMP/333892/2013 20 November 2014 Background review for cyclodextrins used as excipients In the context of the revision of the guideline on 'Excipients in the label and package leaflet of medicinal products for human use' (CPMP/463/00 Rev. 1)
[5] EMA/CHMP/495747/2013 - Questions and answers on cyclodextrins in the context of 4 the revision of the guideline on 'Excipients in the label 5 and package leaflet of medicinal products for human use' 6 (CPMP/463/00 Rev. 1) <http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/12/WC500177944.pdf>

The TGA microbiology section of Office of Laboratory and Scientific Serivces (OLSS) has evaluated these aspects and has found them acceptable after resolution of some issues.

Lyophilisation is conducted on the filled, partially stoppered, Type I clear glass vials, followed by a final stoppering process. The vials are sealed with a rubber stopper, aluminium cap and flip-off seal.

The proposed finished product specifications included controls on appearance, moisture, dissolution rate, colour and turbidity of solution, pH, osmolarity, identity of drug substance, assay of active drug, related substances, enantiomeric purity, uniformity of dosage units, particulate matter, tightness of vials, endotoxins and sterility. The company satisfactorily justified not routinely testing for quantity of HP-β-CD. After some tightening of limits, including for related substances, the proposed finished product specifications are considered adequate to ensure the quality of the finished product at release and throughout the shelf-life.

The product shows good stability and a shelf-life of 30 months when stored below 30°C is considered justified by the submitted stability data.

Drug product; film coated tablets

The sponsor has applied to register voriconazole film coated tablets in strengths of 50 mg and 200 mg, packed in PVC/aluminium blisters.

The proposed tablets are unscored, film coated immediate release tablets and are to be packaged in blisters containing 56 tablets. This is consistent with the innovator's tablets.

The two strengths are direct scales of each other. The active ingredient represents approximately 33% of the core tablet weight. The two strengths are distinguished by size, shape and markings.

The excipients in the product (pre-gelatinised maize starch, lactose monohydrate, povidone K30, croscarmellose sodium, colloidal anhydrous silica, magnesium stearate, Opadry II White OY-LS-28908 film coat) are conventional substances with well-known properties and functions and commonly used as ingredients in this type of medicine. The excipients chosen are very similar to those present in the innovator tablets, Vfend.

The tablets are to be manufactured by a single site: [information redacted].

The cores of the two strengths are direct scales manufactured by a conventional process involving the steps: wet granulation (water solvent), drying, dry granulation, lubrication, compression and coating.

Dissolution performance was monitored during development and for routine testing using the method nominated on FDA's Dissolution Methods Database for voriconazole tablets (0.1 N hydrochloric acid, 900 mL, paddles, 50 rpm). Comparative dissolution studies with the EU innovator's product (Vfend) with media of various pH, showed comparable dissolution with all tablets dissolving rapidly and > 85% dissolution within 15 minutes in all media.

The dissolution profiles of tablets manufactured from un-micronised active were noticeably slower and accordingly, well defined particle size distribution limits for the drug substance were sought, based on batches of drug substance that were used to manufacture the finished products used in the bioavailability studies [that is D(0.1): NMT 30 µm; D(0.5): NMT 65 µm; D(0.9): NMT 90 µm].

The specifications for each strength have acceptable expiry limits and release limits.

The tablets show good stability and a shelf life of 30 months when stored below 30°C, in the original packaging, has been justified.

The chemistry and quality control aspects of the draft PI for the proposed products have been finalised to the satisfaction of the PCS, as have the vial, carton and blister foil labels and the Provisional ARTG Records.

Biopharmaceutics

This submission included two bioavailability studies which are briefly summarised below:

Study VRL-P3-502: Powder for injection

This study was performed to evaluate and compare the relative bioavailability of the proposed formulation of voriconazole 200 mg injection and the EU innovator's product (Vfend voriconazole 200 mg injection) under fasting conditions.

This study was required as the proposed product uses a different solubilising agent (that is HP-β-CD) to that of the EU (and Australian) innovator's product (that is SBE-β-CD).

The sponsor's results for the voriconazole pharmacokinetic parameters are presented below in Table 4.

Table 4: Pharmacokinetic parameters voriconazole, Study VRL-P3-502

PARAMETER	TEST		REFERENCE	
	MEAN	C.V. (%)	MEAN	C.V. (%)
C_{max} (ng/mL)	1686.0	16.1	1767.0	17.5
ln (C_{max})	7.4171	2.2	7.4624	2.3
T_{max} (hours) *	1.50	4.3	1.50	5.9
AUC_T (ng·h/mL)	6374.8	32.6	6849.9	33.9
ln (AUC_T)	8.7116	3.6	8.7816	3.6
AUC_∞ (ng·h/mL)	6573.8	32.2	7054.1	34.1
ln (AUC_∞)	8.7436	3.5	8.8109	3.6
$AUC_{T/\infty}$ (%)	96.87	1.7	97.12	1.7
K_{el} ($hours^{-1}$)	0.1194	35.6	0.1161	29.7
$T_{½el}$ (hours)	6.32	25.3	6.43	26.9

* median is presented

The mean concentration versus time linear and log-linear profiles are provided below in Figures 4 and 5.

Figure 4: Linear profile of the mean; Voriconazole, Study VRL-P3-502

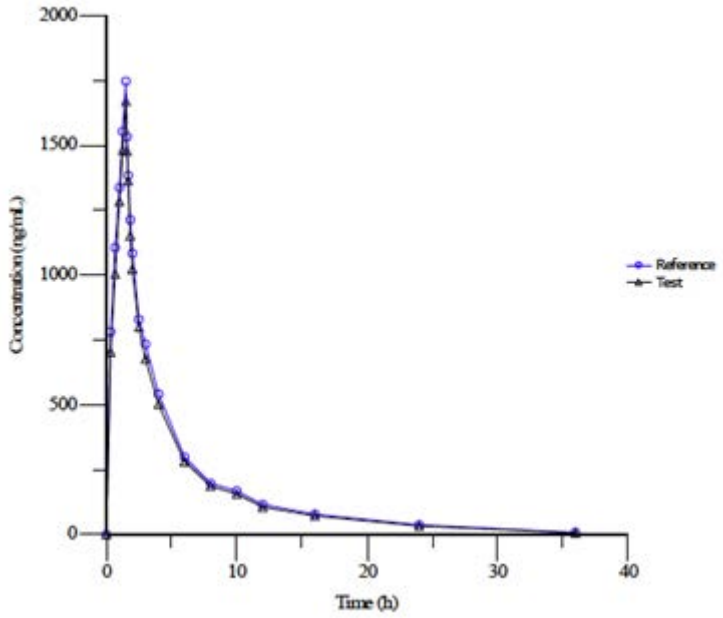
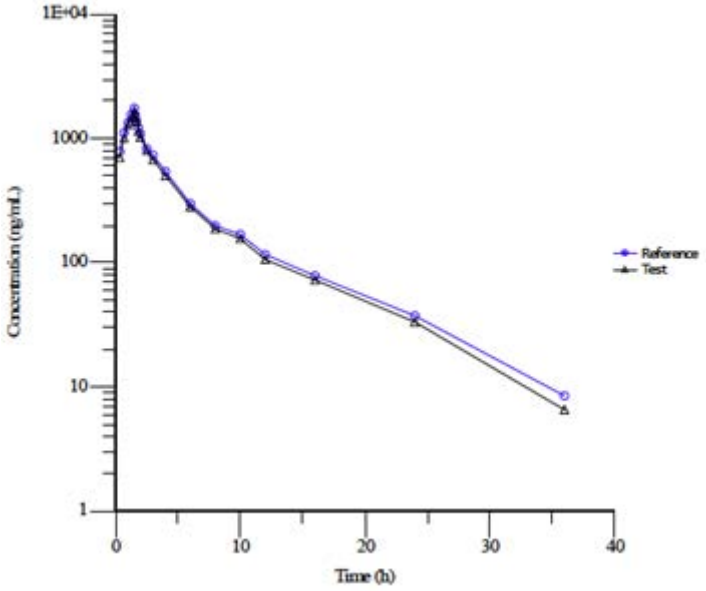


Figure 5: Logarithmic profile of the mean; Voriconazole, Study VRL-P3-502



For the log transformed voriconazole data, the 90% confidence intervals about the ratio of the Test geometric mean to Reference geometric means fell within the 80% to 125% limits for C_{max} and $AUC_{(0\text{-}t)}$ and span unity (Table 5).

Table 5: Log transformed voriconazole data, Study VRL-P3-502

PARAMETER	INTRA-SUBJECT C.V. (%)	GEOMETRIC LSMEANS *		RATIO (%)	90% CONFIDENCE LIMITS (%)	
		TEST	REFERENCE		LOWER	UPPER
C_{max}	9.7	1664.3	1741.2	95.58	91.27	100.09
AUC_T	6.0	6073.2	6513.1	93.24	90.62	95.94

* units are ng/mL for C_{max} and ng·h/mL for AUC_T

The study is considered to have been conducted appropriately and the normal criteria required to conclude bioequivalence have been met.

An acceptable justification for the use of an overseas comparator was also submitted.

Study PHG-P8-129: Film coated tablets

The objective of this study was to evaluate and compare the bioavailability of the proposed 200 mg voriconazole film coated tablets with the EU innovator's Vfend 200 mg tablets, after a single oral dose administration under fasting conditions.

The 'Test' film coated tablets are the same formulation as that proposed by the sponsor for commercial manufacture.

The sponsor's results for the voriconazole pharmacokinetic parameters are tabulated below (Table 6).

Table 6: Summary of plasma Voriconazole pharmacokinetic parameters Study PHG-P8-129

Parameter (Units)	Test		Reference	
	Mean	(C.V. %)	Mean	(C.V. %)
C_{max} (ng/mL)	1309.9	(40.5)	1314.9	(41.9)
ln (C_{max})	7.0861	(6.4)	7.0826	(6.7)
T_{max} (hours)[a]	1.00	(57.8)	1.25	(74.8)
AUC_{0-T} (ng·h/mL)	6133.1	(57.6)	5825.0	(59.2)
ln (AUC_{0-T})	8.5681	(6.7)	8.5143	(6.7)
$AUC_{0-\infty}$ (ng·h/mL)	6100.8	(50.9)	5758.3	(49.2)
ln ($AUC_{0-\infty}$)	8.5834	(6.3)	8.5314	(6.1)
Residual Area (%)	4.20	(57.9)	4.60	(63.7)
λ_Z ($hours^{-1}$)	0.1048	(35.6)	0.1071	(32.7)
T_{half} (hours)	7.15	(25.7)	7.04	(27.0)

[a] Median

Copies of the mean concentration versus time linear and log-linear profiles appear below in Figures 6 and 7.

Figure 6: Linear profile of the mean; voriconazole, Study PHG-P8-129

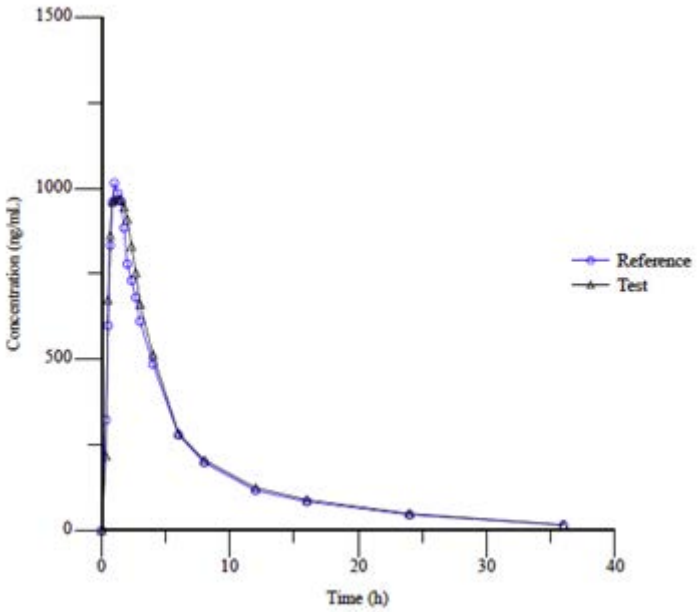
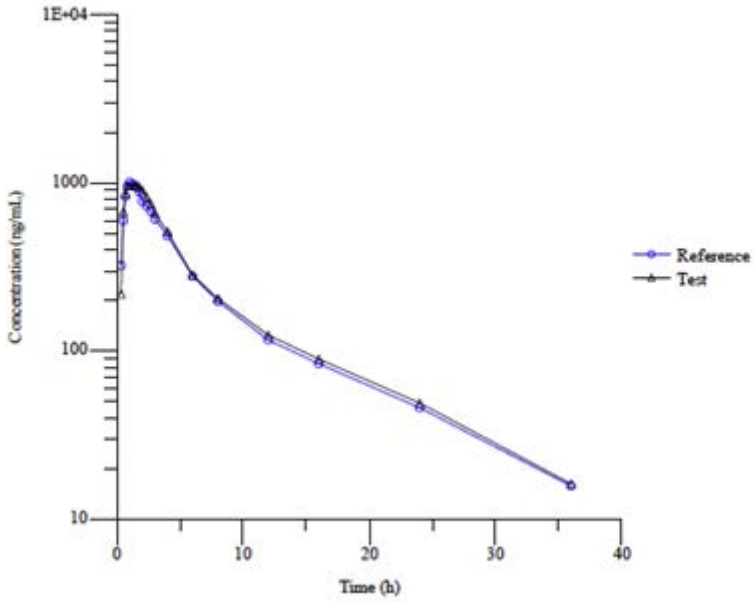


Figure 7: Logarithmic profile of the mean; voriconazole, Study PHG-P8-129



For the log transformed voriconazole data, the 90% confidence intervals about the ratio of the Test geometric mean to Reference geometric means fell within the 80% to 125% limits for C_{max} and AUC_{0-t} and span unity.

Table 7: Summary of the statistical analysis of Voriconazole, Study PHG-P8-129

Parameter	Intra-Subject C.V. (%)	Geometric LSmeans[a]		Ratio (%)	90% Confidence Limits (%)	
		Test	Reference		Lower	Upper
C_{max}	28.9	1192.1	1191.5	100.05	90.71	110.36
AUC_{0-T}	13.6	5253.2	4983.7	105.41	100.58	110.46

[a] units are ng/mL for C_{max} and ng·h/mL for AUC_{0-T}

The study is considered to have been conducted appropriately and the normal criteria required to conclude bioequivalence have been met.

Justifications for the use of an overseas comparator and for not submitting a bioequivalence study on the lower strength (50 mg) tablet were also submitted, and these are considered acceptable with respect to pharmaceutical chemistry issues.

Quality summary and conclusions

All pharmaceutical chemistry and quality control issues raised during the initial evaluation of this application have been satisfactorily resolved.

Microbiological and bacterial endotoxin aspects of the submission have been evaluated separately and all issues raised have been resolved.

However, as a result of the conclusions of the nonclinical evaluation report on the proposed powder for injection product in this submission, *clinical advice has been sought with respect to the potential risk of the substitution of sulfobutyl ether beta-cyclodextrin sodium (SBE-β-CD) in the innovator product with hydroxy-propyl-β-cyclodextrin (HP-β-CD) in this generic product, for juvenile patients (2 to 12 years).*

Apart from the above highlighted issue, registration of the proposed:

- Vorcon voriconazole 200 mg powder for injection to be supplied in glass vials in packs of one
- Vorcon voriconazole 50 mg and 200 mg film-coated tablets to be supplied in PVC/Al blisters in packs of 56 tablets

are recommended with respect to quality and biopharmaceutic aspects.

III. Nonclinical findings

Introduction

The toxicological assessment of this submission addresses two issues:

i. the substitution of a different excipient, HP-β-CD, for the SBE-β-CD excipient in the reference Vfend powder for injection, and

ii. qualification of impurities A and J in Vorcon powder for injection and tablet products.

The HP-β-CD excipient increases the solubility of voriconazole.

At the Vfend IV voriconazole loading dose of 6 mg/kg twice daily (BD) for 24 h and maintenance dose of 4 mg/kg BD, the respective doses of SBE-β-CD (voriconazole: SBE-β-CD ratio 1:16) are 192 mg/kg/day and 128 mg/kg/day in a 50 kg adult. At the same voriconazole doses in Vorcon the respective doses of HP-β-CD (voriconazole: HP-β-CD ratio 1:12) are lower at 144 mg/kg/day and 96 mg/kg/day.

Safety of HP-β-CD excipient

Regulatory background

The European Medicines Agency (EMA) guideline on repeated dose toxicity[6] states that for a new excipient, the same pivotal studies as for a new active substance should be performed. The FDA Guidance for industry[7] stipulates that generic drug products intended for parenteral use (but not oral, dermal or topical use) should contain the same excipients in the same concentrations as the reference product, however this guideline has not been adopted in Australia. The Australian Regulatory Guidelines for Prescription medicines (ARGPM) Appendix 23 states; '*A new route of administration or an increased daily dose of known excipients may result in the need for additional non-clinical data.*'

Registered IV products containing HP-β-CD

No Australian-registered IV products containing HP-β-CD were identified.

Australian registered oral products containing HP-β-CD are intraconazole oral solution (Sporanox, ARTG: 4702, 62008) and cladribine tablets (Movectro, ARTG: 166483). The maximum dose of HP-β-CD in Sporanox oral solution is 16 g/day, and in Movectro tablets was 144 mg/day.

In the USA, an IV formulation of the antifungal drug itraconazole (Sporanox IV) containing HP-β-CD excipient was approved in 1999 (NDA 20-966). The maximum dose of HP-β-CD in Sporanox IV was 16 g/day (320 mg/kg/day in a 50 kg adult) for 2 days, followed by 8 g/day (160 mg/kg/day) for 14 days, then oral Sporanox. Sporanox IV was contraindicated in patients with severe renal impairment (creatinine clearance below 30 mL/min) due to elimination of HP-β-CD by glomerular filtration (USA label). This product has been discontinued.[8] An IV formulation of mitomycin C (Mitozytrex) containing HP-β-CD excipient (3000 mg/m^2 HP-β-CD as a single dose, HP-β-CD:mitomycin ratio 200:1) was approved in 2002 (50-763). Mitozytrex was not recommended in patients with severe renal impairment as clearance of an IV dose of 200 mg of HP-β-CD was reduced 6 fold in comparison with normal subjects (Mitozytrex label). This product was also discontinued.[9] An IV formulation of telavancin (Vibativ) containing HP-β-CD excipient (100 mg/kg/day HP-β-CD, HP-β-CD:telavancin ratio10:1), for use in adult patients for 7 to 14 days, was approved in 2009.

Previously evaluated nonclinical IV data for HP-β-CD (Appl. No. [information redacted] and published data).

Previously evaluated IV studies for HP-β-CD included 3 month IV toxicity studies in rats and dogs at doses up to 400 mg/kg/day. The main effects were in the kidney (vacuolated cortical tubuli, swollen epithelial cells in renal pelvis and bladder, increased weight), liver (increased Kupffer cells, increased alanine aminotransferase (ALT), aspartate aminotransferase (AST)) and lungs (increased foamy cells). The most sensitive organ was the kidney. No observable adverse effect levels (NOAELs) were 50 mg/kg/day in rats and 100 mg/kg/day in dogs. Fourteen day subacute and 90 day IV toxicity studies at dose of 200 mg/kg on alternate days in rats and cynomolgus monkeys showed no adverse effects, and monkeys survived a single IV dose of 2 g/kg followed by 10 g/kg on Day 3.[10]

When HP-β-CD was changed to SBE-β-CD there was no change in the animal toxicology profile of voriconazole (App. No. [information redacted]).

[6] EMA CPMP (18 March 2010) Guideline on repeated dose toxicity (CPMP/SWP/1042/Rev 1 Corr).
[7] FDA (CDER, CBER, May 2005) Guidance for industry; Nonclinical studies for the safety evaluation of pharmaceutical excipients
[8] Drugs@FDA, 2015
[9] Drugs@FDA
[10] Brewster M et al (1990). An intravenous toxicity study of 2-hydroxypropyl-β-cyclodextrin, a useful drug solubilizer, in rats and monkeys. *International Journal of Pharmaceutics* 1990; 59: 231-243.

Standard in vitro and in vivo genotoxicity studies with HP-β-CD were negative.

Two year dietary carcinogenicity studies in mice and rats at doses of 500 to 5,000 mg/kg/day showed no increases in tumours in mice, and significant increases in the incidences of exocrine pancreatic adenomas and adenocarcinomas at all doses in rats. It was suggested that tumours may be due to stimulation of cholecystokinin release as a result of complexation of bile salts by HP-β-CD in the intestinal lumen. The relevance to humans is unclear. A 26 week oral study in Tg(HRAS) mice at 431 mg/kg/day showed no tumourigenicity (Appl. No [information redacted]).

A male and female rat fertility IV study showed no effects on fertility up to 400 mg/kg/day (HD). Embryofetal development studies in rats and rabbits showed no effects up to 400 mg/kg/day (HD). A rat peri-postnatal study showed lower mean pup weights and reduced survival at 400 mg/kg/day (HD), probably secondary to maternotoxicity.

Most of these studies have been published.[11] A more recent published study reported decreased bone mineral density in rats administered HP-β-CD at 50 or 200 mg/kg/day subcutaneous (SC), due to increased bone resorption.[12]

Published human IV data for HP-β-CD

Abdel-Rahman et al (2007)[13] investigated the pharmacokinetics of a single dose of 0.1 g/kg of HP-β-CD in 33 children (6 months to 2 years n = 6, 2 to 6 years n = 9, 6 to 12 years n = 7, 12 to 16 years n = 11). Levels of HP-β-CD fell below quantifiable limits by 12 hours. Total plasma clearance was similar to the glomerular filtration rate. HP-β-CD pharmacokinetic parameters showed no age related dependence. No adverse effects, apart from stinging at the infusion site in one subject, were observed.

Stella and He (2008)[14] reported that IV infusion of 470 mg/kg/day of HP-β-CD in a patient with severe hypervitamosis A, did not produce evidence of renal or liver damage, and a single IV dose up to 3 g was well tolerated, without any evidence of renal toxicity by analysis of urinary excretion of N-acetyl-β-glucoamidase, creatinine, and γ-glutamyl transpeptidase.

No toxicity was observed with IV administration of HP-β-CD up to 12 g BD for 15 days.[15]

Data submitted by the sponsor for HP-β-CD

No new nonclinical toxicity studies of HP-β-CD or HP-β-CD in combination with voriconazole were submitted. The sponsor provided an updated assessment of HP-β-CD use in voriconazole powder for solution for infusion (Manufacturer, Oct 2015) and a copy of the Nov. 2014 draft EMA background review of cyclodextrin excipients in the response to consolidated questions raised by the TGA. It should be noted that Section 4. 'SPC Implications' in the Manufacturer review is based on the European summary of product characteristics (SmPC), and differs from the proposed Australian PI for Vorcon.

The draft EMA review was written 'In the context of the revision of the guideline'[16]. Its purpose was to define dose thresholds for labelling statements. One of the safety concerns was that the excipients guideline did not cover the paediatric population.[17]

[11] Gould S and Scott RC (2005). 2hydroxypropyl-β-cyclodextrin (HP-β-CD): a toxicology review. *Food and Chemical Toxicology* 43: 1451-1459.
[12] Kanter I and Erben RG (2012). Long-term [parenteral administration of 2-hydroxypropyl-β-cyclodextrin causes bobe loss. Toxicological Pathology 40: 742-750.
[13] Abdel-Rahman SM et al (2007). Single-dose pharmacokinetics of intravenous itraconazole and hydroxypropyl-beta-cyclodextrin in infants, children, and adolescents. *Antimicrob. Agents Chemotherap.* 2007; 51: 2668-2673.
[14] Stella VJ and He Q (2008). Cyclodextrins. *Toxicol. Pathol.* 2008; 36: 30-42.
[15] Loftsson T and Brewster ME (2010). Pharmaceutical applications of cyclodextrins: basis science and product development. *Journal of Pharmacy and Pharmacology* 62: 1607-1621.

The Manufacturer review noted that:

- Each 200 mg/vial of Vorcon contains HP-β-CD 2,400 mg/vial, which equates to 144 mg/kg/day at the recommended maximum voriconazole dose of 12 mg/kg/day (6 mg/kg twice daily). The maximum dose of HP-β-CD is therefore 7.2 g/day in a 50 kg adult.
- The maximum daily IV dose of HP-β-CD in itraconazole (Sporanox) is 16 g/day for the first 2 days followed by 8 g/day for the remainder of treatment.
- Single IV doses of HP-β-CD up to 3 g in humans were well tolerated and 470 mg/kg/day did not produce evidence of renal or liver damage.[18]
- A review of HP-β-CD concluded that HP-β-CD was non-toxic, at least for 14 days, if the dose was < 16 g/day.[13]
- A study of the safety, efficacy and pharmacokinetics of a single IV infusion of itraconazole 2.5 mg/kg and HP-β-CD 0.1 g/kg in 33 children aged from 7 months to 17 years showed average peak plasma concentrations of HP-β-CD comparable to or lower than those observed in adults after a 200 mg IV itraconazole dose, with plasma concentrations falling below the limit of detection within 12 hours. Serum chemistry and haematology were normal.[19]
- Animal toxicity studies conducted by oral or IV administration in mice, rats, monkeys and dogs for up to 12 months, including previously unpublished studies by AstraZeneca at IV doses ranging from 225 to 7,200 mg/kg/day, indicate that HP-β-CD is toxicologically safe, with clear no effect dose levels and reversible histopathological and biochemical changes.[20]

The relevant analysis (italics) for parenteral cyclodextrins from the draft EMEA review[4] is as follows:

'2.6. Parenteral products

Kinetics

*IV-administered cyclodextrins disappear rapidly from systemic circulation and are renally excreted intact. Systemically absorbed cyclodextrins distribute mainly in the extracellular compartments, and no deep compartments or storage pools are involved. The total plasma clearance for HP-β-CD and SBE-β-CD in all species tested is similar to the glomerular filtration rate. The (*half-life) *t½ varies from 20 to 100 minutes. Only RM-β-CD has a longer t½ compared to other cyclodextrins derivatives (7h), probably related to its ability to interact with cellular membranes [27].[18]*

Safety

Both α-CD and β-CD showed renal toxicity after parenteral administration and thus are generally not suitable for medicinal products given intravenously. Besides, β-CD has the additional disadvantage of an inherent low solubility, which makes it less suitable for medicines given parenterally. However, one IV product containing α-CD is on the market in Japan.

[16] Excipients in the label and package leaflet of medicinal products for human use' (CPMP/463/00 Rev. 1, July 2003)
[17] EMA (Feb 2012). Concept paper on the need for revision of the guideline on excipients in the label and package leaflet of medicinal products for human use (CPMP/463/00) draft.
[18] Stella VJ and He Q (2008). Cyclodextrins. *Toxicol. Pathol.* 36(1): 30-42.
[19] Abdel-Rahman SM et al (2007). Single-dose pharmacokinetics of intravenous itraconazole and hydroxypropyl-beta-cyclodextrin in infants, children, and adolescents. *Antimicrob. Agents Chemotherap.* 51(8): 2668-73.
[20] Gould S and Scott RC (2005). 2-hydroxyl-beta-cyclodextrin (HP-beta-CD): a toxicology review. *Food Chem. Toxicol.* 43(10): 1451-9.

The intravenous administration of 2000 mg/kg/day of γ-CD to rats for 1 month caused a slight impairment of the renal function. At 600 mg/kg/day for 3 months, this was only seen in the males. Vacuolization showed in the renal tubular epithelium of some rats receiving γ-CD at doses of 630 or 600 mg/kg/day in the 1 and 3 month study, respectively. However, degenerative changes were not observed in the kidneys, and the vacuolization was fully reversible on cessation of the treatment. No medicinal products with γ-CD for intravenous administration are used at the moment in Europe.

The effective intravenous dose of RM-β-CD to induce kidney damage in animals is even lower than that of β-CD, therefore, this modified CD is also not suitable for parenteral use.

HP-β-CD and SBE-β-CD can be found in marketed parenteral formulations with intravenous dosing of up to 16 g HP-β-CD daily in for example products with itraconazole and 14 g SBE-β-CD daily in products with voriconazole (in adults). In rats, a daily dose of up to 15,000 mg/kg SBE-β-CD for 14 days produced only vacuolation of the kidney tubular cells without loss of kidney function. Longer treatments caused these, mostly reversible effects, at lower doses of SBE-β-CD and HP-β-CD, indicating that duration of exposure may be an important parameter. The tubular vacuolation observed in the kidney is the result of a series of alterations in vacuolar organelles of the proximal tubule. These changes begin as an increase in size of apical vacuoles that is followed by the appearance of giant lysosomes. A transient increase in size of apical vacuoles is also observed as an adaptive response to the excretion of osmotic agents such as glucose, mannitol and dextran at extremely high concentrations. The NOEL in the rat is 50 mg/kg for HP-β-CD receiving daily IV injections for 3 months and 80 mg/kg for SBE-β-CD daily IV injections for 1 month, respectively. In humans, no side effects were observed after parenteral administration of up to 24 g of HP-β-CD daily for 15 days. HP-β-CD and SBE-β-CD are considered safe at relatively high doses and used most widely in parenteral products. Amounts of approximately 250 mg/kg/day for 21 days (HP-β-CD) or 6 months (SBE-β-CD) are found safe in humans older than 2 years.

However, these products are not indicated for new-born babies and infants under 2 years old, and for patients with renal impairment, because of insufficient toxicological knowledge in juveniles, and accumulation of cyclodextrins in the kidney at renal impairment (SmPCs Vfend, Vibativ and Sporanox). The major concern in children under 2 years old is the risk of osmotic nephrosis, because they have a lower renal function than adults. Based on ontogeny the lower glomerular filtration rate in young infants can lead to higher blood levels of cyclodextrins, leading to an increase in extra-renal adverse effects. The decreased renal tubular function might reduce the risk of renal toxicity due to lower intra-renal osmotic pressure. However, it is currently not known whether there is a risk of ontogeny-related direct tubular cell toxicity unrelated to osmotic pressure. A small number of neonates treated with SBE-β-CD containing products corresponding with up to 336 mg/kg/day for 18 to 24 days did not show significant toxicity. Two children of 5 years of age treated for Niemann-Pick Type C disease received 2500 mg/kg HP-β-CD intravenously twice weekly for more than one year, which was well tolerated. Treatment of infants from 7 months up to 5 years of age with HP-β-CD containing products caused no harmful effects at 100 mg/kg/day HP-β-CD given single dose or for a few days.

Conclusion

IV-administered cyclodextrins disappear rapidly from systemic circulation and are renally excreted intact. The t½ varies from 20 to 100 minutes, with the exception of RM-β-CD, which has a t½ of 7 h.

Alpha-CD, β-CD and RM-β-CD showed renal toxicity at relatively low doses after parenteral administration and thus are not suitable for medicinal products given intravenously. High doses of ≥ 600 mg/kg of γ-CD showed only reversible vacuolation in the renal tubular epithelium of rats.

HP-β-CD and SBE-β-CD at high doses can cause vacuolation of the kidney tubular cells without loss of kidney function in animals. This transient increase in size of apical vacuoles is also observed as an adaptive response to the excretion of osmotic agents such as glucose, mannitol and dextran at extremely high concentrations. Longer treatments cause these mostly reversible effects, at lower doses of SBE-β-CD and HP-β-CD, indicating that duration of exposure may be of importance. HP-β-CD and SBE-β-CD are considered safe at relatively high doses and used most widely in parenteral products. Amounts of approximately 250 mg/kg/day are found safe in humans older than 2 years when given 21 days (HP-β-CD) or 6 months (SBE-β-CD). Because of their lower renal function, children less than 2 years old may theoretically be less vulnerable to renal toxicity, whereas it is likely to lead to higher blood levels (slower elimination). However, a few cases on the use of intravenous products with high doses of HP-β-CD and SBE-β-CD in neonates and young children have been reported without signs of toxicity.'

3. Risk assessment and thresholds

In order to find indications for the thresholds of triggering labelling, including quantitative information and safety statements in the package leaflet, the Permitted Daily Exposures (PDEs) are calculated according to the Guideline for Residual Solvents (CPMP/ICH/283/95)[21] [14], see tables 2, 3(Table 3 (presented as Table 8 below)*) and Table (Table 4* (presented as Table 9 below)*). The calculations are based on estimations of no observed adverse effect levels (NOAELs) derived from the literature referred to in section 2. A complicating factor is that not all studies have been performed with the cyclodextrins only and that the cyclodextrins may have influenced the effects of the active substance of a medicinal product. For example the nephrotoxic effect of telavancin is substantially reduced by HP-β-CD (EPAR Vibativ), and bioavailability and permeability of active substances may be increased by cyclodextrins (section 2). However, since there are no data where cyclodextrins increase the toxic effects of active substances, the estimated NOAELs given below are considered reasonable, with or without active substances. The safe treatment time is considered to be at least 3 weeks, but presumably much longer.*

Table 8: Parenteral permitted daily exposures of cyclodextrins in different species

Parenteral	α-CD	γ-CD	HP-β-CD	HP-β-CD	SBE-β-CD	SBE-β-CD
Species	rat	rat	rat	human	rat	human
NOAEL, mg/kg/day	100	200	50	320	80	280
F1	5	5	5	1	5	1
F2	10	10	10	1	10	1
F3	10	5	5	1	5	1
F4 = F5 = 1						
PDE mg/kg/day	0,2	0,8	0,2	320	0,32	280

Bodyweight human = 50 kg F1 = A factor to account for extrapolation between species F2 = A factor of 10 to account for variability between individuals F3 = A variable factor to account for toxicity studies of short-term exposure F4 = A factor that may be applied in cases of severe toxicity F5 = A variable factor that may be applied if the no-effect level was not established

[21] Guideline for Residual Solvents (CPMP/ICH/283/95)

Remark the difference between the calculated PDEs and established safe human use of parental administered HP-β-CD and SBE-β-CD: 10 to 1000 times! Very probably, the calculated PDEs are large overestimations of risk.

But because of insufficient data, it is still suggested to introduce an extra safety factor of 10 for newborn babies and infants below 2 years.

Based on human data, and where these are not available, estimations based on animal data, table 4 (Table 9 below) *shows suggested thresholds of triggering safety statements.*

Table 9: Suggested thresholds (TH) above which adverse effects may occur

Parenteral	α-CD	β-CD	Y-CD	RM-β-CD	HP-β-CD/SBE-β-CD[1]
PDE, mg/kg/day	0.2*	N	0.8	N	300*
TH adult	0.2*	-	0.8	-	300*
TH neonate	0.02*	-	0.08	-	10*

*: used in medicinal products N: No data and indication for respective route of administration.
±1: Estimation based on properties. [1] Although the molecular weights of HP-β-CD and SBE-βCD differ approximately 1.5 times, they can be taken together from a property and toxicological point of view.

Recommendations for the guideline

Cyclodextrins are currently not included in the European Commission Guideline on excipients in the label and package leaflet of medicinal products for human use [15].

Although the oral availability of cyclodextrins is very low, high doses may cause reversible diarrhea and cecal enlargement in animals, and therefore also in humans to some minimum extent.

Depending on the amount, cyclodextrins may influence the permeability of tissues and therefore the bioavailability of active substances given topically (nasal, rectal, dermal, ocular).

Cyclodextrins can cause nephrotoxic effects in animals at high systemic exposure. Up to now, there is no proof of these effects in humans; however, data in children less than 2 years old are scarce.

In conclusion, safety information in the package leaflet may be desirable in products with substantial contents of cyclodextrins as excipient. However, because of limited information and possible interaction with active substances, the presence of cyclodextrins should always be stated as a precaution (zero thresholds).'

Nonclinical summary and conclusions

Summary

- At the Vfend IV voriconazole loading dose of 6 mg/kg BD for 24 hours and maintenance dose of 4 mg/kg BD the respective doses of SBE-β-CD (voriconazole: SBE-β-CD ratio 1:16) are 192 and 128 mg/kg/day in a 50 kg adult. At the same voriconazole doses in Vorcon the respective doses of HP-β-CD (voriconazole: HP-β-CD ratio 1:12) are 144 mg/kg/day and 96 mg/kg/day.
- No Australian-registered IV products containing HP-β-CD were identified. Australian registered oral products containing HP-β-CD are intraconazole (Sporanox) oral

solution and cladribine (Movectro). A small number of IV products containing HP-β-CD have been approved in the USA, including itraconazole (Sporanox IV, discontinued), mitomycin C (Mitozytrex), and telavancin (Vibativ). The maximum IV dose of HP-β-CD in Sporanox IV was 320 mg/kg/day for 2 days, followed by 160 mg/kg/day for up to 14 days. Sporanox IV was contraindicated in patients with severe renal impairment since HP-β-CD is eliminated through glomerular filtration and may accumulate (US label).

- No new nonclinical studies of HP-β-CD or HP-β-CD combined with voriconazole were submitted. Previously evaluated IV studies for HP-β-CD included 3 month IV toxicity studies in rats and dogs at doses up to 400 mg/kg/day. The main effects were in the kidney (vacuolated cortical tubuli, swollen epithelial cells in renal pelvis and bladder), liver (increased Kupffer cells, increased ALT, AST) and lungs (increased foamy cells) and adrenals (increased weight). NOAELs were 50 mg/kg/day in rats and 100 mg/kg/day in dogs. Fourteen day subacute and 90 day IV toxicity studies at a dose of 200 mg/kg on alternate days in rats and cynomolgus monkeys showed no effects.[10] A more recent published study reported decreased bone mineral density and increased bone resorption in rats administered HP-β-CD 50 or 200 mg/kg/day SC.[12]
- Standard in vitro and in vivo genotoxicity studies with HP-β-CD were negative.
- Two year dietary carcinogenicity studies of in HP-β-CD mice and rats at doses of 500 to 5000 mg/kg/day showed no increases in tumours in mice, and significant increases in the incidences of exocrine pancreatic adenomas and adenocarcinomas at all doses in rats. A 26 week oral study in Tg(HRAS) mice with 431 mg/kg/day of HP-β-CD showed no tumourigenicity.
- A rat fertility IV study showed no effects of HP-β-CD on male or female fertility up to 400 mg/kg/day (HD). Embryofetal development studies with HP-β-CD in rats and rabbits showed no effects up to 400 mg/kg/day (HD). A rat peri-postnatal study showed lower mean pup weights and reduced survival at 400 mg/kg/day (HD), probably secondary to maternotoxicity. Standard in vitro and in vivo genotoxicity studies were negative.
- A safety assessment of HP-β-CD excipient in Vorcon (Manufacturer, Oct 2015) and a draft EMA review of cyclodextrins [4]were submitted in response to TGA questions. The EMA review determined respective permitted daily exposures (PDEs) for HP-β-CD of 300 mg/kg/day in adults and 10 mg/kg/day in infants (< 2 years), based on human data. The neonatal PDE incorporated a 10 fold safety factor due to the limited data.
- The kidney was the most sensitive organ to HP-β-CD and SBE-β-CD in animals, with renal tubular vacuolation evident in rats, dogs and monkeys. There is a potential risk that renal impairment could lead to HP-β-CD accumulation and manifestation of other toxic effects of HP-β-CD with IV use. The Vorcon PI contains adequate statements regarding this possibility. Overall the data are considered adequate for Vorcon registration in adults.
- There are no nonclinical data for HP-β-CD in young animals. Human safety data for both HP-β-CD and SBE-β-CD are very limited in children and adolescents (2 to 12 years of age) in terms of subject numbers and duration of treatment. It is recommended that clinical advice is sought on registration of Vorcon in children and adolescents.
- The powder for injection drug product shelf-life specification levels for Impurities A and J exceed the ICH Q3B(R2) thresholds, and both impurities A and J in all product forms exceed the ICH M7 step 4 acceptable daily intakes. Qualification studies included a 28 day IV repeat dose toxicity study in rats and in silico analyses. Neither impurity

displays any genotoxic potential based on the currently available data; both impurities are considered qualified at the proposed limits.

Recommendations

There are no nonclinical objections to registration of generic voriconazole (Vorcon) containing HP-β-CD excipient in adults. There are no nonclinical data for the HP-β-CD excipient in young animals. Clinical data for HP-β-CD excipient in children and adolescents are very limited in terms of subject numbers and duration of treatment, and it is recommended that clinical advice is sought regarding use in those age groups.

V. Pharmacovigilance findings

The TGA granted a waiver from the requirement for a Risk Management Plan for this application.

VI. Overall conclusion and risk/benefit assessment

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

Introduction

This is a submission seeking registration of Vorcon as a generic voriconazole to be supplied as oral tablets (50 mg and 200 mg) and lyophilized powder for injection (200 mg). This submission is being referred to the ACPM for advice because Vorcon powder for injection contains a new excipient for which adequate toxicology or clinical data are not available to support use of in young children (2 to 12 years of age) due to an identified potential risk of renal toxicity.

The innovator product is Vfend (voriconazole 50 mg and 200 mg tablets and 200 mg lyophilized powder for injection) from Pfizer Australia, which was approved in 2002 for use in serious, deep fungal infections in patients from 2 years of age and above, including a prophylaxis indication. The proposed therapeutic indications, patient population, age groups and instruction for dosage and administration for the generic product Vorcon are identical to those currently approved for the innovator product Vfend.

In accordance with the regulatory requirements for a generic product ('same active ingredient, in same amount, same dosage form'), the submission was based on an abridged dossier which did not include nonclinical or clinical data. A Risk Management Plan (RMP) was also not required.

The abridged dossier contained appropriate in vivo studies in which bioequivalence was satisfactorily demonstrated for the oral products, whereas the powder for injection did not require bioequivalence data as the expected bioavailability is considered 100%. The quality summary is provided. The submission was not referred to the Pharmaceutical Subcommittee (PSC).

The proposed Vorcon powder for injection, but not the oral forms, includes a different solubilising excipient hydroxypropyl-β-cyclodextrin (HP-β-CD) compared to the innovator Vfend powder for injection which contains sulfobutylether-β-cyclodextrin sodium (SBE-β-CD). No specific explanation has been provided for choosing a different solubilising agent to that in the innovator product. *The sponsor is requested to provide comment on the compulsion to use HP-β-CD in place of SBE-β-CD in its pre-ACPM response.*

A number of oral generics and one generic powder for injection of voriconazole are currently registered in Australia. All contain SBE-β-CD as excipient same as the innovator product. No parenteral product currently on ARTG could be identified with HP-β-CD as an excipient.

A number of generic voriconazole submissions are currently under review with HP-β-CD as excipient in the injectable preparation and this issue applies to all.

Quality

In their evaluation of quality data, the quality evaluators sought opinion from the toxicology area regarding the use of HP-β-CD in place of SBE-β-CD.

Nonclinical

There are no nonclinical objections to registration of generic voriconazole (Vorcon) containing HP-β-CD excipient in adults. There are no nonclinical data for the HP-β-CD excipient in young animals. Clinical data for HP-β-CD excipient in children and adolescents are very limited in terms of subject numbers and duration of treatment, and it is recommended that clinical advice is sought regarding use in those age groups.

SBE-β-CD and HP-β-CD are closely related cyclodextrins and have similar toxicological profiles in adult animals. It is likely that this would also apply to juveniles animals (corresponding to 2 to 12 year olds), but direct nonclinical data are lacking.

An EMA review of cyclodextrins for labelling purposes[4] which became available in 2014 also states that SBE-β-CD and HP-β-CD can be taken together from a property and toxicological point of view. The review concluded that parenteral cyclodextrin permitted daily exposure (PDE) in humans for both juveniles and adults was 320 mg/kg/day and suggested a threshold of 300 mg/kg/day (both HP-β-CD and SBE-β-CD) for triggering inclusion of safety statements in product information documents. This PDE limit was considered as very conservative.

However, the EMA document also differentiates HP-β-CD from SBE-β-CD with respect to the duration of treatment as follows:

> 'In humans, no side effects were observed after parenteral administration of up to 24 g of HP-β-CD daily for 15 days. HP-β-CD and SBE-β-CD are considered safe at relatively high doses and used most widely in parenteral products. Amounts of ca 250 mg/kg/day for 21 days (HP-β-CD) or 6 months (SBE-β-CD) are found safe in humans older than 2 years.'

Clinical

The Delegate notes that the EMA statement as it appears above may imply that 21 days safe limit with HP-β-CD is applicable irrespective of age (from 2 years above).

Note that each Vorcon 200 mg voriconazole injection vial contains 2,400 mg HP-β-CD (innovator product Vfend contains 3,200 mg SBE-β-CD per vial). The recommended daily dose of voriconazole in children (2 to 12 years) is 6 mg/kg/day twice daily that is 12 mg/kg/day equivalent to a daily load of HP-β-CD of 144 mg/kg/day. The daily voriconazole dose in this age group can be increased to 7 mg/kg/day twice daily. Thus daily load of HP-β-CD can be as high as 168 mg/kg/day, but below the 250 mg/kg/day quoted above in the EMA review.

The safety risk identified with HP-β-CD and SBE-β-CD is proximal renal tubular vacuolisation, as has also been reported transiently with osmotic agents at very high concentrations. The effect appears to be dose and duration dependent and may gradually reverse on cessation of the drug. Both HP-β-CD and SBE-β-CD are excreted intact via passive glomerular filtration and appear to cause this 'osmotic nephrosis' effect during transit through the renal tubules likely due to the high solute load. A direct cellular toxic effect on renal tubules has not been confirmed.

Further information from the sponsor

Further information provided by the sponsor, following a request for information from the TGA indicated that a number of generic voriconazole products with HP-β-CD excipient are approved in Europe. The Public Assessment Report[22] in relation to these approvals states as follows:

> 'The MAH has selected a different cyclodextrine, that is hydroxypropylbetadex, than used for Vfend, that is sulfobutylether beta-cyclodextrin sodium.
>
> Cyclodextrins are cyclic (α-1,4)-linked oligosaccharides of α-D-glucopyranose. Cyclodextrins contain a relatively hydrophobic central cavity and a hydrophilic outer surface. They can increase the equilibrium solubility of some hydrophobic molecules. Several commercial oral and injectable cyclodextrin-based products are available throughout the world. The two most common and preferred water-soluble β-cyclodextrin derivatives are hydroxypropylbetadex and sulfobutylether-β-cyclodextrin.
>
> The use of hydroxypropylbetadex has also been evaluated in children. No significant age dependence was observed for AUC and C_{max} among the children evaluated. Concentrations of hydroxypropyl-betadex fell below quantifiable limits by 12 hours. Overall, the use of hydroxypropylbetadex instead of sulfobutylether beta-cyclodextrin is acceptable. The complex is considered rapidly 'dissolved' after the blood stream.'

However, it is noted that EU approved prescribing documents[23] also contain the following statement under 'Pharmacokinetic Properties':

> 'Long term safety of hydroxypropylbetadex in humans is limited to 21 days (250 mg/kg/day).'

Again the Delegate notes that the statement appears irrespective of age group.

Note that the situation is different in the USA where parenteral products, in most cases, are also required to have same excipients as the innovator to be considered a generic. It is not clear whether any parenteral voriconazole products with HP-β-CD excipient are currently approved in the USA. *The sponsor is requested to provide this information in its pre-ACPM response.*

The sponsor in its reply to the TGA's request for information also provided published studies (nonclinical and clinical) and a sponsor justification. These are summarised below:

[22] Public Assessment Report - Scientific discussion: Voriconazol Pharmathen 200 mg powder for solution for infusion (Voriconazole) <https://mri.cts-mrp.eu/Human/Downloads/NL_H_3159_001_PAR.pdf> (accessed 2017)
[23] Voriconazole 200mg Powder for Solution for Infusion <https://www.medicines.org.uk/emc/medicine/32220>

Additional toxicology data

The TGA review of additional nonclinical data (De Schaepdrijver et al 2015[24] and Tanaka et al 2015[25]) found that HP-β-CD-associated osmotic nephrosis lesions in the rat renal proximal tubules are likely to be cumulative and took approximately 3 months to reverse (consistent with cell turnover time) in adult rats. The TGA review further noted as follows: *'Notably, the clearance rate of HP-β-CD in rats generally correlates with the maturation of renal function during development i.e. increased with age and renal functional maturation. Adequate renal function is critically important in terms of the safe use of HP-β-CD that is, reduced renal function, either due to immaturity or pathology, will increase the risk of HP-β-CD associated toxicity.'*

And:

'The new study in juvenile rats confirmed the kidney tubular epithelium as the main toxicity target for HP-β-CD. Juvenile rats were not more sensitive than adults to the renal effects, however renal toxicity occurred at subclinical exposures in both juvenile and adult rats, and adult dogs, hence clinical advice is sought regarding the potential for renal toxicity. Warnings in the PI regarding the possibility of renal toxicity appear adequate.'

And concluded: up to here

*'The juvenile rat study demonstrates that the both the level of HP-β-CD exposure (approximately 17 to 20 X the NOAEL in rats at (*post natal day) *PND 44; based on (*body surface area*) BSA) and the duration of treatment associated with Vorcon powder for injection use will likely result in functionally significant (that is adverse) renal tubular osmotic nephrosis. Human clinical data and clinical advice are needed regarding the levels of HP-β-CD in the Vorcon powder for injection product and the duration of use of this excipient.'*

Additional clinical data

Abdel-Rahman et al (2007)[13]

This was a pharmacokinetic (PK) study which showed that PK profile of HP-β-CD, following a single intravenous infusion (over on hour) of itraconazole with HP-β-CD (0.1 g/kg) as carrier, was similar in children below and above 12 years of age and that HP-β-CD plasma Clearance equates glomerular filtration rate (GFR). This paper, along with another (Grigull et al 2007)[26], is also cited in the EMA review with the following comment: '*Treatment of infants from 7 months up to 5 years of age with HP-β-CD containing products caused no harmful effects at 100 mg/kg/day HP-β-CD given single dose or for a few days.'*

Hastings et al (2010)[27]

In this study HP-β-CD was investigated as active agent in the treatment of Niemann-Pick Type C disease (NPC). This paper is also cited in the EMA review with the following comment: *'Two children of 5 years of age treated for Niemann-Pick Type C disease received 2500 mg/kg HP-β-CD intravenously twice weekly for more than one year, which was well tolerated.'*

[24] De Schaepdrijver L, et al. 2015 Juvenile Animal Testing of Hydroxypropyl-β-Cyclodextrin in Support of Pediatric Drug Development. *Reproductive Toxicology* 2015; 56: 87-96

[25] Tanaka Y et al. (2015) Efficacy of 2-Hydroxypropyl-β-cylodextrin in Niemann-Pick Disease Type C Model Mice and Its Pharmacokinetic Analysis in a Patient with the Disease*. Biol. Pharm. Bull.* 2015; 38: 844-851

[26] Grigull et al (2007). Intravenous and oral sequential itraconazole antifungal prophylaxis in paediatric stem cell transplantation recipients: A pilot study for evaluation of safety and efficacy. *Pediatric Transplantation* 2007; 11: 261-266.

[27] Hastings, C. (2010) Request for intrathecal delivery of HPBCD for Niemann Pick Type C patients, Caroline Hastings, M.D. Principal Investigator Department of Pediatric Hematology Oncology Children's Hospital & Research Center Oakland Submission Date to FDA: August 13, 2010, http://addiandcassi.com/wordpress/wp-content/uploads/Hempel-Cyclodextrin-Intrathecal-FDA-Filing-2010-Aug.pdf)

Other published papers

The EMA review also refers to other published papers involving exposure of SBE-β-CD in neonates with the following comment:

'A small number of neonates treated with SBE-β-CD containing products corresponding with up to 336 mg/kg/day for 18 to 24 days did not show significant toxicity.'

Matsuo et al (2013)[28]

This is a case report of 2 patients who received HP-β-CD by intravenous infusion for the treatment of NPC starting with a dose of 80 mg/kg increased gradually to 2 g/kg given twice weekly (14 years old) or 2.5 g/kg given three times per week (4 years old female child) for a period of 2 years. The authors noted the potential for renal toxicity but reported no adverse effects. The PK results in one patient in this study were reported in another paper (Tanaka et al 2015) which found that PK parameters of HP-β-CD such as systemic Clearance (2.89 L/h) and volume of distribution (0.26 L/kg) were consistent with the physiological parameters such as GFR (2.65 L/h) and extracellular fluid volume (0.25 L/kg) respectively.

Risk-benefit analysis

Delegate's considerations

1. In making a decision for this generic voriconazole powder for injection, the issue is whether HP-β-CD and SBE-β-CD excipients can be considered to have equivalent toxicity with respect the osmotic nephrosis effect on proximal renal tubules in children and adults from 2 years and above.
2. The statements in the EMA review of cyclodextrins (Amounts of approximatley 250 mg/kg/day for 21 days (HP-β-CD) or 6 months (SBE-β-CD) are found safe in humans older than 2 years) and the EU approved prescribing information for voriconazole/HP-β-CD injectable products (Long term safety of hydroxypropylbetadex in humans is limited to 21 days (250 mg/kg/day)) appear to suggest that clinical use may not exceed 21 days in any age group.

   It is to be noted that the EMA document is not an adopted regulatory document. In addition, the recommendations regarding permitted daily exposure (PDE) cut-off are in draft form, conservative and have associated considerable uncertainty. These are also intended to trigger HP-β-CD related advisory statements in the prescribing information rather than be used as a risk/benefit assessment tool.

   The recommendation from the TGA review of toxicology concludes that data are sufficient to support the proposed use above 12 years of age in line with the approval in the innovator product.
3. Hence the outstanding issue is the use of voriconazole/HP-β-CD in 2 to 12 year old age group for which the toxicology data in juvenile animals are not sufficient. The clinical data are also very limited.

   It is noted that similar issues arose at the time of registration of voriconazole/SBE-β-CD (Vfend).

   The Delegate, at that time, in requesting advice from the then Australian Drug Evaluation Committee (ADEC), noted as follows: *'The preclinical evaluation has recommended rejection of use in children on the basis of absence of studies in juvenile*

[28] Matsuo M et al (2013). Effects of cyclodextrin in two patients with Niemann–Pick Type C disease. *Molecular Genetics & Metabolism* 2013; 108: 76-81.

animals. I consider this recommendation should be balanced against the severity of the underlying condition, availability of alternative therapies and the human paediatric experience that has occurred to date. I consider use can be supported in treatment of serious fungal injections which are life-threatening…'

The ADEC noted as follows: '*There were some initial Part II (quality) concerns which had subsequently been resolved. There were no outstanding Part II concerns, but SBECD, used as vehicle in the IV form and renally excreted, caused some concern.'*

And

'*The committee endorsed the PI changes proposed by the Delegate. Additional data on the possible toxicity of the excipient SBECD* (SBE-β-CD), *in the IV form, especially on haemodialysis patients were desirable. The PI should include a precautionary statement in relation to use of the IV route in dialysis patients and those with poor creatinine clearance.'*

Subsequently, the innovator product (Vfend) was approved for the therapeutic indication as they stand now (including preventative use) from 2 years of age and older.

4. The regulatory options in the present circumstance are as follows:

- Rejection of voriconazole/HP-β-CD powder for injection as 'not a generic form of voriconazole/ SBE-β-CD powder for injection'.

  This is considered not appropriate as it does not manage risk relative to benefit in the context of use in serious, life threatening disease/infection.

- Approval of voriconazole/HP-β-CD powder for injection with an advisory that 'long term safety of HP-β-CD in humans is limited to 21 days' applicable to all age groups.

  This is not supported as recommendation from the Toxicology area concluded that data allow use from 12 years of age and above, consistent with the approved use in the innovator product.

- Approval of voriconazole/HP-β-CD powder for injection with an advisory that 'long term safety of HP-β-CD in humans is limited to 21 days' specifically in 2-12 years age group.

  Pending advice from the ACPM, this is the preferred option as it considers risk/benefit in a graded manner, acknowledges uncertainty in a specified sub-population and provides clinical direction.

  If this option is adopted, it presents the difficulty of automatic assumption of efficacy/safety/directions for usage same as the innovator by the prescribing physicians. Hence, effective mechanisms for communicating this important difference to the health professionals and consumer are required. These may include information letter to health professionals, label statements, pharmacist information, patient education leaflets and RMP/ASA. *The sponsor is requested to provide comment and proposals in this regard in its pre-ACPM response.*

- Approval of voriconazole/HP-β-CD powder for injection as a 'generic of voriconazole/SBE-β-CD powder for injection' without any restriction of use.

  Pending advice from the ACPM, this is not the preferred option as it ignores uncertainty and lack of data which has been acknowledged elsewhere by the regulators. If this option is adopted, the PI will still include all relevant texts regarding HP-β-CD but not include statement regarding lack of data for use more than 21 days. *The sponsor is requested to provide any post-market usage data and safety surveillance data available from voriconazole/HP-β-CD containing injectable products available overseas which might support this use.*

It may also be noted here, that the Australian approved PI for the innovator product Vfend does not have a statement about re-consideration of risk/benefit beyond 180 days of treatment with voriconazole, as is the case in overseas approvals in EU. There is currently no proposal to change this aspect and consistency with the innovator PI will be maintained.

Proposed action

The Delegate had no reason to say, at that time, that the application for Vorcon should not be approved for registration.

Request for ACPM advice

ACPM was requested to provide advice on the following specific issues:

1. Whether generic Vorcon 200 mg powder for injection can be approved same as the innovator product Vfend 200 mg powder for injection or a restriction of duration of use to 21 days is appropriate in 2 to 12 years old age group?
2. Advice is requested on how best to control risk, and prevent presumption of automatic extrapolation of efficacy/safety/directions for use from innovator to the generic if the above restriction of use if placed with respect to 2 to 12 years old patients.

The Committee was also requested to provide advice on any other issues that it considers may be relevant to a decision on whether or not to approve this application.

Response from sponsor

The proposed Vorcon powder for injection, but not the oral forms, includes a different solubilising excipient hydroxypropyl-β-cyclodextrin (HP-β-CD) compared to the innovator Vfend powder for injection which contains sulfobutylether-β-cyclodextrin sodium (SBE-β-CD). No specific explanation has been provided for choosing a different solubilising agent to that in the innovator product. The sponsor is requested to provide comment on the compulsion to use HP-β-CD in place of SBE-β-CD in its pre-ACPM response.

Sponsor response:

The use of SBE-β-CD with voriconazole is patent protected (EP-B-1001813) until June 2018. The HP-β-CD derivative has been used in Manufacturer's formulation providing a final drug product with equivalent in vitro and in vivo activity to the reference product, as detailed in the quality section and in further communications with TGA during the submission process.

Note that the situation is different in the USA where par enteral products, in most cases, are also required to have same excipients as the innovator to be considered a generic. It is not clear whether any parenteral voriconazole products with HP-β-CD excipient are currently approved in the USA. The sponsor is requested to provide this information in its pre-ACPM response.

The applicant is not aware of any voriconazole products in the USA that utilises HP-β-CD as a solubilising agent.

If this option is adopted, it presents the difficulty of automatic assumption of efficacy / safety / directions for usage same as the innovator by the prescribing physicians. Hence, effective mechanisms for communicating this important difference to the health professionals and consumer are required. These may include information letter to health professionals, label statements, pharmacist information, patient education leaflets and RMP / ASA. The sponsor is requested to provide comment and proposals in this regard in its pre-ACPM response.

Section 4.2 of the SmPC of the approved European SPC for the applicant's product, does not limit administration to 21 days in any age group. This section cautions that data are limited and that careful assessment of risk-benefit are warranted. The statement 'Long term safety of hydroxypropylbetadex in humans is limited to 21 days (250 mg/kg/day)' appears in Section 5.2, providing the background for the careful assessment of risk-benefit. There is no requirement, in Europe, for physicians to limit use to 21 days of the intravenous formulation should they warrant the risk-benefit is favourable for the patient. The EMA review and statement states that although data is limited beyond 21 day use, based on their assessment the safety of HP-β-CD was estimated to be at least as safe as SBE-β-CD. Based on the conservative nature of their assessment, no restrictions for use were applied to the 2 to 12 year old age group. The applicant also provided a few case reports of extended use of high dose HP-β-CD in patients with Niemann–Pick type C (NPC) disease to showcase its safe use beyond 21 days. In two patients administered HP-β-CD for greater than 8 months (Matsuo et al and Tanaka et al papers),[28, 25] the exposure to HP-β-CD was more than six times the maximum they would undergo under voriconazole posology, and neither displayed toxicity. Of note, the oral formulation does not contain HP-β-CD and physicians are free to switch to this formulation should concerns over HP-β-CD use arise. As such, there was no request to include a letter to health professionals, label statements, pharmacist information, patient education leaflets and RMP during the European submissions

Pending advice from the ACPM, this is not the preferred option as it ignores uncertainty and lack of data which has been acknowledged elsewhere by the regulators. If this option is adopted, the PI will still include all relevant texts regarding HP-β-CD but not include statement regarding lack of data for use more than 21 days. The sponsor is requested to provide any post-market usage data and safety surveillance data available from voriconazole/HP-β-CD containing injectable products available overseas which might support this use.

Sponsor response:

This is the applicant's preferred option. The parenteral and tablet formulations have been approved in Europe; however they cannot be marketed until July when a basic API patent expires. Since the formulations have not been placed on any markets, no pharmacovigilance data has been generated. Please note periodic safety update report (PSUR) for voriconazole generic products is not required as per European reference dates (EURD) list in Europe. Thus, no PSUR is available.

Adverse reactions update

The parenteral and tablet formulations have been approved in Europe; however they cannot be marketed until July when the API patent expires. Since the formulations have not been placed on any markets, no pharmacovigilance data has been generated. Therefore, there are no serious unexpected adverse drug reactions to report which are not mentioned in the proposed Australian PI.

Advisory committee considerations

The Advisory Committee on Prescription Medicines (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, agreed with the Delegate and considered Vorcon film coated tablets 50 mg and 200 mg and lyophilised powder for injection 200 mg containing voriconazole to have an overall positive benefit–risk profile for the proposed indication;

Voriconazole is indicated for the 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 risk of developing invasive fungal infections. The indication is based on studies including patients undergoing haematopoietic stem cell transplantation.

In making this recommendation the ACPM

- Was of the view that the advisory 'long term safety of HP-β-CD in humans is limited to 21 days' specifically in the 2 to 12 years age group should be included in the PI.
- Advised that the sponsor should provide post-market usage data and safety surveillance data to the TGA from voriconazole/HP-β-CD containing injectable products available overseas, including Periodic Safety Update Reports to the TGA as a condition of approval.

Proposed Product Information (PI) / Consumer Medicine Information (CMI) amendments

The ACPM agreed with the Delegate to the proposed amendments to the PI and CMI and specifically advised on the inclusion of the following:

- noted that reference to hydroxypropyl beta cyclodextrin (HP-β-CD) in the PI should be changed to hydroxypropylbetadex as per the naming convention on the TGA website: https://www.tga.gov.au/updating-medicine-ingredient-names-list-affected-ingredients.
- repeat the precaution statement included under *PRECAUTIONS, 'Renal': 'Oral voriconazole should be administered to these patients unless an assessment of the risk to the patient justifies the use of intravenous voriconazole*' under a new heading *PRECAUTIONS: 'Paediatric'* to remind prescribers that prolonged use of intravenous therapy has at this time an unknown safety risk due to the inclusion of a different solubilising agent to the innovator.

Specific advice

The ACPM advised the following in response to the delegate's specific questions on this submission:

1. *Whether generic Vorcon 200 mg powder for injection can be approved same as the innovator product Vfend 200 mg powder for injection or a restriction of duration of use to 21 days is appropriate in 2 to 12 years old age group?*

The ACPM noted that there may be further clarification on the safety of HP-β-CD when pharmacovigilance data are available after the product is marketed in the EU. The ACPM advised that appropriate pre-clinical studies would also provide further clarification on the safety of HP-β-CD. However, until these studies are completed, due to the uncertainty regarding safety of prolonged use in the 2 to 12 years of age group, the ACPM advised that the following advisory statement for voriconazole powder for injection should be specifically applied to that age group: '*long term safety of HP-β-CD in humans is limited to 21 days*.'

2. *Advice is requested on how best to control risk, and prevent presumption of automatic extrapolation of efficacy/safety/directions for use from innovator to the generic if the above restriction of use if placed with respect to 2 to 12 years old patients.*

The ACPM advised that there should be a clear description of the issue regarding the safety of the solubilising agent, HP-β-CD, in the PI. In addition, the precaution statement included under PRECAUTIONS, 'Renal': 'Oral voriconazole should be administered to these patients unless an assessment of the risk to the patient justifies the use of intravenous Voriconazole 'should be repeated under a new heading PRECAUTIONS: 'Paediatric' to remind prescribers that the prolonged use of intravenous therapy may have inherent risk. The ACPM was of the view that the sponsor should also provide any post-market usage data and safety surveillance data from voriconazole/HP-β-CD containing injectable products when available from overseas.

The Committee is also requested to provide advice on any other issues that it considers may be relevant to a decision on whether or not to approve this application.

- The ACPM noted that reference to hydroxypropyl beta cyclodextrin in the PI is now referred to as hydroxypropylbetadex as per the naming convention on the TGA website: https://www.tga.gov.au/updating-medicine-ingredient-names-list-affected-ingredients. The PI should be changed accordingly.

The ACPM advised that 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 Vorcon Voriconazole 50 mg tablet, 200 mg tablet and 200 mg powder for injection vial, indicated for:

> *Voriconazole is indicated for the 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 risk of developing invasive fungal infections. The indication is based on studies including patients undergoing haematopoietic stem cell transplantation.*

Attachment 1. Product Information

The PI for Vorcon approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

Therapeutic Goods Administration

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