



Australian Government

Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Micafungin (as sodium)

Proprietary Product Name: Mycamine

Sponsor: Astellas Pharma Australia Pty Ltd

August 2013

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- 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, in that it will provide 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.

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Contents

I. Introduction to product submission	5
Submission details	5
Product background	5
Regulatory status	7
Product Information	7
II. Quality findings	7
Drug substance (active ingredient)	7
Drug product	8
Biopharmaceutics	9
Advisory committee considerations	9
Quality summary and conclusions	9
III. Nonclinical findings	9
Introduction	9
Pharmacology	10
Pharmacokinetics	14
Toxicology	15
Nonclinical summary and conclusions	25
IV. Clinical findings	27
Introduction	27
Pharmacokinetics	27
Pharmacodynamics	29
Efficacy	30
Safety	34
List of questions	36
Clinical summary and conclusions	36
V. Pharmacovigilance findings	37
Risk management plan	37
VI. Overall conclusion and risk/benefit assessment	43
Quality	43
Nonclinical	43
Clinical	44
Risk management plan	52
Risk-benefit analysis	52
Outcome	58
Attachment 1. Product Information	58

Attachment 2. Extract from the Clinical Evaluation Report _____ 58

I. Introduction to product submission

Submission details

<i>Type of Submission:</i>	New Chemical Entity
<i>Decision:</i>	Approved
<i>Date of Decision:</i>	2 May 2013
<i>Active ingredient:</i>	Mycafungin (as sodium)
<i>Product Name:</i>	Mycamine
<i>Sponsor's Name and Address:</i>	Astellas Pharma Australia Pty Ltd Level 4, 6 Eden Park Drive Macquarie Park NSW 2113
<i>Dose form:</i>	Powder for injection
<i>Strengths:</i>	50 mg and 100 mg
<i>Container:</i>	Glass vial
<i>Pack sizes:</i>	1 and 10
<i>Approved Therapeutic use:</i>	Mycamine is indicated for: <ul style="list-style-type: none">• treatment of invasive candidiasis in children and adults• treatment of oesophageal candidiasis in adults, adolescents greater than or equal to 16 years of age and the elderly patients for whom intravenous therapy is appropriate• prophylaxis of <i>Candida</i> infection in children and adult patients undergoing allogeneic haematopoietic stem cell transplantation or patients who are expected to have neutropenia (absolute neutrophil count < 500 cells/μL) for 10 or more days.
<i>Route of administration:</i>	Intravenous infusion
<i>Dosage (abbreviated):</i>	Once daily (see attached Product Information for full <i>Dosage and Administration</i>)
<i>ARTG Numbers:</i>	196108 and 196109

Product background

Micafungin (as sodium) is a water soluble, semi-synthetic derivative of a fermentation product from the environmental mould *Coleophoma empetri*. Micafungin belongs to a new class of antifungal agents, the echinocandin lipopeptides. These compounds non-competitively inhibit the synthesis of 1,3-b-D-glucan, an essential component of the fungal cell wall, which is not present in mammalian cells. Micafungin exhibits fungicidal activity

against most *Candida* species and prominently inhibits actively growing hyphae of *Aspergillus* species.

Invasive fungal infections (IFIs) are an important cause of morbidity and mortality in high-risk, immunocompromised patients. This patient group is increasing due to expanding use of intensive cancer treatments and immunosuppressive regimens for autoimmune disease, improving success rates of solid organ and bone marrow transplantation and increasing incidence of immune diseases such as human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS).

Emerging resistance of fungi to standard treatments is an important consideration in the development and subsequent availability of new treatments.

This AusPAR describes the application by Astellas Pharma Australia Pty Ltd to register Mycamine powder for intravenous (IV) injection, containing micafungin 50 mg and 100 mg. The proposed indications are:

Adults, adolescents ≥16 years of age and the elderly:

- treatment of invasive candidiasis
- treatment of oesophageal candidiasis in patients for whom intravenous therapy is appropriate
- prophylaxis of *Candida* infection in patients undergoing allogeneic haematopoietic stem cell transplantation or patients who are expected to have neutropenia (absolute neutrophil count <500 cells/ μ L) for 10 or more days.

Children (including neonates) and adolescents <16 years of age:

- treatment of invasive candidiasis
- prophylaxis of *Candida* infection in patients undergoing allogeneic haematopoietic stem cell transplantation or patients who are expected to have neutropenia (absolute neutrophil count <500 cells/ μ L) for 10 or more days.

Mycamine is proposed to be administered once daily by intravenous (IV) infusion according to the dosage regimens shown in Table 1 and Table 2.

Table 1. Dosage for adults, adolescents ≥ 16 years of age and the elderly

Indication	Body weight > 40 kg	Body weight ≤ 40 kg
Treatment of invasive candidiasis	100 mg/day*	2 mg/kg/day*
Treatment of oesophageal candidiasis	150 mg/day	3 mg/kg/day
Prophylaxis of <i>Candida</i> infection	50 mg/day	1 mg/kg/day

*** If the patient's response is inadequate, e.g. persistence of cultures or if clinical condition does not improve, the dose may be increased to 200 mg/day in patients weighing > 40 kg or 4 mg/kg/day in patients weighing ≤ 40 kg.**

Treatment duration

The proposed treatment duration for *Candida* infection is a minimum of 14 days. The antifungal treatment should continue for at least one week after two sequential negative blood cultures have been obtained and after resolution of clinical signs and symptoms of infection.

For the treatment of oesophageal candidiasis, Mycamine is to be administered for at least one week after resolution of clinical signs and symptoms. For prophylaxis of *Candida*

infection, Mycamine should be administered for at least one week after neutrophil recovery.

Table 2. Dosage for children (including neonates) and adolescents < 16 years of age

Indication	Body weight > 40 kg	Body weight ≤ 40 kg
Treatment of invasive candidiasis	100 mg/day*	2 mg/kg/day*
Prophylaxis of <i>Candida</i> infection	50 mg/day	1 mg/kg/day

* If the patient's response is inadequate, e.g. persistence of cultures or if clinical condition does not improve, the dose may be increased to 200 mg/day in patients weighing > 40 kg or 4 mg/kg/day in patients weighing ≤ 40 kg.

Treatment duration

The treatment duration for *Candida* infection is for a minimum of 14 days and should continue for at least one week after two sequential negative blood cultures have been obtained and after resolution of clinical signs and symptoms of infection. For prophylaxis of *Candida* infection, Mycamine should be administered for at least one week after neutrophil recovery.

Regulatory status

The product received initial registration in the Australian Register of Therapeutic Goods on 8 May 2013.

At the time this application was considered by TGA, a similar application for Micafungin powder for injection, for use in indications similar to those proposed for Australia, was approved in several overseas countries, including Japan (October 2002), the EU (April 2008), USA (March 2005, extended indications June 2006), and Canada (May 2007, extended indications May 2008).

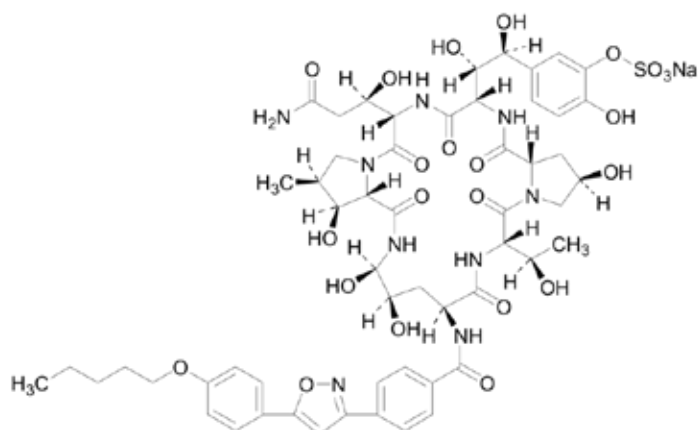
Product Information

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

II. Quality findings

Drug substance (active ingredient)

The drug substance has the following structure:

Figure 1. Structure of micafungin

It is manufactured in a single synthetic step from a substance obtained by fermentation of the environmental mould, *Coleophoma empetri*. The product of the fermentation process is a macrocyclic peptide. Insufficient information has been provided concerning the starting material, FR-195752, and further information has been sought.¹

The drug substance has multiple chiral centres, but is produced as a single stereoisomer.

Micafungin sodium drug substance is an amorphous, white, hygroscopic powder that is freely soluble in water over the physiological pH range. It has a pKa of 9.15 corresponding to the weakly acidic phenol group. The pKa value of the sulfate ester group was not stated but would be expected to be about 2. The partition coefficient (log P) of micafungin sodium (octanol/ pH 7 buffer) is -0.39.

Limits proposed for five specified impurities in the drug substance have been assessed as acceptable by the Medicines Toxicology Evaluation Section. However, the Medicines Toxicology Evaluation Section has advised that the residual solvent, diisopropyl ethylamine, has not been adequately qualified at the proposed limit.²

Fermentation aspects of the manufacture of the drug substance have been assessed as satisfactory.

Drug product

Mycamine micafungin (as sodium) powder for injection (50 mg/vial and 100 mg/vial) is a white, sterile, lyophilised powder for IV infusion. Each vial is reconstituted with 5 mL of either 0.9% sodium chloride injection solution or 5% glucose injection solution to yield 10.17 mg/mL or 20.35 mg/mL of micafungin sodium (equivalent to 10.0 mg/mL or 20.0 mg/mL of micafungin), prior to further dilution with the IV infusion solution. The reconstituted solution has a pH of 5.0-7.0 and is colourless, clear and essentially free of particulate matter.

Each 10 mL Type I glass vial is sealed with a teflon-laminated isobutylene-isoprene rubber stopper, and an aluminium and polypropylene overseal. The vial is wrapped in a polyethylene terephthalate (PET) shrink-wrap film to provide protection from light.

In addition to the active ingredient, each vial (of each strength) contains lactose as a stabiliser, together with citric acid and sodium hydroxide for pH adjustment. The vials contain overfills to facilitate withdrawal and administration of the labelled quantity of

¹ Satisfactory information was subsequently provided to the TGA.

² Adequate toxicological data to qualify an acceptable limit was subsequently provided to the TGA

micafungin after reconstitution. The product is sterilised by filtration prior to lyophilisation.

The finished product specifications include limits for the same specified impurities as in the drug substance. The limits proposed are acceptable.

Adequate data have been provided to support the proposed shelf life of 3 years below 25°C. In-use stability data have also been provided. The data are satisfactory except that significant amounts of a photodegradant are observed when diluted solutions of the drug are stored in IV infusion lines for one hour. Although the PI states that infusion bags or bottles should be enclosed in an opaque bag, it does not recommend that IV lines be shielded from light. Data to qualify the proposed limits for the photodegradant on toxicological grounds is provided. However, further data have been sought.³

Sterile manufacture and sterility aspects of the product have been assessed as satisfactory.

Biopharmaceutics

No bioavailability data have been provided as the product, after reconstitution, is a simple aqueous solution intended only for IV administration.

Advisory committee considerations

The submission was considered by the Pharmaceutical Subcommittee of the ACPM at its 146th meeting on 23 July 2012. The subcommittee endorsed the issues raised by the TGA and had no additional concerns.

Quality summary and conclusions

Registration approval was not recommended until the company satisfactorily addressed the concerns highlighted above.

All matters relating to the concerns described above were resolved to the satisfaction of the TGA prior to a decision being made on this application (see also *Overall conclusion and risk/benefit assessment; Delegate's overview*, below).

III. Nonclinical findings

Introduction

The sponsor provided a comprehensive package of nonclinical studies examining primary and safety pharmacology *in vitro* and *in vivo*, acute and repeat-dose toxicity, genotoxicity, reproductive toxicity, local tolerance and antigenicity studies. Standard carcinogenicity studies were not performed but this is acceptable for a product proposed for short-term use. Additional toxicology studies were performed to evaluate the safety of specified impurities, metabolites, photodegraded micafungin, and in juvenile animals to support paediatric use. Pivotal safety and toxicology studies complied with good laboratory practice (GLP) guidelines and were generally adequately conducted. However, toxicokinetic data were limited for some rat and dog repeat dose toxicity studies and absent for all rat reproductive toxicity studies, and metabolic profiling was not performed in rabbits to establish its validity as a nonclinical model. Nonetheless, the nonclinical

³ Matters relating to the limits of the photo-degradant, RS5 were subsequently resolved.

submission was adequate to characterise the pharmacological and toxicological profile of micafungin.

Pharmacology

Primary pharmacology

Mechanism of action

Micafungin was found to be a non-competitive inhibitor of 1,3- β -D-glucan synthesis using standard biochemical assays and morphological techniques. In crude lysates of *Candida albicans* and *Aspergillus fumigatus*, the incorporation of [¹⁴C]-uridine diphosphate (UDP)-glucose into glucan polymers was inhibited at low concentrations in a non-competitive way (affinity constant, $K_i = 0.208 \mu\text{M}$ and $K_i = 0.0158 \mu\text{M}$, respectively). Morphological changes in *C. albicans* (yeast and hyphal form) and *A. fumigatus* after exposure to micafungin were consistent with inhibition of cell wall synthesis.

In vitro antifungal spectrum and activity of micafungin metabolites, M1 and M2

In vitro susceptibility testing was performed with modifications according to the Clinical and Laboratory Standards Institute (CLSI) methods M27-A2 (*Candida* species) and M38-A (*Aspergillus* species), which are generally acceptable methods for these species^{4,5}.

In *in vitro* susceptibility tests, micafungin displayed activity against clinically relevant *Candida* species. The minimum inhibitory concentration (MIC) rank order was: *C. albicans* (99 isolates including azole resistant strains; 0.0039-0.0625 $\mu\text{g}/\text{mL}$) < *C. tropicalis* (61 isolates; 0.0078-0.0625 $\mu\text{g}/\text{mL}$), *C. glabrata* (56 isolates; 0.0039-0.0625 $\mu\text{g}/\text{mL}$) < *C. krusei* (11 isolates; 0.125 $\mu\text{g}/\text{mL}$) << *C. parapsilosis* (42 isolates; 0.5-4 $\mu\text{g}/\text{mL}$), *C. guilliermondii* (31 isolates; 0.25-8 $\mu\text{g}/\text{mL}$) (data from two studies only). The MIC₉₀ values observed against *C. albicans*, *C. tropicalis* and *C. glabrata* (three of the most common species involved in invasive candidiasis) were similar to the anticipated clinical maximum concentration (C_{max} ; free fraction; 46 ng/mL)⁶. With the exception of *C. parapsilosis* and *C. guilliermondii*, micafungin was generally more potent against the tested *Candida* species than amphotericin B, fluconazole and itraconazole. Compared to caspofungin, MIC values for micafungin were generally lower.

Micafungin had fungicidal activity against standard strains (and clinical isolates) of *C. albicans*, *C. glabrata* and *C. krusei* with 99% reduction in growth by 24 h at concentrations $\geq 0.0078 \mu\text{g}/\text{mL}$. The minimum fungicidal concentration (MFC) range was similar to the MIC range for these species, suggesting the primary activity was fungicidal. Fungicidal activity was not enhanced at concentrations above 1 \times MIC, but appeared to be dependent on time. Fungicidal activity was seen with lower concentrations of micafungin compared with amphotericin B and caspofungin. The kill rate was slower than amphotericin B, which may be related to the different mechanisms of action. Poor fungicidal activity was seen for *C. parapsilosis* and *C. guilliermondii* strains (MFC range 1- \rightarrow 64 $\mu\text{g}/\text{mL}$) while not all *C. tropicalis* isolates were susceptible (MFC range 0.0313- \rightarrow 64 $\mu\text{g}/\text{mL}$). The *in vitro* data suggest micafungin will have fungicidal activity on most *C. albicans*, *C. tropicalis* and *C. glabrata* strains. Strains of *C. parapsilosis*, a species that is a common cause of candidaemia in paediatric patients, and *C. guilliermondii* are likely to be resistant to micafungin. Generally, the profile of activity of micafungin against *Candida* species was similar to

⁴ Chen, S.C.-A., M.A. Slavin, T.C. Sorrell. Echinocandin antifungal drugs in fungal infections. *Drugs* 2011;71:11-41.

⁵ Lass-Flörl, C. and S. Perkhofer. *In vitro* susceptibility-testing in *Aspergillus* species. *Mycoses* 2008;51:437-446.

⁶ Based on a C_{max} of 28.7 $\mu\text{g}/\text{mL}$ for a 4 mg/kg dose (Clinical study FG-463-21-03) and a free fraction of 0.16%.

casposfungin and anidulafungin, with 100-fold higher MIC values seen for *C. parapsilosis* and *C. guilliermondii* than *C. albicans*, *C. glabrata* and susceptible *C. tropicalis* strains.

Micafungin had inhibitory activity against clinical isolates of *Aspergillus fumigatus* (45 isolates), *A. niger* (21 isolates), *A. flavus* (13 isolates) and *A. terreus* (11 isolates) (data from two studies). Inhibition occurred at clinically relevant concentrations ($MIC_{90} \leq 62.5$ ng/mL compared with an anticipated clinical C_{max} [free fraction] of 46 ng/mL). In MFC assays, micafungin displayed fungistatic rather than fungicidal activity ($MFC_{50} > 64$ µg/mL on *A. fumigatus* strains [19 tested]), which is typical for echinocandins.

Micafungin had virtually no *in vitro* inhibitory activity against *Cryptococcus neoformans*, *Trichosporon cutaneum*, *Trichosporon asahii*, *Fusarium solani*, *Pseudallescheria boydii*, *Absidia corymbifera*, *Cunninghamella elegans*, *Rhizopus oryzae* or *Rhizopus microsporus* (MIC values > 64 µg/mL).

The *in vitro* antifungal activity of the main metabolites of micafungin (M1, M2 and M5) was assessed against a battery of standard *Candida*, *Saccharomyces*, *Cryptococcus*, *Trichosporon* and *Aspergillus* strains. With the exception of low activity against *Trichosporon cutaneum* and *Cryptococcus neoformans* (MIC 16 µg/mL), the profile of activity of M1 was similar to micafungin albeit with 4–16 times lower potency. The antifungal activity of M2 was similar to the parent drug, while M5 had very poor activity against all strains (MIC ≥ 1 µg/mL). These metabolites are not expected to contribute to the pharmacological activity, as M1 and M2 levels in human plasma are low (generally $< 6\%$ of the parent for M1 and $< 1\%$ for M2) and M5 has poor antifungal activity and is only found at low levels in plasma ($< 9\%$ of the parent).

***In vivo* antifungal spectrum and activity of micafungin**

The *in vivo* antifungal efficacy of micafungin was assessed using standard mouse models of infection. These included models of disseminated candidiasis, oesophageal and oropharyngeal candidiasis and disseminated and pulmonary aspergillosis in immunocompetent and in immunocompromised mice.

In a mouse model of disseminated candidiasis (*C. albicans* infection), micafungin (administered daily for 4 days from 1 hour after infection) dose-dependently prolonged survival (≥ 0.125 mg/kg/day IV). At 1 mg/kg/day, all infected mice survived to the end of the study (22 days) [all control mice died within 11 days]. A significant reduction in the residual fungal titres (by 22–48% *cf* prior to treatment values) was seen in kidney tissues 24 hours after treatment with micafungin (0.5–1 mg/kg/day IV). The efficacy of micafungin was not obviously influenced by various states of immunosuppression. Delay of the start of treatment from 1 h to 24 h post infection had no influence on the protective effect of micafungin. The 50% effective dose (ED_{50}) (based on survival to 15 days post infection) against disseminated infections with *C. albicans*, *C. glabrata*, *C. tropicalis* and *C. guilliermondii* strains ranged from 0.14–0.77 mg/kg IV, while the ED_{50} values were higher for *C. krusei* and *C. parapsilosis* strains (1.61 and 3.21 mg/kg IV, respectively). In general, the ED_{50} values were superior to fluconazole and itraconazole and inferior to those of amphotericin B and casposfungin. The minimum effective plasma concentration of micafungin against *C. albicans* infection in disseminated candidiasis was 0.16–0.26 µg/mL with fungal kidney burden of *C. albicans* below the detection limit at plasma concentrations > 0.37 µg/mL. These values are well below the anticipated clinical C_{max} values, thus supporting the use of micafungin at the proposed dose for the treatment of disseminated candidiasis.

In a mouse model of oropharyngeal and oesophageal candidiasis [*C. albicans* infection], a reduction in the viable colony count of *C. albicans* was seen in both tongue and oesophageal tissues when assessed immediately after treatment with 2–10 mg/kg IV twice daily (bid) micafungin. However, a relapse of infection was seen 8 days after the end of treatment with a 2 mg/kg IV bid dose. Such a relapse was not seen at doses ≥ 5 mg/kg IV

bid, suggesting these higher doses are eradicated doses. A minimum effective plasma concentration was not determined for the eradicated treatment of oropharyngeal and oesophageal candidiasis, but based on dose comparisons in animal studies, higher doses are likely to be required for this indication compared with disseminated candidiasis.

While at this stage, the sponsor is not proposing use of micafungin for *Aspergillus* infections, a number of studies assessing efficacy of micafungin in animal models of disseminated and pulmonary aspergillosis were submitted. The ED₅₀ values (based on survival at 15 days) for micafungin in a disseminated aspergillosis model [*A. fumigatus* infection] ranged from 0.23 to 0.36 mg/kg IV. The ED₅₀ values were generally comparable to those for caspofungin and amphotericin B and lower than those for fluconazole and itraconazole. In a mouse model of pulmonary aspergillosis, micafungin given once daily for 4 days from 1.5 hours after infection with *A. fumigatus*, significantly prolonged mouse survival. In a comparative efficacy study against *A. fumigatus*, ED₅₀ values were similar to those of amphotericin B and significantly less than those of fluconazole and itraconazole. Relative efficacies of micafungin and caspofungin were dependent on the strain used for infection.

The submitted data provide evidence for efficacy of micafungin for the treatment of disseminated candidiasis (caused by *C. albicans*, *C. glabrata* and *C. tropicalis*) at the proposed clinical dose and at higher doses, the treatment of oesophageal candidiasis (caused by *C. albicans*). No data were provided to support the use of micafungin as a prophylaxis for *Candida* infection.

Resistance induction

In vitro, no change in MIC values was seen after 15 passages of a *C. albicans* strain through cultures containing subinhibitory concentrations of micafungin, suggesting that there was no induction of resistance. There was no evidence of resistance induction in patients with oesophageal candidiasis who had a persistent positive culture for *C. albicans* when treated with 50–75 mg micafungin for up to 22 days. However, these data are considered too limited to suggest resistance induction is unlikely.

Resistance of *Candida* species to echinocandins has been well-documented^{7, 8} and is commonly associated with mutations in the *FKS1* gene which encodes a subunit of the β -1,3-glucan synthase. Amino acid polymorphisms in the *FKS1* gene of *C. parapsilosis* and *C. guilliermondii* are suggested to be the mechanism of reduced susceptibility of strains of these species. Spontaneous micafungin-resistant mutants as well as resistant clinical isolates of *C. albicans* have been reported⁹, confirming resistance induction is possible. Micafungin-resistant strains are likely to have some resistance to the other echinocandins, caspofungin and anidulafungin, and the converse is also likely to be the case.

Interactions with other classes of antifungal agents

The combination of micafungin with amphotericin B was additive against *C. albicans* and *A. fumigatus* isolates *in vitro*. Of note, micafungin in combination with amphotericin B had synergistic or an additive effect against *C. neoformans* isolates while micafungin alone was inactive. *In vivo* combined treatment of micafungin (1 mg/kg) and amphotericin B (0.25 mg/kg) (once daily for 6 days from day 1 after infection) was more effective in the reduction of fungal burden in lungs and reduction of pulmonary lesion scores than single drug treatment at the same dose in intranasally *A. fumigatus* infected mice.

⁷ Chen, S.C.-A., M.A. Slavin, T.C. Sorrell. Echinocandin antifungal drugs in fungal infections. *Drugs* 2011;71:11–41.

⁸ Perlin, D.S. Resistance to echinocandin-class antifungal drugs. *Drug Resist. Updat.* 2007;10:121–130.

⁹ Niimi, K., B.C. Monk, A. Hirai *et al.* Clinically significant micafungin resistance in *Candida albicans* involves modification of a glucan synthase catalytic subunit *GSC1* (*FKS1*) allele followed by loss of heterozygosity. *J. Antimicrob. Chemother.* 2010;65:842–852.

Secondary and safety pharmacology

No secondary pharmacology studies were performed. However, an adequate package of GLP compliant safety pharmacology studies for micafungin examined potential central nervous system (CNS), cardiovascular, respiratory, renal and gastrointestinal systems, in addition to autonomic nervous system (ANS), blood system and hepatic effects *in vitro* and/or *in vivo*.

CNS effects were confined to mild decreases in locomotor activity in both mice and rats hypotonia, loss of reflexes, hypothermia and abdominal respiration seen in rats at 100 mg/kg IV. No effects on body temperature were seen in rabbits with 100 mg/kg IV infused over 30 min. The peak plasma levels at the no observed effect level (NOEL) in rats (32 mg/kg IV) are estimated to be 3 times the maximum clinical levels.¹⁰

Haemodynamic effects of decreased blood pressure and increased heart rate were observed in rats at ≥ 32 mg/kg IV micafungin, which appeared to be associated with increased histamine release. A mechanistic study suggested histamine release may be due to degranulation of cutaneous mast cells. Histamine release was also seen in dogs given a 30 min IV infusion of 100 mg/kg micafungin. The estimated C_{max} at 32 mg/kg IV in rats, a dose at which histamine release and haemodynamic effects was seen, is only 3 times the clinical C_{max} , suggesting these effects may be clinically-relevant. Similar effects (histamine release, increased heart rate and decreased blood pressure) were seen in rats given caspofungin.

In vitro, there was no significant effect on action potential duration in isolated guinea pig papillary muscle or on human *Ether-à-go-go*-Related Gene potassium (hERG K⁺) channel current at 10 μ g/mL (217 times the maximum clinical free plasma concentration). No effect on electrocardiogram (ECG) parameters was seen in dogs receiving a 30 min IV infusion of 100 mg/kg micafungin. Therefore, no effect on QT (ECG wave interval) prolongation is predicted based on nonclinical data.

Renal effects included increased urinary volume and excretion of electrolytes (sodium, chloride, potassium) in the rats at IV bolus doses of 32-100 mg/kg IV. These findings are consistent with urinary tract changes observed in rats after repeated dosing for 4-26 weeks at doses of 10-32 mg/kg/day IV. The urinary tract has also been identified as a target organ of toxicity in rats (see *Repeat dose toxicity* section). No effect on renal function was seen in dogs at ≤ 100 mg/kg IV.

Haemolysis was observed in rabbit blood *in vitro* at concentrations of 0.5-1 mg/mL. The no effect concentration was 100 μ g/mL.

Haemolytic anaemia was also observed in rats at IV bolus doses of 10-32 mg/kg/day after dosing for 4-26 weeks. Blood has also been identified as a target organ of toxicity in rats (see *Repeat dose toxicity* section).

A direct concentration-dependent hepatotoxic effect of micafungin was also demonstrated in rat hepatocytes *in vitro*. However, all other antifungals investigated (amphotericin B, caspofungin and ketoconazole) with the exception of fluconazole were also hepatotoxic in a concentration-dependent manner. The liver has also been identified as a target organ of toxicity in both rats and dogs (see *Repeat dose toxicity* section).

No significant effects on acetylcholine, histamine and barium chloride induced contractions in isolated guinea pig ileum preparations, histamine induced contractions of isolated guinea pig trachea preparations, noradrenaline induced contractions of isolated rat vas deferens and serotonin induced contractions of isolated rat gastric fundus at ≤ 10 μ g/mL (217 times the maximum clinical free plasma concentration). There was no

¹⁰ Using a $C_{5\ min}$ of 2.92 μ g/mL for a 1 mg/kg IV bolus dose to rats (Study CRR970243) and assuming linear pharmacokinetics with a clinical C_{max} of 28.7 μ g/mL for a 4 mg/kg dose.

significant effect on gastrointestinal transit was seen in rats given 100 mg/kg IV micafungin (estimated C_{\max} 10 times the clinical C_{\max}).

Pharmacokinetics

Plasma concentration profiles of micafungin in nonclinical species (mice, rats, dogs and rabbits) used in both the pharmacology and toxicology studies were compared to those of humans. After single or repeated IV bolus administration, micafungin peak plasma levels declined in a bi-phasic manner in all species. Clearance was within a factor of two for the animal species investigated but was 3- to 6-fold higher than in humans. The higher clearance value observed in animals resulted in a shorter half-life and exposure (area under the plasma concentration-time curve to infinity ($AUC_{0-\infty}$)) values in humans. Terminal elimination half-life ranged between 3 and 6 hours in animals and around 13-14 hours in adult patients.

In the single dose studies pharmacokinetic (PK) parameters were linear within the dose ranges studied. Linearity, however, was not maintained with repeated dosing in the rat. After repeated administration of high doses of micafungin in the rat accumulation was observed. In humans, similar to dogs, there was no evidence of accumulation of micafungin with repeated dosing with steady state reached by day 4/5. No gender differences in pharmacokinetic parameters were observed in rats (only species examining both genders). When micafungin was administered as a 1 hour infusion, no remarkable differences in PK parameters were observed compared to bolus injection.

Micafungin was extensively bound to serum proteins in mice, rats, dogs, rabbits and humans (99.73-99.84%). Protein binding was concentration independent over a range of 10-100 $\mu\text{g/mL}$ (around clinically relevant plasma levels). In human serum, micafungin was primarily bound to albumin, with α_1 -acid glycoprotein also contributing to the overall binding. The percentage of micafungin bound to human serum albumin (HSA) was constant at concentrations up to 100 $\mu\text{g/mL}$.

In vitro data also demonstrated a covalent binding of micafungin to rat, dog and human plasma proteins, such as rat albumin, human albumin α -glycoprotein and globulin, and guinea pig serum proteins.

Micafungin was not extensively taken up by blood cells. The blood/plasma partition ratio at concentrations of 0.1 to 10 $\mu\text{g/mL}$ micafungin was between 0.96-0.99 in rats, 0.85-0.87 in mice, 0.73-0.74 in dogs and 0.82-0.85 in humans and did not change over a concentration range of 0.1 to 10 $\mu\text{g/mL}$ in all species.

The volume of distribution was lower than total body in all species. Consistent with this, following IV dosing of ^{14}C -micafungin to rats, tissue levels of radioactivity were generally lower than plasma levels with the exception of the spleen, liver, kidneys and lungs, where the levels were similar or greater than plasma levels. It is notable that the tissues with high levels of radioactivity (kidney, liver, and lungs) are also common sites of fungal infections. A high tissue to plasma ratio was maintained in the excretory organs (liver, kidneys) for 72 hours. Both organs were targets in repeat dose toxicity studies. Drug related material was shown to cross the blood-brain barrier but brain concentrations were low.

Disposition studies with ^{14}C -labelled micafungin suggested that metabolites were slowly formed and slowly eliminated from the plasma of rats and dogs. Qualitatively, the metabolites detected in humans were also found in rats and dogs. Major metabolites identified in all three species included M1 (the desulfated form of micafungin, M2 (the methylation form of M1), M3 (to a lesser extent; ring opened form of micafungin) and M5 (has the mother nucleus of micafungin and a hydroxyl form at the side chain [ω -1 position]). However, metabolic profiling was not performed in rabbits, the animal species

used in reproductive toxicity testing, shedding uncertainty on the validity of this animal model.

In contrast to rat and dog, unchanged micafungin remained the major drug-related component in human plasma at 24-48 hours after administration, reflecting slower tissue uptake and longer half-life in humans. M1 and M2 were excreted primarily *via* the faecal route and little of these metabolites were detected in plasma. M3 was detected in the plasma of all species investigated and appears to be excreted *via* the faeces. M1, M2 and M3 were observed in various rat tissues after IV administration. M5 was the major metabolite in human and rat plasma after 24 hours and was predominantly excreted *via* the urine. In the dog plasma, primarily M4 (a sulfoconjugate of the hydroxy group at the ω -1 position of M5) was the primary metabolite in dogs, but it was not detected in humans or rats.

Micafungin metabolism was shown to take place in the liver where micafungin is metabolised to M1 (catechol form) by arylsulfatase, with further metabolism to M2 (methoxy form) by catechol-O-methyltransferase. M3 is formed in solutions under neutral or basic conditions, suggesting a non-enzymic conversion. M5 is formed by hydroxylation at the side chain (ω -1 position) of micafungin catalysed by multiple cytochrome P450 (CYP) isoenzymes (CYP1A2, 2B6, 2C, 3A4 and 3A7). These major metabolites do not markedly affect the overall efficacy profile of micafungin.

The biliary-faecal route was the major excretion route in rats, dogs and humans.

Micafungin was found to be a substrate for CYP3A *in vitro*. However, it was not a significant inducer or inhibitor of CYP isoenzymes (including CYP3A4) at clinically relevant micafungin concentrations. Interactions with other protein bound drugs are not anticipated at therapeutic micafungin doses. Micafungin was not an inhibitor of P-glycoprotein mediated transport *in vivo*.

Toxicology

A comprehensive toxicology program for micafungin examined single-dose and repeat-dose toxicity in rats and dogs (up to 6 and 9 months, respectively), reproductive toxicity in rats and rabbits, genotoxicity *in vitro* and *in vivo*, local tolerance and antigenicity. Additional toxicology studies were performed to evaluate the safety of specified impurities, metabolites and photodegraded micafungin. No standard carcinogenicity studies were performed since dosing longer than six months was prevented by the extent of local IV reactions. However, this is acceptable for a substance indicated for short-term use. The carcinogenic potential of micafungin was evaluated to some extent, by following the treated rats over their entire life span (see *Carcinogenicity* section), though only the liver was extensively examined. Repeat dose toxicity studies were also conducted in juvenile rats and dogs to support paediatric use. Treatment free periods were included in the pivotal repeat-dose studies to assess the reversibility of any toxicity findings. Pivotal studies complied with GLP, with micafungin administered once daily by bolus injection or infusion, consistent with the proposed clinical route of administration. The chosen animal species (rats and dogs) were exposed to micafungin and its metabolites and are therefore considered appropriate models for toxicity testing (see *Pharmacokinetics* section). However, while a similar absorption and distribution profile was demonstrated in rabbits to that of humans and other animal species, no metabolic profiling was performed to demonstrate its adequate exposure to micafungin metabolites, shedding some uncertainty on the relevance of this animal model. Group sizes were generally acceptable, although were low in some studies. Dose levels employed were adequate to identify target organs of toxicity and were limited by dose-limiting toxicity at least in rats. However, toxicokinetics were not determined in all studies and limited plasma samples (n=2 sampling times) were taken in some studies limiting the accuracy of AUC extrapolations. Nonetheless, the overall

quality and design of studies was considered adequate to assess the toxicological profile of micafungin.

Acute toxicity

The acute toxicity of micafungin was examined in rats (62.5, 125 and 250 mg/kg) and dogs (100 and 200 mg/kg) given a single bolus IV dose. Use of the single IV administration route was appropriate for a product intended for clinical IV use. Clinical signs of toxicity including decreased spontaneous movement, clonic convulsions, prone position, oligopnoea, dark red ear auricles and extremities, and swelling of the face were observed in rats prior to death at lethal doses of 125 mg/kg (males) and 250 mg/kg (males and females). Clinical signs of toxicity including salivation, paleness of the buccal mucous membrane and auricle, swelling of the palpebra and its surrounding area, and abdominal skin were also observed at 200 mg/kg in dogs. Abnormal haematological and clinical chemistry parameters suggestive of haemolytic anaemia and hepatic injury were also observed at dogs at 200 mg/kg IV. In both species, the clinical signs observed are thought to be at least partly related to endogenous histamine release and in dogs potential target organs were tentatively identified. The maximum non-lethal IV dose was determined as 62.5 and 125 mg/kg in male and female rats, respectively and >200 mg/kg in dogs. Overall, the acute toxicity was low in both species.

Repeat-dose toxicity

The toxicity of repeated IV doses of micafungin was examined in rats and dogs dosed for up to 26 and 39 weeks, respectively. Doses were administered as an IV bolus injection, with the exception of one 4 week rat study whereby rats were given a 1 hour IV infusion (similar concentration profiles were reported after IV bolus and IV infusion in rats; see *Pharmacokinetics* section). An additional set of 13- and 26-week repeat dose toxicity studies was conducted to assess the development of micafungin-induced foci of altered hepatocytes (FAH) in female rats after cessation of micafungin treatment over periods which approximately covered the life span in rats. The reversibility of urinary tract findings was assessed as part of the 26-week study.

Decreased body weight and body weight gain was observed in rats given 32 mg/kg/day IV micafungin over 13 or 26 weeks (4-6 fold the anticipated maximum clinical exposure). The effect was less pronounced or absent in the studies of 4 week duration. Reduced food consumption accompanied the decrease in body weight gain in some studies. No similar effect on body weight or food consumption was observed in dogs.

Relative exposure

Relative exposure ratios were calculated based on animal:human plasma AUC_{0-24h} and C_{max} in the rat and dog repeat dose toxicity studies. Given the absence of sex-related differences in these parameters, values were averaged for both genders. In the pivotal rat 13 and 26 week studies and dog 13 week studies, insufficient blood sampling (two sampling points at 15 min and 24 h only) was undertaken for accurate determination of AUC. Moreover, no calculation for AUC with two sampling points would account for the bi-exponential concentration-time curve observed in both species. Nonetheless, in these studies, exposure (AUC) values were determined by two means, where required. Exposure (AUC) was calculated based on two sampling points and also by extrapolation from different doses in the same study or doses from a study of identical duration/treatment period. Importantly, both values obtained were similar and provided a rough estimate of likely clinical safety margins in these studies.

Table 3. Relative exposure after repeated daily IV bolus micafungin administration

Species	Study duration	Dose (mg/kg/day)	AUC _{0-24 h} [*] (µg.h/mL)	C _{max} (µg/mL)	Exposure ratio [#]		
					AUC	C _{max}	
Rat (SD)	4 weeks	3.2	56	8.1	0.2	0.3	
		10	224	30	0.7	1.0	
		32	853	105	2.5	3.6	
	13 weeks	1.25	52 ⁱ /49 ^φ	4.1	0.1-0.2	0.1	
		2.5	113 ⁱ /98 ^φ	8.9	0.3	0.3	
		5	244 ⁱ /196 ^φ	19	0.6-0.7	0.7	
		10	527 ⁱ /391 ^φ	40	1.1-1.6	1.4	
		32	1357 ^φ	173 ^φ	4	6	
	26 weeks	1	55 ⁱ /50 ^φ	4.3	0.1	0.1	
		3.2	181 ⁱ /148 ^φ	14	0.4-0.5	0.5	
		10	601 ⁱ /501 ^φ	45	1.5-1.8	1.5	
		20	1003	141	3	5	
		32	1478	205	4	7	
	Dog (Beagle)	4 weeks	3.2	52	10	0.2	0.3
			10	159	33	0.5	1.1
32			591	109	1.7	3.7	
13 weeks		3.2	107 ⁱ /94 ^φ	9	0.3	0.3	
		10	381 ⁱ /261 ^φ	28	0.8-1.1	1.0	
		32	1291 ⁱ /993 ^φ	106	2.9-3.8	3.6	
39 weeks		3.2	114	13	0.3	0.4	
		10	302	34	0.9	1.2	
		32	1132	131	3	4.5	
Patients^φ		steady state	4	339	29.2	-	-

*Males and females combined; # = animal:human plasma AUC_{0-24 h}; ⁱ Estimated from two plasma samples only; ^φExtrapolated from different dose in same study or study of identical duration/treatment period; ^φClinical Study FG-463-21-3 (in adult patients undergoing a bone marrow or peripheral stem cell transplant).

Major toxicities

The liver, urinary tract, blood, male genital tract and injection site were identified as the primary target organs for micafungin toxicity. Signs of toxicity observed in repeat-dose toxicity studies were generally more severe in rats compared to dogs.

Liver

In rats, micafungin-induced liver injury consisted of signs of degeneration and signs of compensatory regeneration. Hepatotoxicity was indicated by increased liver enzymes (alanine transferase (ALT), aspartate transferase (AST), alkaline phosphatase (ALP) and total bilirubin), single cell necrosis, cellular and nuclear hypertrophy, vacuolation, acidophilic bodies in hepatocytes and pigmentation of Kupffer cells. Liver effects were observed at doses from 10 mg/kg/day in the 4-26 week rat studies (associated with micafungin exposure levels similar to those anticipated clinically at the maximum recommended human dose [MRHD] of 4 mg/kg/day). After 13-26 weeks of treatment, foci of altered hepatocytes (FAH) were also observed in rats given 32 mg/kg/day micafungin, even after a 4 or 13 week recovery period. The NOAEL for FAH development was established at 10 mg/kg (similar to anticipated clinical exposure at the MRHD).

FAH observed in rats at the end of 3- and 6-month treatment periods also showed a potential for progression to tumour formation after withdrawal periods equivalent to the life span of the rat. A significant increase in the number of hepatocellular adenomas was observed at 32 mg/kg/day in both studies (corresponding to 4 times the anticipated clinical exposure at the MRHD) at the end of the respective recovery periods. Two hepatic carcinomas were also detected at this dose in the 6 month study. While in the 6 month study, 18 months after recovery, two adenomas and one carcinoma were also seen at the 20 mg/kg/day dose, these incidences were not significant and were within the range of historical control data. Thus, the no observed adverse effect level (NOAEL) for hepatic adenomas and carcinomas was therefore determined as 20 mg/kg/day (3 times the anticipated clinical exposure at the MRHD).

Micafungin was not genotoxic in a standard battery of studies, including a unscheduled deoxyribonucleic acid synthesis (UDS) assay in rat hepatocytes, suggesting the formation of FAH and subsequent tumour development, is not associated with a genotoxic effect. The preneoplastic and neoplastic lesions are likely associated with sustained liver injury.

In dogs, liver effects observed included increased weights, enlarged, swollen and/or discoloured livers and centrilobular hypertrophy, without degenerative changes of hepatocytes at doses of 32 mg/kg/day in the 4 and 13 weeks studies, and at all doses (3.2-32 mg/kg/day) in the 39 week study. The NOAEL (10 mg/kg/day) in the 4-13 week studies was associated with micafungin exposure levels similar to those anticipated clinically at the MRHD. A NOAEL was not determined in the 39 week study, with the lowest dose associated with anticipated subclinical micafungin exposure levels.

In the absence of a safety margin for hepatotoxic effects in rats and dogs after 4 weeks dosing, the potential for hepatotoxic effects in the therapeutic setting cannot be dismissed. Thus, consistent with the sponsor's recommendation (draft PI document) and those of other antifungal echinocandins, it is recommended that liver function be carefully monitored during micafungin treatment. Early discontinuation of treatment in the presence of significant and persistent elevation of AST/ALT levels is also recommended. The findings in rats would suggest that prolonged clinical use of micafungin should be avoided.

Urinary tract

Urinary tract changes were observed in the rat. In 4-week repeat-dose toxicity studies, slight to mild vacuolation of the transitional epithelium in the renal pelvis and urinary bladder were noted at an IV dose of 32 mg/kg/day. These changes were reversible after a

2 week recovery period. After 26 weeks, toxic changes were increased in incidence and severity and included haemosiderin deposition in the proximal tubular epithelium, dilatation of the collecting duct and swelling of the collecting duct epithelium, slight to mild vacuolation of the renal pelvic epithelium as well as mild vacuolation and thickening (hyperplasia) of the bladder epithelium at 32 mg/kg/day. The NOAEL for these toxic changes was determined as 10 mg/kg/day (similar to the anticipated clinical exposure at the MRHD). A 6-18 month recovery period (after 26 weeks dosing) demonstrated recovery of these bladder and kidney findings, with the exception of pigmentation/deposition in the kidney tubular epithelium. The haemosiderin-like deposits observed in renal tubules of rats are considered to be secondary to the haemolytic action of micafungin¹¹.

Urinalysis findings consisting of increased urine volume, decreased urine pH and/or increased excretion of electrolytes, mainly sodium and chloride, were noted in the 26-week study and to a lesser extent in the 4 and 13 week studies at doses from 10-32 mg/kg/day. Increased urinary volume and excretion of electrolytes (sodium, chloride, potassium) was also observed in the rat safety pharmacology studies at doses of 32-100 mg/kg IV. Small increases in blood urea nitrogen, and inconsistent changes in creatinine levels were also reported. However, decreased serum electrolytes as a potential consequence of electrolyte loss via the urine were not generally found in repeat-dose studies.

Overall, generally reversible urinary tract changes were observed in rats at micafungin doses of 10-32 mg/kg/day IV (equivalent to 1-3 times the anticipated clinical exposure at the MRHD). In studies in dogs, there were no changes in the urinary tract at doses up to 32 mg/kg/day and treatment duration of up to 39 weeks (3 times the anticipated clinical exposure at MRHD). Thus the clinical relevance of the rat findings appears limited, although monitoring of kidney function may be warranted if there is clinical evidence to suggest cause for concern.

Blood

In rats, signs of haemolytic anaemia were present in all repeat-dose studies at doses of 10 and 32 mg/kg/day IV. At 32 mg/kg/day, the haemolytic action of micafungin was evident by a decrease in red blood cells, haemoglobin and haematocrit. The changes were accompanied by a regenerative response manifested by increased reticulocytes, hypercellularity of the bone marrow and extramedullary haematopoiesis in the spleen observed at doses as low as 1.25-3.2 mg/kg/day in the 13 and 4 week studies, respectively. Increased total bilirubin and serum potassium were also found, although they are not regarded as specific indicators of haemolytic anaemia. Splenic congestion was considered to be due to haemosiderin deposition, as damaged red blood cells were broken down in the red pulp of the spleen. Haemosiderin-like deposits were also observed in the renal tubular epithelium where they are usually not associated with degenerative or functional alterations (Gopinath *et al*, 1987). Pigmentation of Kupffer cells and swelling/mobilization of sinusoidal cells in the liver may be also related to haemosiderin uptake. Thus, the NOAEL for the induction of haemolysis could often not be determined due to the evidence of even mild regenerative responses observed at low doses in the rat.

Although signs of haemolytic anaemia were observed in dogs following single administration of 200 mg/kg IV (see *Acute toxicity* section), there were no abnormal haematological parameters indicating haemolysis in the repeat-dose studies at doses up to 32 mg/kg/day IV for 39 weeks. Congestion of the spleen and increased spleen weight was only observed at 32 mg/kg/day IV in one animal each of the 13-week and 39-week studies.

¹¹ Gopinath C, Prentice DE, Lewis DJ eds. The urinary system. In: *Atlas of experimental toxicological pathology*. MTP Press Limited, Lancaster, 1987:77-90.

In safety pharmacology tests, micafungin had a significant haemolytic effect in rabbit blood at concentrations $\geq 500 \mu\text{g/mL}$. No haemolysis was also observed at $100 \mu\text{g/mL}$. The haemolytic effect of micafungin *in vivo* appears to be based on C_{max} values.

Given the potential relevance of haemolytic events in the clinical setting at clinical exposure levels, monitoring of haematological parameters may be warranted.

Male genital tract

In dogs, treatment for 39 weeks was associated with effects on testes consisting of reduced testis weight, mild to moderate atrophy of the seminiferous tubules, slight to mild vacuolation of the seminiferous epithelium and a reduction of sperm in the epididymides at 10-32 mg/kg/day IV. Slight to mild interstitial inflammatory cell infiltration was also noted in the testis and epididymides of some animals. The epididymal changes observed were considered to be secondary to the atrophy of seminiferous tubules. The NOAEL for the testicular effects was established at 3.2 mg/kg/day (less than the anticipated clinical exposure at the MRHD).

In rats treated with micafungin for 9 weeks prior to mating and throughout mating, vacuolation of the epithelium in the caput epididymides (at 10 and 32 mg/kg/day), reduced sperm count and increased epididymides weight was observed at IV doses of 32 mg/kg/day, however no effect on male fertility was observed (see *Reproductive toxicity* section).

In a 39-week repeated dose study in juvenile dogs (3 weeks old at the start of the dosing) these findings were not confirmed at similar micafungin exposure levels (about 10 months old at analysis; pubertal age¹²). While a small number of animals showed testicular hypoplasia, these findings were not dose-related (occurred in 1 dog at 3.2 mg/kg and 3 dogs at 10 mg/kg but not at 32 mg/kg). Also, there was no clear drug-related effect on testis weight or on the incidence of testicular atrophy (values were within the historical control range).

Given the short duration of treatment with micafungin in patients the risk during clinical use is likely minimal. However, precautionary statements are warranted in the fertility section of the PI document.

Injection site

In rats, injection site irritation characterised by slight to mild perivascular haemorrhage, cellular infiltration, necrosis and fibrosis were observed in studies at doses as low as 1.25-3.2 mg/kg/day and subclinical concentrations. While similar findings were not observed in dogs, the potential for local injection site irritation following IV micafungin injection should not be dismissed and it is recommended that injection sites be checked routinely for signs of excessive local irritation.

Genotoxicity

The genotoxicity of micafungin was examined in a standard battery of *in vitro* (bacterial reverse mutation, chromosome aberration and UDS) and *in vivo* (mouse micronucleus) studies. All pivotal studies were GLP compliant, utilised appropriate concentrations or doses, study design and relevant controls. Micafungin did not demonstrate any mutagenic or clastogenic potential *in vitro* or *in vivo*.

¹² Marty, M.S., R.E. Chapin, L.G. Parks and B.A. Thorsrud. Development and maturation of the male reproductive system. *Birth Defects Res. (Part B)* 2003;68:125–136.

Carcinogenicity

No standard carcinogenicity studies were performed for micafungin due to the inability to perform IV dosing for more than 6 months. This is acceptable for a substance intended for short-term (<3 months continuous) use. Nonetheless, repeat dose toxicity studies were performed in female rats given repeated daily IV micafungin doses for 3 or 6 months with recovery periods up to 20 months to specifically follow the progression of the AHF observed in rats with repeated dosing.

A significant increase in the number of hepatocellular adenomas was observed at 32 mg/kg/day in both studies (corresponding to 4 times the anticipated clinical exposure at MRHD) at the end of the respective recovery periods. Two hepatic carcinomas were also detected at this dose in the 6 month study. The NOAEL for hepatic adenomas and carcinomas was determined as 20 mg/kg/day (3 times the anticipated clinical exposure at MRHD). These and other hepatic changes are further discussed in the *Repeat dose toxicity (Major toxicities – Liver)* section.

Given the low safety margins, monitoring for liver function is advisable during clinical use. Prolonged use is also not recommended.

Reproductive toxicity

A standard battery of GLP compliant reproductive toxicity studies was performed in rats and rabbits given repeated IV bolus doses of micafungin. Rat were considered appropriate animal models based on PK parameters, however, metabolite profiling in rabbits was not performed, therefore the appropriateness of this species could not be verified (see *Pharmacokinetics* section). Nonetheless, studies were performed with the intended route of administration, with appropriate animal numbers and at appropriate upper doses determined by dose-range finding studies to determine potential reproductive effects.

Toxicokinetic data were only provided for the rabbit embryofetal development study. Rat toxicokinetic data were extrapolated from repeat dose toxicity studies whereby male rats were dosed for 3 months at identical doses and non-pregnant female rats were dosed for 1 month at identical doses. Exposure margins were low in these studies ranging from subclinical to 2-3 fold the MRHD in female rats and rabbits and 4 fold the MRHD in male rats. In contrast, body surface area calculations suggested slightly lower (0.1-1.3-fold) micafungin exposure ratios in rats and similar (0.3-3 fold) micafungin exposure ratios in rabbits over the 3.2-32 mg/kg dose range (based on 4 mg/kg dose x 37 (average body weight of 70 kg) = 148 mg/m²). Regardless, relative micafungin exposure was low over the 3.2-32 mg/kg dose range in both species.

Table 4. Relative exposure in the reproductive toxicity studies

Species	Study	Dose (mg/kg/day)	AUC _{0-24 h} (ng·h/mL)	Exposure ratio [#]
Rat (SD)	Male Fertility*	3.2	135/160	0.4-0.5
		10	421/530	1.2-1.6
		32	1449	4
	Female Fertility, Embryofetal and Pre- and Postnatal Development [†]	3.2	51.2	0.2
		10	205	0.6
		32	844	2.5

Species	Study	Dose (mg/kg/day)	AUC _{0-24 h} (ng·h/mL)	Exposure ratio [#]
Rabbit (NZW)	Embryofetal development	3.2	60.3	0.2
		10	217	0.6
		32	688	2
Patients^φ	steady state	4	339	–

[#] = animal:human plasma AUC_{0-24 h}; ¹ Extrapolated from rat repeat dose toxicity study male toxicokinetics incorporating 3 months dosing; ^φExtrapolated from one month rat repeat dose toxicity study female toxicokinetics; ^φClinical Study FG-463-21-3 (in adult patients undergoing a bone marrow or peripheral stem cell transplant).

In all rat studies, signs of maternal or paternal toxicity (including decreased body weight gain, food consumption, injection site changes or impaired liver function [increase in plasma ALT activity]) were observed at 32 mg/kg/day IV. In the rabbit embryofetal development study, maternal effects were limited to a reduction in faeces and an abortion in one doe.

No effects on fertility were observed in rats dosed prior to and throughout mating at doses up to 32 mg/kg/day IV micafungin. However, vacuolation of the epithelium in the caput epididymides (at 10 and 32 mg/kg/day), reduced sperm count and increased epididymides weight was observed at IV doses from 32 mg/kg/day. The NOAEL for male reproductive organ effects was 3.2 mg/kg/day (less than the anticipated clinical exposure at the MRHD). Although treatment-related effects on reproductive organs have not been observed in 26 week studies in rats, similar effects were noted in dogs at identical dose levels. The NOAEL for testicular effects in the dogs was also 3.2 mg/kg/day (less than the anticipated clinical exposure at the MRHD).

Micafungin and/or its metabolites were shown to cross the placenta and distribute to the fetus in rats after a single IV 1 mg/kg dose. Nonetheless, no remarkable effects on embryofetal development were observed in rats given IV micafungin doses up to 32 mg/kg/day throughout organogenesis (2-3-fold the anticipated clinical exposure at the MRHD). However, treatment of rabbits at doses of 32 mg/kg/day IV was associated with visceral abnormalities and an abortion (2-fold the anticipated clinical exposure at the MRHD). The abortion was consistent with abortions observed at 60 mg/kg/day IV in the preliminary dose-range finding study. The visceral abnormalities were observed in 10 fetuses from 5 dams and included abnormal lobation of the lung (6 fetuses), levocardia (3 fetuses), retrocaval ureter (3 fetuses), anomalous right subclavian artery (1 fetus) and dilatation of the ureter (1 fetus). Visceral abnormalities were only observed in a single control fetus and consisted of abnormal lobation of the lung and retrocaval ureter. Visceral and skeletal abnormalities were not assessed at the 3.2 and 10 mg/kg/day doses. Therefore, a NOAEL could not be determined.

Significant excretion of micafungin and its metabolites was observed in the milk of lactating rats after a single IV dose of 1 mg/kg. By 6 and 72 hours-post dose, milk levels were similar to and up to 4-fold those of plasma. In a pre- and postnatal development study in rats, doses of 32 mg/kg/day IV micafungin were associated with reduced pup birth weights and a possible delay in the time of opening of the eyelids and cleavage of the balanopreputia. However, no effect on pup fertility or mating performance was observed. The NOAEL for pre- and postnatal pup effects was 10 mg/kg/day which was similar to the anticipated clinical exposure at the MRHD.

Pregnancy classification

The sponsor has proposed Pregnancy Category B3¹³. This is appropriate and is consistent with the findings of abortion and visceral abnormalities in rabbits dosed with IV micafungin during organogenesis. It is also consistent with that of the other echinocandin antifungals, anidulafungin and caspofungin, which demonstrated embryofetal effects.

Local tolerance

The dermal tolerance of a single intramuscular, peri-venous or intra-arterial injection of micafungin was examined in rabbits. Micafungin (0.02-0.025%; lower concentrations than the clinical concentration) was a slight irritant after IM injection. The effect was weaker than that of amphotericin B (0.01%). At concentrations ranging from 0.5 to 4.0 mg/mL, micafungin did not produce any dose-related local tissue reactions following peri-venous or intra-arterial injection at 0.2 mL/site.

Antigenicity

Micafungin did not induce any delayed or immediate hypersensitivity reactions as assessed in a guinea pig skin test and active systemic anaphylaxis (ASA) and passive cutaneous anaphylaxis (PCA) tests in monkeys, guinea pigs and mice.

Impurities

Five specified micafungin-related impurities were qualified by the submitted module 4 data.

Photodegradant

A range of GLP compliant toxicity (single-dose rat, repeat-dose (4 weeks) rat, genotoxicity *in vitro* and antigenicity) studies were submitted in module 4 to support the safety of photodegraded micafungin. No novel toxicities, genotoxicity or antigenicity findings were observed with the photodegraded batches. However, levels of specified photodegradants in the relevant study batches were not supplied and therefore insufficient information has been provided to establish whether any specified photodegradant has been adequately qualified.¹⁴

Paediatric use

To support paediatric administration of micafungin, juvenile repeat dose toxicity studies were conducted in rats and male dogs dosed for up to 13 and 39 weeks respectively with IV daily bolus doses of micafungin. The toxicity of repeated IV bolus doses of the M5 metabolite was also examined in juvenile rats dosed for up to 8 weeks. Toxicokinetics for micafungin and M5 were also determined concurrently or in subsequent studies. Pivotal studies were GLP compliant, used comparable doses to those employed in standard repeat doses toxicity studies and adequate animal numbers were assessed.

The toxicological susceptibility towards micafungin was similar in newborn/juvenile and adult rats and male dogs. No substantial differences existed in the toxicological target organs or NOAELs, with toxicological findings confined to the 32 mg/kg groups in rats and

¹³ Category B3 is defined as "Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed.

Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans."

¹⁴ Adequate data to qualify an acceptable limit were subsequently provided to the TGA before a decision was made on this application (see *Overall conclusion and risk/benefit assessment; Delegate's overview*, below).

10-32 mg/kg groups in male dogs, as observed in previous repeat dose toxicity studies. There was also no remarkable difference in micafungin exposure levels at these doses, with only slightly lower (10-30%) exposure in newborns/juvenile animals as compared to those in adults. Similarly in humans, no remarkable differences based on age were observed in the PK profile of micafungin.

Table 5. Relative exposure in juveniles and adults at identical doses

Species	Treatment Duration	IV Dose (mg/kg/day)	Adult AUC _{0-24h} (µg·h/mL)	Juvenile AUC _{0-24h} (µg·h/mL)
Rat (SD)	4 week	32	853	644 (0.8-fold)
	13 week	32	1383	1302 (0.9-fold)
Male Dog (Beagle)	39 week	32	1234	883 (0.7 fold)
Patients	Day 7 (adults)/Day 4 (children)	4	339	302 (0.9-fold)

Clinical Study FG463-21-03 (adults; undergoing bone marrow or peripheral stem cell transplant); Clinical Study 98-0-043 (children 2-17 years; Febrile neutropenic patients)

The absence of any novel toxicities or altered clinical safety margins at comparable micafungin exposure levels in juvenile (4 day old rat and 3 week old dog) animals suggests the same safety concerns exist for paediatric patients as it does for adults: the potential for histamine release (and associated reactions), risk for haemolytic anaemia, hepatotoxicity, effects on the male genital tract and injection site reactions.

M5 metabolite

In clinical studies in which micafungin was administered to neonates and young infant patients the exposure of micafungin M5 metabolite, was greater than 20% of total drug-related exposure (AUC_{0-24h} = 266.4 µg.h/mL for patients dosed at 10 mg/kg/day [Study 9463-CL-2104]) and higher than M5 exposure demonstrated in the previous micafungin toxicity studies in animals. Therefore an evaluation of the repeated dose toxicity in juvenile rats and genotoxicity with the M5 metabolite was conducted.

No remarkable toxicities were identified in juvenile rats given IV bolus doses of M5 up to 32 mg/kg/day for up to 8 weeks. At this NOAEL (32 mg/kg/day), rat exposure (AUC_{0-24h} = 1472 µg.h/mL) was 5-6 fold higher than that reported for human neonates and young infants.

Non-GLP compliant *in vitro* genotoxicity studies conducted in the presence M5 were negative and *in silico* tools (DEREK and Lead Scope) did not indicate any genotoxic alerts for the M5 chemical structure. The higher exposure and longer duration of dosing with M5 in neonatal rats and negative genotoxicity profile suggests no safety concerns are warranted for the potential clinical exposure to M5 at proposed micafungin dose regimen in adult or paediatric patients.

Comments on the safety specification of the Risk Management Plan

Results and conclusions drawn from the nonclinical program for micafungin detailed in the sponsor's draft Risk Management Plan (RMP) are in general concordance with those of the nonclinical evaluator with the following exceptions:

- Toxicological Studies: There were occasional discrepancies between NOAELs reported for toxicity findings, however this does not markedly alter the safety profile for micafungin.
- Reproductive/developmental toxicity: There were embryofetal effects in rabbits with an abortion and visceral abnormalities observed in rabbits at micafungin doses of 32 mg/kg/day IV. However, these findings are captured in the nonclinical evaluator's recommendations for the PI document.

Nonclinical summary and conclusions

- Astellas Pharma Australia Pty Ltd has applied to register a new chemical entity, micafungin (Mycamine) for the treatment of invasive candidiasis, the treatment of oesophageal candidiasis and prophylaxis of *Candida* infection in patients undergoing allogeneic HSCT or patients who are expected to have neutropenia for 10 or more days. The maximum proposed clinical dose for any indication is 200 mg/day once daily by IV injection in patients weighing greater than 40 kg. With the exception of oesophageal candidiasis, these indications are proposed for patients of all ages. The minimum treatment duration is for 14 days and at least one week after the resolution of relevant serology parameters, clinical signs or symptoms of infection.
- Micafungin was shown to possess a broad spectrum and activity against relevant *Candida* species *in vitro* and relevant murine models of fungal infections (disseminated candidiasis and oesophageal and oropharyngeal candidiasis) *in vivo*.
- An adequate battery of safety pharmacology studies demonstrated a range of CNS, cardiovascular and renal effects of micafungin in rodents. Haemodynamic effects (decreased blood pressure and increased heart rate) consistent with histamine release were seen in rats. Haemolysis was seen *in vitro* and haemolytic anaemia were seen *in vivo* in toxicity studies. Renal effects included urinary volume and excretion of electrolytes in rats. All of these occurred at clinically-relevant exposures/concentrations. No significant effect on autonomic nervous system or gastrointestinal function was seen.
- Micafungin demonstrated a similar biphasic plasma concentration time profile after IV administration in all nonclinical species including humans, with evidence of accumulation observed in rats, but not dogs or humans following repeated dosing. Micafungin was extensively protein bound in all species and rapidly distributed to organs and tissues. All human metabolites were also detected in rats and dogs, however no metabolite profiling was performed in rabbits, therefore the validity of this model is uncertain. The biliary-faecal route was the major excretion route in rats, dogs and humans.
- Micafungin was a substrate for CYP3A *in vitro*. However, it was not a significant inducer or inhibitor of CYP isoenzymes at clinically relevant micafungin concentrations *in vitro*. Interactions with other protein bound drugs were not anticipated at therapeutic micafungin doses. Micafungin was also not an inhibitor of P-glycoprotein *in vivo*.
- A comprehensive toxicology dossier for micafungin was provided, with pivotal studies GLP compliant and generally adequately conducted. The acute IV toxicity of micafungin in rats and dogs was low.
- The toxicity of repeated IV doses of micafungin was examined in relevant animal species, rats and dogs, dosed for up 6 and 9 months, respectively. The primary organs for toxicity were identified as the liver (increased liver enzymes, single cell necrosis, cellular and nuclear hypertrophy, foci of altered hepatocytes with further progression

to tumour formation) and urinary tract (vacuolation of the transitional epithelium and haemosiderin deposition in the proximal tubular epithelium) in rats, and blood (haemolytic anaemia) and male reproductive organs (reduced testicular weight, atrophy of the seminiferous tubules and oligospermia) in both rats and dogs. All of these occurred at clinically-relevant exposures and suggest monitoring for liver and kidney function, as well as potential haemolytic anaemia, would be warranted in the clinical setting.

- Injection site irritation was observed in rat studies at subclinical IV doses and concentrations. Therefore it is recommended that injection sites be checked routinely for signs of excessive local irritation.
- Micafungin did not demonstrate any mutagenic or clastogenic potential in an adequate battery of *in vitro* and *in vivo* studies. No standard carcinogenicity studies were performed for micafungin. This is acceptable for a substance intended for short-term (<3 months continuous) use.
- A standard battery of reproductive toxicity studies was performed in rats and rabbits given repeated IV bolus doses of micafungin. Testicular and epididymal changes with reduced sperm counts were seen in treated male rats at subclinical exposures. However, there was no effect on functional fertility when both male and female rats were treated. Micafungin and/or its metabolites crossed the placenta in rats with evidence of embryofetotoxicity seen in rabbits at low exposures. Significant excretion of micafungin and its metabolites was observed in the milk of lactating rats. In a pre- and postnatal development study in rats, reduced pup birth weights and a possible delay in the time of eyelid opening and balanopreputia cleavage were seen. Exposure at the NOAEL for pre- and postnatal pup effects was similar to the anticipated clinical exposure at the MRHD.
- Micafungin was a slight intramuscular irritant.
- Micafungin did not induce any delayed or immediate hypersensitivity reactions.
- Specified micafungin-related impurities were qualified by the submitted nonclinical data. Micafungin photodegradants have not been adequately characterised for evaluation.¹⁵
- Repeat dose toxicity studies performed in juvenile rats and dogs at identical doses and similar micafungin exposure levels to those of adult rats and dogs, identified no novel toxicities or remarkable change in the clinical safety margins for potential toxicities.

Overall conclusions and recommendation

- A comprehensive nonclinical submission was provided for micafungin which demonstrated efficacy against relevant *Candida* strains *in vitro* and in appropriate murine models *in vivo*.
- The toxicological profile of micafungin was well-defined and identified potential hepatotoxic, renal, haemolytic, male reproductive tract and injection site irritation effects with repeated IV micafungin administration at low micafungin exposure levels. However, the toxicity profile of micafungin is typical of that seen with other echinocandin antifungal agents and has similar safety margins.
- Given the intended short duration of treatment proposed and unclear clinical relevance for some of these toxicities, routine clinical monitoring of liver and kidney

¹⁵ Adequate data to qualify an acceptable limit were subsequently provided to the TGA before a decision was made on this application (see *Overall conclusion and risk/benefit assessment; Delegate's overview*, below).

function, haematological parameters and local injection reactions may be sufficient to mitigate any potential safety concerns associated with repeated micafungin use.

- There are no nonclinical objections to the registration of Mycamine provided an adequate safety monitoring program is implemented, as deemed appropriate by the clinical evaluator.
- Some changes to the RMP are noted.
- Recommended revisions to the nonclinical aspects of the draft PI are beyond the scope of this AusPAR.

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

Astellas Pharma Australia Pty Ltd has applied to register a new chemical entity, micafungin (Mycamine) for the treatment of invasive candidiasis, the treatment of oesophageal candidiasis and prophylaxis of *Candida* infection in patients undergoing allogeneic haematopoietic stem cell transplantation (HSCT) or patients who are expected to have neutropenia for 10 or more days.

Invasive fungal infections are associated with significant morbidity and mortality in immunocompromised and immunodeficient patients. Micafungin is a semi-synthetic derivative of natural echinocandin B belonging to the echinocandin class of antifungal agents. Other class members include anidulafungin (Eraxis) and caspofungin (Cancidas). Micafungin and other echinocandins inhibits 1,3- β -D-glucan synthase, thereby inhibiting the synthesis of 1,3- β -D-glucan, a major component of the cell wall of most fungi.

Contents of the clinical dossier

Clinical study information was provided in support of this application. This consisted of information from a total of 63 studies, comprising 35 PK studies, 20 efficacy and safety studies, and 8 post-marketing studies. Of the PK studies, 5 assessed PK in healthy subjects, 12 assessed PK in infected patient groups, 4 assessed PK in special populations, and 14 assessed potential drug interactions.

Of the efficacy/safety studies, 10 assessed efficacy in patients with confirmed candidaemia or invasive candidiasis, 4 assessed efficacy in oesophageal candidiasis and 6 assessed efficacy in prophylaxis of *Candida* infection.

Good clinical practice

No issues were identified in the clinical development program.

Pharmacokinetics

Studies providing pharmacokinetics data

Information on PK was provided in both the nonclinical and clinical submissions. In the clinical submission, information was provided by 35 clinical studies, including 5 studies assessing PK in healthy subjects, 12 studies in infected patient groups, 4 studies in special

populations and 14 studies involving potential drug interactions. Basic PK parameters were obtained from the 5 clinical studies involving healthy subjects.

Evaluator's overall conclusions on pharmacokinetics

The PK of micafungin administered by IV infusion have been extensively characterised. Information was available from 5 PK studies in healthy subjects, 12 PK studies in infected patient groups, 4 PK studies in special populations and 14 PK studies assessing possible drug interactions. The PK of micafungin was evaluated in healthy subjects, HSCT recipients and patients with invasive and oesophageal candidiasis up to a maximum dose of 8 mg/kg.

There is no evidence of systemic accumulation with repeated administration and increases in systemic exposure (AUC and C_{max}) are proportional to increases in dose. Steady-state is generally reached by Day 4. Following IV administration, concentrations of micafungin show a bi-exponential decline as the drug is rapidly distributed into tissues. Micafungin is highly protein bound (> 99%), primarily to albumin and to a lesser extent to alpha-1-acid glycoprotein. Binding to albumin is independent of micafungin concentration (10 to 100 µg/mL). Micafungin does not displace albumin-bound bilirubin at clinically relevant concentrations and is therefore not expected to cause kernicterus. From information provided in the application, the blood to plasma ratio was approximately 0.85 and was independent of concentration over the range of 0.1 to 10 µg/mL micafungin. The percent transfer into human red blood cells was approximately 35%. The volume of distribution of micafungin at terminal phase was 0.24 to 0.41 L/kg body weight. Unchanged micafungin is the principal circulating compound in the systemic circulation.

Metabolism takes place in the liver where micafungin is metabolised to M1 (catechol form) by arylsulfatase, with further metabolism to M2 (methoxy form) by catechol-O-methyltransferase. M5 is formed by hydroxylation at the side chain (ω -1 position) of micafungin catalysed by cytochrome P450 (CYP) isoenzymes. Exposure to these metabolites is low and they do not contribute to the overall efficacy of micafungin. Although micafungin is a substrate for CYP3A *in vitro*, hydroxylation by CYP3A is not a major pathway for metabolism *in vivo*. The mean half-life of micafungin is approximately 10 to 17 hours and stays consistent across doses up to 8mg/kg after single and repeated administration in patients and healthy volunteers.

Faecal excretion is the major route of elimination. In 97-0-040, following a single IV dose of ^{14}C -micafungin (25 mg) to healthy volunteers, 11.6% of the radioactivity was recovered in the urine and 71.0% in the faeces over 28 days.

With regard to PK in special populations, subjects with severe renal impairment (glomerular filtration rate (GFR) < 30 mL/min), moderate hepatic dysfunction (Child-Pugh score of 7-9) or severe hepatic dysfunction (Child-Pugh score of 10-12) showed no marked differences in micafungin PK compared with age-, weight-, and sex-matched normal subjects, and elderly male subjects showed no significant differences in micafungin PK parameters compared with young male subjects.

With regard to PK interactions, no interaction that altered the PK of micafungin was observed. There was no effect of single-dose or steady-state micafungin on the PK of mycophenolate mofetil (MMF), cyclosporin, tacrolimus, prednisolone, fluconazole, voriconazole, ritonavir or rifampicin. Increases in exposure (AUC) for sirolimus (by 21%), nifedipine (by 18%) amphotericin B (by 30%) and itraconazole (by 22%) in the presence of steady-state micafungin were noted.

Pharmacodynamics

Studies providing pharmacodynamics data

Information on pharmacodynamics (PD) was provided in the application, and was supported by a description of the mechanism of action, information on microbiology (including both susceptibility and resistance considerations), and information from clinical studies, which are described in the *Efficacy* section of this report.

Secondary pharmacology was assessed in the nonclinical evaluation.

Evaluator's overall conclusions on pharmacodynamics

Information on PD was largely provided from nonclinical data, although it was supported by information from the clinical development program.

Micafungin is a member of the echinocandin lipopeptide family and inhibits non-competitively the synthesis of 1,3- β -D-glucan, an essential component of fungal cell walls which is not present in mammalian cells. Micafungin displayed potent activity against clinically relevant *Candida* species. The MIC rank order was: *C. albicans* (including azole resistant strains) < *C. tropicalis*, *C. glabrata* < *C. krusei* << *C. parapsilosis*, *C. guilliermondii*. With the exception of *C. parapsilosis* and *C. guilliermondii*, micafungin was generally more potent against the tested *Candida* species than amphotericin B, fluconazole and itraconazole. MIC values for micafungin were lower compared to caspofungin. Micafungin has virtually no activity against *Cryptococcus neoformans*, *Trichosporon cutaneum*, *Trichosporon asahii*, *Fusarium solani*, *Pseudallescheria boydii*, *Absidia corymbifera*, *Cunninghamella elegans*, *Rhizopus oryzae* or *Rhizopus microspores*.

The primary pharmacology of micafungin has been extensively characterised, and is consistent with the other members of the same pharmacological class as shown below.

Table 6. *In vitro* activities of the Echinocandins Micafungin, Caspofungin and Anidulafungin

	MIC ₉₀ (MIC range when MIC ₉₀ not available)					
	n	Micafungin	n	Caspofungin	n	Anidulafungin
<i>C. albicans</i>	966	0.01-0.25	4265	0.12-1.0	2394	0.01-0.5
<i>C. glabrata</i>	524	0.01-0.5	1289	0.25-1.0	993	0.03-8
<i>C. parapsilosis</i>	439	1.0->8	1034	1-4	231	2->8
<i>C. tropicalis</i>	364	0.03-2	811	0.12-1.0	548	0.06-2
<i>C. krusei</i>	82	0.12-0.25	221	0.5-2	207	0.03-1.0
<i>C. dubliniensis</i>	40	0.03-0.5	177	0.5	92	0.06-4
<i>C. guilliermondii</i>	24	2	158	1.0->8	27	(0.06-4)
<i>C. lusitaniae</i>	23	2	114	0.5-2	81	0.12->8
<i>A. fumigatus</i>	35	≤ 0.01	480	0.12-0.5	94	0.06
<i>A. flavus</i>	18	0.01	127	0.12-0.5	53	≤ 0.03
<i>A. niger</i>	20	< 0.01	68	0.5	21	≤ 0.03
<i>A. terreus</i>	12	< 0.01	42	0.5	10	(<0.03)

MIC₉₀: Minimum inhibitory concentration of study compound needed to prevent 90% of the test organism from growing. Data were obtained in accordance with the National Committee for Clinical Laboratory Standards (NCCLS) guidelines for antifungal susceptibility testing of yeasts or by modified versions. MIC₉₀ values are from the review article by A Espinel-Ingroff [2003], which takes into account MIC₉₀ values from several studies.

n: number of isolates.

Efficacy

Studies providing efficacy data

Information on clinical efficacy of micafungin was provided for each of the three indications: Invasive Candidiasis (IC), Oesophageal Candidiasis (OC), and Prophylaxis of Invasive Fungal Infection (IFI).

The efficacy and safety of micafungin in IC was assessed in the pivotal Phase III reference therapy controlled non-inferiority trials FG-463-21-08 and 03-0-192. Supportive data for the efficacy and safety of micafungin in IC was provided by a further 8 studies, 98-0-047, FJ-463-0003, 98-0-046, FJ-463-0006, FJ-463-FP01, 01-0-125, 9463-CL-1302 and MCFGCAN-03.

Clinical studies that assessed the efficacy and safety of micafungin in the treatment of EC include the pivotal Phase III Studies 03-7-005 and 03-7-008. Supportive data for the efficacy and safety of micafungin in EC was provided by a further 2 studies, 97-7-003 and FG463-21-09.

A pivotal Phase III, reference therapy controlled trial was also conducted for prophylaxis of IFI, Study 98-0-050. Supportive data for the efficacy and safety of micafungin in prophylaxis of IFI was provided by a further 5 studies, 01-0-124, 97-0-041, 98-0-043, FG-463-21-03, and MCFGCN02-0.

In addition, a total of 5 ongoing studies were noted in the application. These included 9463-EC-0001 (Phase IIIb, high risk liver transplant recipients), 9463-EC-0002 (Phase III, high risk surgical subjects), 9463-CL-2101 (Phase I, children and adolescents with oesophageal candidiasis or other invasive candidiasis), 9463-CL-2303 (Phase III, treatment of neonatal candidiasis) and 9463-CL-1401 (observational study, safety).

Evaluator's overall conclusions on clinical efficacy

Information on clinical efficacy was provided by a total of 19 studies. Claims of clinical efficacy were separated into the three specific indications, oesophageal candidiasis and prophylaxis of candidiasis. For invasive candidiasis, there were 2 pivotal studies and 8 supporting studies, for oesophageal candidiasis there were 2 pivotal studies and 2 supporting studies, and for prophylaxis there was one pivotal study and 5 supporting studies. The 2 pivotal studies for efficacy and safety of micafungin in **invasive candidiasis** were Phase III reference therapy controlled non-inferiority trials FG-463-21-08 and 03-0-192. These studies had the following characteristics:

- Micafungin 100 mg once daily was included as one of the treatment arms.
- Entry criteria were similar. Patients could be neutropenic or non-neutropenic; Study 03-0-192 allowed 2 days of prior therapy while Study FG-463-21-08 allowed 3 days of prior therapy; Study 03-0-192 excluded patients with known endocarditis, osteomyelitis or meningitis due to *Candida*.
- Patients had to have proven invasive candidiasis/candidemia documented by culture and clinical signs and symptoms within 4 days prior to study entry.
- Patients were stratified by Acute Physiology And Chronic Health Evaluation II (APACHE II) score and region in Study 03-0-192 and by neutropenic status in Study FG-463-21-08.
- Length of treatment was at least 14 days for both Study 03-0-192 and Study FG-463-21-08; in Study 03-0-192, patients could be switched to an oral antifungal after 10 doses of IV study drug if predefined criteria were met, including two negative blood cultures drawn at least 24 hours apart.

- Non-inferiority margin was set at 15% for both studies.
- The definition of the primary endpoint was similar; patients with missing efficacy data at the end of therapy were counted as failures in both studies. The primary endpoint was the response rate from the investigator's assessment of overall treatment success, which was defined as a clinical response (complete or partial) and a mycological response (eradication or presumed eradication) at end of therapy (EOT).
- The primary analysis set was the full analysis set (FAS) in Study 03-0-192 and the per protocol set (PPS) in Study FG-463-21-08. The FAS in Study 03-0-192 excluded patients with endocarditis, osteomyelitis or meningitis due to *Candida*; these patients were included in the PPS in Study FG-463-21-08.
- An independent review panel was utilised to confirm diagnosis and outcome for each patient who received at least one dose of study medication.
- Patients were followed for 6 weeks after the last dose of study drug for relapse and safety in both studies; Study FG-463-21-08 also included a 12-week follow-up visit.

Guidance on study design for clinical evaluation of antifungal agents is provided by EMEA CHMP/EWP/1343/01 *Guideline on the Clinical Evaluation of Antifungal Agents for the Treatment and Prophylaxis of Invasive Fungal Disease*. This requires that for monotherapy, data from at least one randomised and double blind study that compares test and reference antifungal regimens would normally be considered necessary to demonstrate a satisfactory risk-benefit relationship for use of an agent in a specific type of IFD. These studies should be of adequate power to demonstrate at least non-inferiority for the test versus reference regimen using an appropriate value of delta. For this indication, 2 studies were provided that met this requirement.

FG-463-21-08 was a multicentre, double-blind, comparative, randomised study to evaluate the efficacy and safety of micafungin (FK463) versus liposomal amphotericin B (Ambisome) in the treatment of invasive candidiasis and candidaemia. Treatment success was experienced by 89.6% (181/202) and 89.5% (170/190) of patients in the micafungin and Ambisome groups, respectively (PPS). The difference in proportions of micafungin *minus* Ambisome adjusted for neutropenic status was 0.7%. Noninferiority of micafungin compared with Ambisome was demonstrated; the lower bound of the 1-sided 97.5% confidence interval (CI) adjusted for neutropenic status at baseline of [-5.3%, 100%] was above the pre-defined non-inferiority margin of -15%.

03-0-192 was a multicentre, double-blind, comparative, randomised study to evaluate the efficacy and safety of micafungin (FK463) versus caspofungin in the treatment of invasive candidiasis and candidaemia. A total of 147/199 (73.9%), 142/202 (70.3%), and 137/192 (71.4%) patients in the micafungin 100 mg, micafungin 150 mg, and caspofungin treatment groups, respectively, were assessed by the investigator as treatment successes at the end of blinded therapy. The 95% CI for the comparison of micafungin 100 mg to caspofungin was [-5.9%, 11.0%]. The 95% CI for the comparison of micafungin 150 mg to caspofungin was [-9.3%, 7.8%]. The 95.0% CIs constructed around the treatment differences (experimental regimen, caspofungin) for the investigator's assessment of treatment success at the end of blinded therapy had lower bounds > -15%, indicating both micafungin regimens were non-inferior to caspofungin for the primary endpoint.

There were 8 supporting studies. Three of the studies were not applicable to the indication, as they considered aspergillosis only (98-0-046, 01-0-125, and 9463-CL-1302). Of the remaining studies, 4 were open-label (98-0-047, FJ-463-0003, FJ-463-0006 and FJ-463-FP01) and 1 study (MCFGCAN-03) was a randomised controlled study conducted in China comparing micafungin with fluconazole.

The two pivotal studies for **oesophageal candidiasis** were Phase III studies 03-7-005 and 03-7-008. The primary endpoint for both studies was treatment success (endoscopic

cure), which was defined as an oesophageal mucosal grade of 0 at EOT. Both studies were formally designed as non-inferiority studies, and met the requirement of EMEA CHMP/EWP/1343/01 *Guideline on the Clinical Evaluation of Antifungal Agents for the Treatment and Prophylaxis of Invasive Fungal Disease*.

03-7-005 was a Phase III, randomised, double-blind, comparative trial of micafungin (FK463) versus fluconazole for the treatment of oesophageal candidiasis. The endoscopic cure rate was 87.7% for micafungin patients as compared to 88.0% for fluconazole patients. The -0.3% treatment difference had a 95% CI of [-5.9%, 5.3%]. Since the -5.9% lower bound was greater than -10%, micafungin was considered non-inferior to fluconazole.

03-7-008 was a Phase III, randomized, double-blind, comparative trial of two dosing regimens of micafungin (FK463) versus caspofungin for the treatment of oesophageal candidiasis. The treatment difference for success (mucosal grade = 0) at end of therapy between the micafungin 150 mg once daily (qd) and caspofungin 50 mg qd treatment groups was 0.6%, with a 95% CI of (-5.6%, 6.8%). These data indicate micafungin 150 mg qd was non-inferior to caspofungin 50 mg qd based on the pre-defined non-inferiority limit of 15%. The treatment differences and 95% CIs in treatment success for the modified FAS and PPS supported the conclusion that micafungin 150 mg qd was non-inferior to caspofungin 50 mg qd. The 95% CI for the difference in treatment success (mucosal grade = 0) at the end of therapy was (-2.5%, 8.9%) for micafungin 300 mg every other day (qod) versus caspofungin 50 mg qd and (-3.1%, 8.2%) for micafungin 300 mg qod versus micafungin 150 mg qd. These results indicate that micafungin 300 mg qod was non-inferior to caspofungin 50 mg qd and comparable to micafungin 150 mg qd.

There were 2 supporting studies. Study 97-7-03 was an open-label study in adult HIV-positive patients with oesophageal candidiasis. Study FG-463-21-09 was a RCT/ dose response study comparing micafungin and fluconazole in adult HIV-positive patients with oesophageal candidiasis. Clinical response at EOT in the FAS showed a clearance rate of 75.8% (47/62), 92.9% (52/56), 92.7% (51/55) for the 50 mg/day, 100 mg/day and 150 mg/day micafungin groups, respectively, and 93.0% (53/57) for the fluconazole group. Mycological findings at EOT in the FAS showed mycological eradication for 35.1% (20/57), 78.3% (36/46) and 57.1% (28/49) of patients in the 50 mg/day, 100 mg/day and 150 mg/day micafungin groups, respectively, and 67.3% (35/52) of patients in the fluconazole group. Overall dose response findings from this study indicated greater efficacy with 100 mg/day and 150 mg/day micafungin compared with 50 mg/day micafungin.

It should be noted for this indication that over 90% of the subjects for all clinical studies were HIV-positive. Several patient groups are at risk for developing oesophageal candidiasis, including HIV infected patients, cancer patients, transplant patients and hospitalised patients on antibiotics and steroids. As such, only limited data was available for non HIV-positive patients with oesophageal candidiasis. EMEA CHMP/EWP/1343/01 *Guideline on the Clinical Evaluation of Antifungal Agents for the Treatment and Prophylaxis of Invasive Fungal Disease* requires that if it is anticipated that the study population will include a substantial proportion of subjects infected with HIV it would be appropriate that the analyses should include an assessment of outcomes according to response to anti-retroviral therapy (that is, maintenance of viral suppression and CD4 count). Study 3-7-005 indicated that exploratory logistic regression analysis of the effect of potential prognostic factors on endoscopic cure rate indicated that the odds of curing HIV patients was approximately 3.6 times higher than the odds of curing non-HIV patients. In addition, every 1-point increase in the total baseline clinical symptom score was associated with a 16% reduction in the odds of achieving endoscopic cure. In HIV patients with a baseline CD4 count ≥ 100 , the odds of endoscopic cure was approximately 2.6 times higher than the odds in HIV patients with a baseline CD4 count < 100 . Every 1-point increase in total

baseline clinical symptom score was associated with an 18% reduction in the odds of achieving endoscopic cure.

The pivotal study for **prophylaxis of candidiasis** was Study 98-0-050. The primary efficacy endpoint was treatment success, defined as the absence of a proven, probable, or suspected systemic fungal infection through the EOT and the absence of a proven or probable systemic fungal infection through the end of the 4-week post-treatment period. Both criteria had to be met in order for the patient to be considered a treatment success. The difference in the success rates between patients treated with micafungin and those treated with fluconazole defined the magnitude of the treatment effect. A large sample normal approximation of the binomial distribution was used to construct a 2-sided 95% CI for the difference in the success rates. If the lower limit of the CI was $\geq -10\%$, then micafungin was considered to be non-inferior to fluconazole. If the lower limit of the CI exceeded 0%, then micafungin was considered to be statistically superior to fluconazole.

98-0-050 was a Phase III, randomised, double-blind, comparative trial of micafungin (FK463) versus fluconazole for prophylaxis of fungal infections in patients undergoing a HSCT. In the FAS, the overall success rate for FK463 was significantly higher than the rate for fluconazole patients (80.0% versus 73.5%). The treatment difference was +6.5% (95% CI: 0.9%, 12.0%). The Kaplan-Meier estimate of treatment success was significantly different between the two treatment arms ($p=0.025$). This treatment difference was consistent in patients who underwent an allogeneic (+3.0%) or autologous (+9.1%) transplant. The treatment benefit of FK463 was consistent across all subgroups analyzed, including the PPS which required an absolute neutrophil count (ANC) <200 cells/mm³. A Cox regression analysis showed that FK463 and the use of haematopoietic growth factors were associated with treatment success. The overall incidence of proven or probable systemic fungal infections was 1.6% in the FK463 treatment arm and 2.4% in the fluconazole treatment arm based on a blinded review of the cases using the protocol-specified diagnostic criteria. Both study drugs were effective in preventing candidiasis with an incidence of 0.9% in the FK463 arm and 0.4% in the fluconazole arm.

There were 5 supporting studies. Study 01-0-124 was an RCT in intensive care patients, and was terminated early due to low incidence of fungal endpoints. Study 97-0-041 was an RCT to assess the maximum tolerated dose (MTD) of micafungin in combination with fluconazole, which is not the proposed indication. Study 98-0-043 was an open-label study to assess MTD in paediatric patients. Study FG463-21-03 was an open-label study to assess MTD in adults undergoing bone marrow or peripheral stem cell transplant. Study MCFGN02 was an RCT to assess efficacy of micafungin versus itraconazole in patients undergoing autologous or allogeneic HSCT.

EMA CHMP/EWP/1343/01 *Guideline on the Clinical Evaluation of Antifungal Agents for the Treatment and Prophylaxis of Invasive Fungal Disease* requires that it is expected that studies that assess the use of an antifungal agent for prophylaxis of IFD would be conducted only after an agent has demonstrated satisfactory clinical efficacy in the treatment of several types of IFD. The general principles outlined in respect of the design of studies for the treatment of IFD are relevant to studies of prophylaxis. At least one randomised, comparative study with sufficient statistical power to demonstrate superiority or exclude inferiority of the investigational regimen versus an appropriate active comparative regimen would be necessary in order to support the use of an antifungal agent for prophylaxis against IFD. These principles appear to have been met by the clinical study information provided.

Specific information on dose selection was also provided in the application for each of the three proposed indications. EMA CHMP/EWP/1343/01 *Guideline on the Clinical Evaluation of Antifungal Agents for the Treatment and Prophylaxis of Invasive Fungal Disease* notes that the need for and extent of formal dose-ranging studies in patients with IFD and the possibility of conducting confirmatory studies that employ an adaptive design

may be considered on a case by case basis. This requirement appears to have been met in the clinical information and justification provided. For invasive candidiasis, dosage information was largely based on Study 98-0-047/FG-463-21-02, in which a mean \pm standard deviation (SD) daily dose of 74.9 ± 34.1 mg for adults and 1.5 ± 0.9 mg/kg for children were associated with high success rates in candidaemia and IC patients who received micafungin monotherapy. The treatment success rate for these patients was 79.5% (105/132) of patients, with 79/98 (80.6%) newly diagnosed patients and 26/34 (76.5%) efficacy failure patients having experienced treatment success (PPS). For oesophageal candidiasis, dosage information was obtained from 2 dose response studies, studies 97-7-003 and FG-463-21-09. No rationale for a paediatric dosage was given, and the vast majority of subjects were HIV positive adults. Use of micafungin in the paediatric population for this indication is not being sought in this application. For prophylaxis of invasive fungal disease, paediatric dosage information was based on the consideration of a 30% lower body weight in children than adults. An adult body weight of 54 kg was used (the mean body weight in study FG-463-21-09) for this calculation, as micafungin is likely to be used in patients who weigh less than the normal population (generally 70 kg). For adult patients, dosage information was supported by Study 98-0-050. At a daily dose of 50.0 mg (1.0 mg/kg for patients < 50 kg), micafungin was significantly more effective in preventing IFI and reducing the use of empirical antifungal therapy than fluconazole (400 mg/day, 8 mg/kg/day for patients weighing < 50 kg) in high risk patients (HSCT patients with neutropenia).

No pivotal study was provided that assessed efficacy in only paediatric patients, although some studies did include paediatric patients. EMEA CHMP/EWP/1343/01 *Guideline on the Clinical Evaluation of Antifungal Agents for the Treatment and Prophylaxis of Invasive Fungal Disease* notes that in general, factors that predispose to IFD in children are similar to those in adults and the range of fungal pathogens encountered is the same. Therefore, a demonstration of efficacy in specific circumstances in adults may be extrapolated to use in the same circumstances in children. Information provided in the clinical development program supported this extrapolation.

Safety

Studies providing safety data

Information on safety was available from the clinical development program, as well as extensive post-marketing experience. In addition, a total of 8 post-marketing surveillance studies were conducted.

Patient exposure

The cumulative safety population comprises 5102 subjects who were enrolled and received at least one dose of study drug in 41 clinical studies. Of these, 3584 subjects ("all micafungin subjects"), including 3083 patients ("all micafungin-treated patients") and 501 volunteers, received at least one dose of micafungin. A total of 82.8% of the 3083 patients who received at least one dose of micafungin had ≥ 10 days of treatment with a mean duration of treatment of 20 days. A summary of exposure to micafungin in the clinical studies is shown in Table 7.

Table 7. Summary of patient exposure

	Micafungin	Fluconazole	Caspofungin	AmBisome	Placebo	Total
Volunteers	501	0	0	0	14	515
Patients	3083	787	345	321	51	4587
TOTAL	3584	787	345	321	65	5102

Subject base: all randomized/enrolled subjects who received at least one dose of study drug.

Indication	Cumulative Safety Population		
	Patients	Volunteers	Total
Prophylaxis	1226	142	1368
	1405	176	1581
Esophageal candidiasis	1667	416	2083
	1980	422	2402
Esophageal candidiasis Alternative dosing regimen	2310	443	2753
	2650	501	3151
Invasive candidiasis/ candidemia	3083	501	3584

Evaluator's overall conclusions on clinical safety

Information on safety was available from the clinical development program, as well as extensive post-marketing experience. In addition, a total of 8 post-marketing surveillance studies were conducted. The safety database comprised 5102 subjects who were enrolled and received at least one dose of study drug in 41 clinical studies. Of these, 3584 subjects, including 3083 patients and 501 volunteers, received at least one dose of micafungin. A total of 82.8% of the 3083 patients who received at least one dose of micafungin had ≥ 10 days of treatment with a mean duration of treatment of 20 days.

Guidance on study design for clinical evaluation of antifungal agents is provided by EMEA CHMP/EWP/1343/01 *Guideline on the Clinical Evaluation of Antifungal Agents for the Treatment and Prophylaxis of Invasive Fungal Disease*. This notes that the evaluation of the safety of anti-fungal agents is not straightforward due to factors such as serious underlying diseases in the majority of patients with IFD, large numbers of concomitant medications, and, in many cases, the considerable potential for clinically significant drug-drug interactions to occur.

The most frequently reported adverse events (AEs) irrespective of causality were diarrhoea not otherwise specified (NOS), nausea, vomiting, pyrexia. A treatment-related AE was experienced by 32.2% of patients. The most frequently reported AEs assessed by the investigator as having at least a possible relationship to micafungin ($\geq 1\%$, Medical Dictionary for Regulatory Activities (MedDRA) preferred term) in the clinical database or in a pivotal study were the hepatic AEs (AST increased, ALT increased, ALP increased, liver function test (LFT) abnormal and hyperbilirubinemia); the haematological AEs (leukopenia, neutropenia and anaemia); the electrolyte disturbances (hypokalemia, hypocalcemia and hypomagnesaemia); the allergic like/histamine-related AEs (rash and rigors); the injection-site reaction phlebitis; as well as headache, nausea, vomiting, diarrhoea, pyrexia, thrombocytopenia, abdominal pain, pruritus, blood creatinine increased, blood bilirubin increased, blood urea increased, blood lactate dehydrogenase (LDH) increased, hypertension, hypophosphataemia, renal impairment, cholestasis and infusion site inflammation. Treatment-related haemolytic AEs were rare.

A total of 28.3% (873/3083) of micafungin-treated patients had a serious treatment-emergent adverse event during study participation. Serious treatment-emergent adverse events considered to be related to study drug by the investigators were reported in 3.6% (111/3083) of micafungin-treated patients. The most frequent serious treatment-emergent adverse events in micafungin-treated patients, regardless of relationship to study drug, were respiratory failure (3.1%), sepsis NOS (2.8%), septic shock (1.7%),

hypotension NOS (1.4%), pneumonia NOS (1.2%), multi-organ failure (1.2%), and respiratory distress (1.0%).

Death occurred in 671 of 3083 (21.8%) of micafungin-treated patients: 134 (4.3%) deaths occurred in patients during study drug treatment, and 537 (17.4%) deaths occurred during the post treatment period. The most common primary causes of death that were reported for micafungin-treated patients were septic shock (1.6% [50/3083]), sepsis NOS (1.6% [48/3083]), respiratory failure (1.6% [50/3083]), and multi-organ failure (1.3% [40/3083]).

In the paediatric population, the incidence of some AEs in the clinical study database (thrombocytopenia, tachycardia, hypertension, hypotension, hyperbilirubinemia, hepatomegaly, renal failure acute, blood urea increased) was higher in paediatric patients than adult patients. Additionally, paediatric patients < 1 year of age experienced about two times more often an increase in ALT, AST and ALP than older paediatric patients. No clinically meaningful differences in the safety profile could otherwise be discerned.

A total of 13.3% (409/3083) of all micafungin-treated patients were withdrawn from study drug due to AEs, regardless of causality. In all micafungin-treated patients, the most frequent AEs leading to drug withdrawal, regardless of relationship to study drug, were septic shock (0.9%), sepsis NOS (0.8%), respiratory failure (0.8%), and multiorgan failure (0.8%).

Considerable post-marketing information was also provided. The total exposure was 38,498 patient-months. The cumulative exposure to date is estimated to be 436,885 patient-months. There were no actions taken regarding micafungin for safety reasons by either the regulatory authorities or by the Marketing Authorisation Holder (MAH). Overall, a total of 106 medically confirmed case reports fulfilled the criteria for inclusion as significant AEs. The cumulative number of cases that fulfilled these criteria was 1,498. There were 22 case reports with a fatal outcome. In addition, results from 8 post-marketing surveillance studies were provided. No new safety issues were identified as a result of these studies.

List of questions

There were no clinical questions.

Clinical summary and conclusions

Assessment of benefits

From the clinical information provided, application has been sought for micafungin for treatment of invasive candidiasis, oesophageal candidiasis and prophylaxis for invasive fungal infections. As part of the clinical development program, a total of 5 pivotal Phase III studies were provided, with 2 studies addressing each of the first 2 indications, and 1 study addressing the latter indication. These studies demonstrated non-inferiority of micafungin compared to active comparators which are registered for use in Australia. Given the morbidity and mortality associated with the three proposed indications, it would appear that there are significant benefits to the introduction of this therapeutic product.

Assessment of risks

The safety profile has been well characterised from both the clinical development program and an extensive post-marketing surveillance program. While the target population has

significant morbidity and mortality due to their underlying conditions, the safety profile of micafungin appears to be at least comparable to other antifungal agents. This has been further reinforced by the post-marketing surveillance and experience with other antifungal agents in the same pharmacological class.

Assessment of benefit-risk balance

The application provided includes an assessment of possible benefits and risks of micafungin. This assessment is supported, and appears to be reasonable. The safety specification provided appears to address all significant risks.

On balance, micafungin appears to have an acceptable benefit-risk profile.

Recommendation regarding authorisation

The clinical evaluation supports the indications as proposed by the sponsor.

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted the Mycamine RMP for Australia (Version 1, March 2012) which was reviewed by the TGA's Office of Product Review (OPR).

Safety specification

Subject to the evaluation of the non-clinical aspects of the Safety Specification (SS) by the Toxicology area of the TGA Office of Scientific Evaluation and the clinical aspects of the SS by the Office of Medicines Authorisation (OMA), the summary of the Ongoing Safety Concerns as specified by the sponsor is as shown at Table 8.

Table 8. Ongoing safety concerns

Important <i>identified</i> risks	Clinical trial program/post-marketing experience: <ul style="list-style-type: none"> · Allergic-like/possible histamine-mediated AEs · Haemolytic AEs · Hepatic AEs · Renal AEs · Echinocandin cross-hypersensitivity · Stevens-Johnson syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) · Disseminated Intravascular Coagulation
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Important <i>potential</i> risks	Clinical trial program/post-marketing experience: <ul style="list-style-type: none"> · Pancytopenia · Relevance in humans of the development of liver tumours in rats · Effects on the male reproductive tract · Development of resistant strains
Important missing information	Non-clinical pharmacological and toxicity studies: <ul style="list-style-type: none"> · Reproductive and developmental toxicity

The sponsor proposes routine pharmacovigilance activities to monitor all of the ongoing safety concerns. Additional pharmacovigilance activities are also proposed for the important identified risks: 'allergic-like/possible histamine mediated AEs', 'haemolytic AEs', 'hepatic AEs' and 'renal AEs' and important potential risks: 'relevance in humans of the development of liver tumours in rats' and 'development of resistant strains'.

OPR reviewer comment:

Notwithstanding the evaluation of the non-clinical and clinical aspects of the SS, use in pregnant/lactating women has not been studied. Therefore it is recommended that the sponsor add 'use in pregnant/lactating women' as important missing information or provide justification for its omission.

The FDA previously requested additional paediatric information on micafungin to supplement the initial US paediatric program and at least one paediatric study is ongoing. As this study is considered additional pharmacovigilance it is recommended that the sponsor add 'use in paediatric patients' as important missing information or provide justification for its omission.

It is expected that if the above safety concerns are included they should be appropriately reflected in the RMP including consideration of the pharmacovigilance and risk minimisation activities that may apply.

Pharmacovigilance plan

The following is a summary of the pharmacovigilance plan proposed by the sponsor:

Table 9. Summary of the pharmacovigilance plan

Risk Classification	Safety Concern	Planned action(s)
Important <i>identified</i> risks	Allergic-like/possible histamine-mediated AEs	Specific standardised follow-up questionnaire and routine pharmacovigilance
	Haemolytic AEs	
	Hepatic AEs	Observational study and routine pharmacovigilance
	Renal AEs	
	Echinocandin cross-hypersensitivity	Routine pharmacovigilance

Risk Classification	Safety Concern	Planned action(s)
	SJS and TEN	Routine pharmacovigilance
	Disseminated Intravascular Coagulation	Routine pharmacovigilance
Important potential risks	Pancytopenia	Routine pharmacovigilance
	Relevance in humans of the development of liver tumours in rats	Observational study Routine pharmacovigilance
	Effects on the male reproductive tract	Routine pharmacovigilance
	Development of resistant strains	Routine pharmacovigilance Propose susceptibility breakpoints in a micro surveillance study protocol
Important missing information	Reproductive and developmental toxicity	Routine pharmacovigilance

OPR reviewer's comments in regard to the pharmacovigilance plan (PP) and the appropriateness of milestones

For the important identified risk 'allergic-like/possible histamine-mediated AEs' and 'haemolytic AEs' the use of a specific standardised follow-up questionnaire is proposed. This approach is considered to be acceptable and the draft questionnaires provided are appropriate.

Important identified risks 'hepatic AEs' and 'renal AEs' and the important potential risk 'relevance in humans of the development of liver tumours in rats' will be subject to additional pharmacovigilance by a multi-centre observational study. The risk of hepatic damage and dysfunction is the primary endpoint, and the risks of hepatocellular carcinoma (HCC) and renal damage and dysfunction are secondary endpoints.

The important potential risk 'development of resistant strains' will also be subject to additional pharmacovigilance by means of a resistance surveillance program.

The sponsor proposes that all other safety concerns are to be monitored with routine pharmacovigilance. This approach is considered acceptable. However insufficient detail is provided regarding the routine pharmacovigilance system.

The FDA had requested additional paediatric information on micafungin to supplement the initial US paediatric program. A safety and efficacy study comparing micafungin to amphotericin B deoxycholate for the treatment of neonatal candidiasis appears to be currently ongoing. This study is considered to be an additional pharmacovigilance activity and should be attributable to a safety concern within the RMP.

Risk minimisation activities

Planned actions

Routine risk minimisation is proposed for all ongoing safety concerns. Educational materials are proposed as additional risk minimisation for important identified risks: 'allergic-like/possible histamine-mediated AEs', 'haemolytic AEs', 'hepatic AEs' and 'renal

AEs' and the important potential risk: 'relevance in humans of the development of liver tumours in rats'.

The following is a summary of the proposed risk minimisation plan:

Table 10. Summary of the proposed risk minimisation plan

Risk Classification	Safety Concern	Planned action(s)
Important <i>identified</i> risks	Allergic-like/possible histamine-mediated AEs	Routine Educational materials: · Prescriber checklist
	Haemolytic AEs	Routine Educational materials: · Prescriber checklist
	Hepatic AEs	Routine Educational materials: · Prescriber checklist · Nurse administration and monitoring guide
	Renal AEs	Routine Educational materials: · Prescriber checklist · Nurse administration and monitoring guide
	Echinocandin cross-hypersensitivity	Routine
	SJS and TEN	Routine
	Disseminated Intravascular Coagulation	Routine
	Important <i>potential</i> risks	Pancytopenia
Relevance in humans of the development of liver tumours in rats		Routine Educational materials: · Prescriber checklist · Nurse administration and monitoring guide
Effects on the male reproductive tract		Routine
Development of resistant strains		Routine

Risk Classification	Safety Concern	Planned action(s)
Important missing information	Reproductive and developmental toxicity	Routine

Educational materials are proposed by the sponsor as additional risk minimisation activities for some of the ongoing safety concerns. A 'prescriber checklist' is proposed for the important identified risks 'allergic-like/possible histamine mediated AEs', 'haemolytic AEs', 'renal AEs', and 'hepatic AEs' and important potential risk 'relevance in humans of the development of liver tumours in rats'. A 'nurse administration and monitoring guide' is proposed for the important identified risks 'hepatic AEs' and 'renal AEs' and the important potential risk 'relevance in humans of the development of liver tumours in rats'. Draft copies of both documents were provided with the RMP.

As part of the risk minimisation plan the sponsor commits to having "tests of usage" of the educational materials as well as surveys to assess their effectiveness.

The justification of the need for educational materials as risk minimisation in addition to the use of the PI to mitigate some of the ongoing safety concerns is acceptable.

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 draft PI and consumer medicine information (CMI) documents should not be revised until the Delegates overview has been received.
- Safety considerations may be raised by the nonclinical and clinical evaluators. It is important to ensure that the information provided in response to these include a consideration of the relevance for the RMP, and any specific information needed to address this issue in the RMP.
- The European public assessment report (EPAR) for Mycamine mentions that there were some deficiencies in the EU-RMP that needed to be updated however the EU-RMP has not been provided with this submission. Therefore the sponsor is requested to provide an overview of the identified deficiencies and how they were addressed including the differences if any between the EU-RMP and the AU-RMP with particular attention to risk minimisation and pharmacovigilance activities.
- Notwithstanding the evaluation of the nonclinical and clinical aspects of the SS, use in pregnant/lactating women has not been studied. Therefore it is recommended that the sponsor add 'use in pregnant/lactating women' as important missing information or provide justification for its omission.
- The FDA previously requested additional paediatric information on micafungin to supplement the initial US paediatric program and at least one paediatric study is ongoing. As this study is considered additional pharmacovigilance it is recommended that the sponsor add 'use in paediatric patients' as important missing information or provide justification for its omission.
- It is expected that if the above safety concerns are adopted they should be appropriately reflected in the RMP including consideration of the pharmacovigilance and risk minimisation activities that may apply.
- The sponsor is requested to confirm if the observational study is currently planned or ongoing and if Australian patients will be included. If it is planned, the protocol of the study should be provided to the TGA. Similarly, if interim data are available they

should be provided. It is expected that ongoing results of the observational study will be reported in Periodic Safety Update Reports (PSURs).

- The important potential risk ‘development of resistant strains’ will also be subject to additional pharmacovigilance by means of a resistance surveillance program. The sponsor is requested to confirm the current status of the microbiological surveillance program and also whether it will be undertaken in Australia to monitor emergence of local resistance. It would be expected that changes in resistance that have implications to local treatments would be communicated in the PSUR.
- The sponsor proposes that all other safety concerns are to be monitored with routine pharmacovigilance. This approach is considered acceptable. However insufficient detail has been provided regarding the routine pharmacovigilance system. The sponsor is requested to provide information on routine pharmacovigilance practices to ensure that they comply with the activities outlined in section 3.1.2 *Routine pharmacovigilance practices, Note for Guidance on Planning Pharmacovigilance Activities* (CPMP/ICH/5716/03).
- The paediatric study is considered to be an additional pharmacovigilance activity and should be attributable to a safety concern within the RMP. Therefore ‘use in paediatric patients’ is recommended as a safety concern. Additionally, the sponsor is requested to confirm if this or any other paediatric studies are planned or ongoing. If it is planned the protocol of the study should be provided to the TGA.
- The sponsor should provide details of the assessment of the educational materials including the timing, distribution and how the results will be communicated to the TGA.
- The nurse administration and monitoring guide describes the importance of monitoring for anaphylactic reactions, exfoliative cutaneous reactions (including SJS and TEN) and haemolysis, however the RMP does not make reference to this. It is recommended that for completeness, the RMP should reflect that the nurse administration and monitoring guide is also additional risk minimisation for the important identified risks ‘allergic/histamine-like AEs’, ‘haemolytic AEs’ and ‘SJS and TEN’.
- A tabulation in the ‘Summary of the Risk Management Plan’ does not include the educational materials as proposed risk minimisation activities. This should be amended in a future update to the RMP to reflect the proposed use of the educational materials as risk minimisation for the respective safety concerns.
- In regard to the proposed risk minimisation activities, it is recommended that the draft PI document is revised as follows:
 - The *Precautions* in the Australian PI should be amended to better reflect the EU Summary of Product Characteristics (SmPC) advice with regards to the possible association of ALT/AST elevation and liver tumour formation as well as the occurrence of other severe liver reactions including hepatitis and hepatic failure.
 - Inclusion of a precaution regarding SJS and TEN, similar to that in the EU SmPC to reflect these important identified risks.

Outcome from the RMP evaluation

All matters relating to the above recommendations were resolved to the satisfaction of the TGA prior to a decision being made on this application (see also *Overall conclusion and risk/benefit assessment; Delegate’s overview*, below).

VI. Overall conclusion and risk/benefit assessment

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

This submission seeks registration of a new chemical entity, Mycamine, containing the active ingredient, micafungin (50 mg and 100 mg powder for injection). See *Product background*, above, for the proposed indications and dosage.

Quality

The drug is manufactured in a single synthetic step from a substance obtained by fermentation of the environmental mould, *Coleophoma empetri*. The product of the fermentation process is a macrocyclic peptide. Limits proposed for five specified impurities in the drug substance have been assessed as acceptable by the Medicines Toxicology Evaluation Section. Fermentation aspects of the manufacture of the drug substance have been assessed as satisfactory.

Micafungin powder for injection is a white, sterile, lyophilised powder for IV infusion. Each vial is reconstituted with 5 mL of either 0.9% sodium chloride injection solution or 5% glucose injection solution to yield 10.17 mg/mL or 20.35 mg/mL of micafungin sodium, prior to further dilution with the IV infusion solution. Each 10 mL Type I glass vial is sealed with a teflon-laminated isobutylene-isoprene rubber stopper, and an aluminium and polypropylene overseal. The vial is wrapped in a polyethylene terephthalate (PET) shrink-wrap film to provide protection from light.

In addition to the active ingredient, each vial (of each strength) contains lactose as a stabiliser, together with citric acid and sodium hydroxide for pH adjustment. The vials contain overfills to facilitate withdrawal and administration of the labelled quantity of micafungin after reconstitution. The product is sterilised by filtration prior to lyophilisation. The finished product specifications include limits for the same specified impurities as in the drug substance. The limits proposed are acceptable.

No bioavailability data have been provided as the product, after reconstitution, is a simple aqueous solution intended only for IV administration. Sterile manufacture and sterility aspects of the product have been assessed as satisfactory.

Adequate data have been provided to support the proposed shelf life of 3 years below 25°C. In-use stability data have also been provided. The data are satisfactory except that significant amounts of a photodegradant are observed when diluted solutions of the drug are stored in IV infusion lines for one hour. Advice from Medicines Toxicology Evaluation Section was sought on the limit (the maximum amount that would be observed under worst case conditions when the infusion solution is exposed to light in IV tubing) for the photodegradant in the drug substance. The Medicines Toxicology Evaluator advises that the nonclinical studies have some limitations, but are adequate to toxicologically qualify the photodegradant at a specified level.

Nonclinical

The non-clinical evaluator concluded that a comprehensive nonclinical submission was provided for micafungin which demonstrated efficacy against relevant *Candida* strains *in vitro* and in appropriate murine models *in vivo*. Micafungin displayed inhibitory activity against clinically relevant *Candida* species. The MIC rank order was: *C. albicans* (including azole resistant strains) < *C. tropicalis*, *C. glabrata* < *C. krusei* << *C. parapsilosis*, *C. guilliermondii*. Micafungin displayed inhibitory activity against clinically relevant *Aspergillus* species (*A. fumigatus*, *A. niger*, *A. flavus*, *A. nidulans*, *A. terreus* and *A. versicolor*).

The toxicological profile of micafungin was well-defined and identified potential hepatotoxic, renal, haemolytic, male reproductive tract and injection site irritation effects with repeated IV micafungin administration at low micafungin exposure levels. However, the toxicity profile of micafungin is typical of that seen with other echinocandin antifungal agents, with similar safety margins seen. Given the intended short duration of treatment proposed and unclear clinical relevance for some of these toxicities, routine clinical monitoring of liver and kidney function, haematological parameters and local injection reactions may be sufficient to mitigate any potential safety concerns associated with repeated micafungin use.

Of note, the toxicity of repeated IV doses of micafungin was examined in rats and dogs for up to 6 and 9 months, respectively. The primary organs for toxicity were identified as the liver [increased liver enzymes, single cell necrosis, cellular and nuclear hypertrophy, FAH with further progression to tumour formation] and urinary tract in rats, and blood [haemolytic anaemia] and male reproductive organs (reduced testicular weight, atrophy of the seminiferous tubules and oligospermia) in both rats and dogs. All of these occurred at clinically relevant exposures and monitoring for liver and kidney function, as well as potential haemolytic anaemia would be warranted in the clinical setting.

There are no nonclinical objections to the registration provided an adequate safety monitoring program is implemented, as deemed appropriate by the clinical evaluator. A number of amendments to the PI have been recommended by the evaluator and sponsor as a requirement to update the PI with these changes.

Clinical

Clinical data consisted of 63 studies, including 35 PK studies, 20 efficacy and safety studies, and 8 post-marketing studies. Of the efficacy/ safety studies, 10 (2 pivotal and 8 supportive) assessed efficacy in patients with confirmed candidaemia or invasive candidiasis, 4 (2 pivotal and 2 supportive) assessed efficacy in oesophageal candidiasis and 6 (1 pivotal and 5 supportive) assessed efficacy in prophylaxis of candida infection.

Pharmacokinetics

Information on PK was provided in both the nonclinical and clinical submissions. In the clinical dossier, there were 35 PK studies, including 5 studies assessing PK in healthy subjects, 12 studies assessing PK in various patient groups, 4 studies in special populations and 14 studies involving potential drug interactions. The evaluator is of the view that the PK of IV micafungin have been extensively characterised and is consistent across studies.

There is no evidence of systemic accumulation with repeated administration and the increases in systemic exposure (AUC and C_{max}) are proportional to increases in dose. Steady-state is generally reached by Day 4. Following IV administration, concentrations of micafungin show a bi-exponential decline as the drug is rapidly distributed into tissues. Micafungin is highly protein bound (> 99%), primarily to albumin and to a lesser extent to alpha-1-acid glycoprotein. Binding to albumin is independent of micafungin concentration (10 to 100 µg/mL). Micafungin does not displace albumin-bound bilirubin at clinically relevant concentrations and is therefore not expected to cause kernicterus. The blood to plasma ratio was approximately 0.85 and was independent of concentration over the range of 0.1 to 10 µg/mL micafungin. The percent transfer into human red blood cells was approximately 35%. The volume of distribution at terminal phase was 0.24 to 0.41 L/kg body weight. Unchanged micafungin is the principal circulating compound in the systemic circulation.

The metabolism of micafungin involves multiple CYP isoenzymes including CYP1A2, 2B6, 2C and 3A4. Five metabolites have been detected after administration of micafungin to humans: M-5 (main metabolite in plasma), M-1 and M-2 (minimal to undetectable in plasma), and M-3 and M-11 (faeces/urine). Micafungin is metabolised to M1 (catechol form) by arylsulfatase, with further metabolism to M2 (methoxy form) by catechol-O-methyltransferase. M5 is formed by hydroxylation at the side chain (ω -1 position) of micafungin catalysed by cytochrome P450 (CYP) isoenzymes. I, M-2 has a potency and spectrum of activity similar to that of the parent compound; M-1 is 4- to 16-fold less potent than the parent compound; and M-5 has no activity (< 1% of parent compound). Overall the exposure to these metabolites is low and they do not contribute to the overall efficacy of micafungin. Although micafungin is a substrate for CYP3A *in vitro*, hydroxylation by CYP3A is not a major pathway for metabolism *in vivo*. The mean half-life of micafungin is approximately 10 to 17 hours and stays consistent across doses up to 8 mg/kg after single and repeated administration in patients and healthy volunteers. Faecal excretion is the major route of elimination. In Study 97-0-040, following a single IV dose of ¹⁴C-micafungin (25 mg) to healthy volunteers, 11.6% of the radioactivity was recovered in the urine and 71.0% in the faeces over 28 days.

PK in special populations: subjects with severe renal impairment (GFR < 30 mL/min), moderate hepatic dysfunction (Child-Pugh score of 7-9) or severe hepatic dysfunction (Child-Pugh score of 10-12) showed no marked differences in micafungin PK compared with age-, weight-, and sex-matched normal subjects, and elderly male subjects showed no significant differences in micafungin PK parameters compared with young male subjects.

Drug interactions: no interaction that altered the PK of micafungin was observed. There was no effect of single-dose or steady-state micafungin on the PK of MMF, cyclosporin, tacrolimus, prednisolone, fluconazole, voriconazole, ritonavir or rifampicin. Increases in exposure (AUC) for sirolimus (by 21%), nifedipine (by 18%) amphotericin B (by 30%) and itraconazole (by 22%) in the presence of steady-state micafungin were noted. Information relating to these interactions should be included in the Product Information.

Pharmacodynamics

Pharmacodynamics information was mainly provided from nonclinical data, and was supported by information from the clinical development program. Micafungin is a member of the echinocandin lipopeptide family and inhibits non-competitively the synthesis of 1,3- β -D-glucan, an essential component of fungal cell walls which is not present in mammalian cells. Micafungin displayed potent activity against clinically relevant *Candida* species. The MIC rank order was: *C. albicans* (including azole resistant strains) < *C. tropicalis*, *C. glabrata* < *C. krusei* << *C. parapsilosis*, *C. guilliermondii*. With the exception of *C. parapsilosis* and *C. guilliermondii*, micafungin was generally more potent against the tested *Candida* species than amphotericin B, fluconazole and itraconazole. MIC values for micafungin were lower compared to caspofungin. Micafungin has virtually no activity against *Cryptococcus neoformans*, *Trichosporon cutaneum*, *Trichosporon asahii*, *Fusarium solani*, *Pseudallescheria boydii*, *Absidia corymbifera*, *Cunninghamella elegans*, *Rhizopus oryzae* or *Rhizopus microspores*.

Clinical efficacy

Clinical efficacy was evaluated for three specific indications: treatment of invasive candidiasis (IC), treatment of oesophageal candidiasis, and prophylaxis of candidiasis. There were 2 pivotal studies for invasive candidiasis, 2 pivotal studies for oesophageal candidiasis, and one pivotal study for prophylaxis. Information on dose selection was provided for each of the three proposed indications. Supportive studies are not discussed in this overview.

Dose selection studies

For invasive candidiasis, dosage information was largely based on Study 98-0-047/FG-463-21-02, in which a mean \pm SD daily dose of 74.9 ± 34.1 mg for adults and 1.5 ± 0.9 mg/kg for children were associated with high success rates in IC and candidaemia patients who received micafungin monotherapy. The treatment success rate for these patients was 79.5% (105/132), with 79/98 (80.6%) newly diagnosed patients and 26/34 (76.5%) efficacy failure patients having experienced treatment success. For oesophageal candidiasis, dose-finding information was obtained from Studies 97-7-003 and FG-463-21-09, and the vast majority of subjects were HIV positive adults. Use of micafungin for oesophageal candidiasis is not being sought for paediatric population. For prophylaxis of invasive fungal disease, paediatric dosage information was based on the consideration of a 30% lower body weight in children than adults. An adult body weight of 54 kg was used (the mean body weight in study FG-463-21-09) for this calculation, as micafungin is likely to be used in patients who weigh less than the normal population (generally 70 kg). For adult patients, dosage information was supported by study 98-0-050. At a daily dose of 50.0 mg (1.0 mg/kg for patients < 50 kg), micafungin was significantly more effective in preventing IFI and reducing the use of empirical antifungal therapy than fluconazole (400 mg/day, 8 mg/kg/day for patients weighing < 50 kg) in high risk patients (HSCT patients with neutropenia).

Invasive Candidiasis and Candidaemia

Pivotal studies: FG-463-21-08 and 03-0-192 were the two pivotal Phase III, active-controlled non-inferiority trials submitted to support the efficacy and safety of micafungin in invasive candidiasis. The two studies had the following characteristics:

Inclusion criteria were similar. Patients could be neutropenic or non-neutropenic; Study 03-0-192 allowed 2 days of prior therapy while Study FG-463-21-08 allowed 3 days of prior therapy; Study 03-0-192 excluded patients with known endocarditis, osteomyelitis or meningitis due to *Candida*.

- Patients had to have proven invasive candidiasis/candidaemia documented by culture and clinical signs and symptoms within 4 days prior to study entry.
- Patients were stratified by APACHE II score and region in Study 03-0-192 and by neutropenic status in Study FG-463-21-08.
- Length of treatment was at least 14 days for both studies; in Study 03-0-192, patients could be switched to an oral antifungal after 10 doses of IV study drug if predefined criteria were met, including two negative blood cultures drawn at least 24 hours apart.
- Non-inferiority margin was set at 15% for both studies.
- The primary endpoint was the response rate from the investigator's assessment of overall treatment success at the end of therapy (EOT). Patients with missing efficacy data at the end of therapy were counted as failures in both studies.
- The primary analysis set was the FAS in Study 03-0-192 and the PPS in Study FG-463-21-08. The FAS in Study 03-0-192 excluded patients with endocarditis, osteomyelitis or meningitis due to *Candida*; these patients were included in the PPS in Study FG-463-21-08.
- An independent review panel was utilised to confirm diagnosis and outcome for each patient who received at least one dose of study medication.
- Patients were followed for 6 weeks after the last dose of study drug for relapse and safety in both studies; Study FG-463-21-08 also included a 12-week follow-up visit.

Study FG-463-21-08 was a multicentre, double-blind, randomised, comparative study. The study compared the efficacy and safety of micafungin versus Ambisome in treating

neutropenic and non-neutropenic patients with confirmed invasive candidiasis or candidaemia caused by *candida albicans* and non-*albicans candida* species. Patients were randomised 1:1 to receive either micafungin or Ambisome. Overall 264 and 267 patients were included in the FAS for the micafungin and Ambisome group and 202 and 190 in the PPS set for the micafungin and Ambisome group. The two treatment groups were well balance with regards to demographic and baseline disease characteristics. Micafungin was administered at a daily dose of 100 mg for patients weighing > 40 kg (dose increase to 200 mg permitted) and 2.0 mg/kg for patients ≤ 40 kg (dose increase to 4.0 mg/kg). No decrease in the micafungin dose was allowed. Ambisome was given at a daily dose of 3 mg/kg (dose increase to 5 mg/kg permitted). A dose decrease of 50% for Ambisome was allowed in drug-related nephrotoxicity. The minimum treatment duration was 14 days and the maximum duration was 4 weeks, except for patients with chronic disseminated candidiasis, *Candida* osteomyelitis or *Candida* endocarditis, for whom study drug administration could be prolonged up to a maximum of 8 weeks.

The primary endpoint was the response rate based the investigators assessment of overall treatment success, which was defined as a clinical response (complete or partial) and a mycological response (eradication or presumed eradication) at EOT. Secondary efficacy endpoints included clinical response, mycological response, emergent fungal infections, recurrence of fungal infections, and the independent data review board assessment of overall success. The primary endpoint was analysed using a 1-sided 97.5% CI for the difference in the proportions (micafungin *minus* fluconazole) adjusted for neutropenia (yes/no) based on the PPS. The CI lying above the pre-defined non-inferiority margin (-15%) would indicate non-inferiority.

In the PPS, the treatment success was experienced by 89.6% (181/202) and 89.5% (170/190) of patients in the micafungin and Ambisome groups, respectively. The difference in proportions was 0.1% (95% CI: -5.9, 6.1). The lower bound of the 95% CI (-5.9%) was above the margin of -15%, therefore non-inferiority of micafungin compared with Ambisome was demonstrated. Consistent results of non-inferiority were also seen for the FAS.

The FG-463-21-08 paediatric sub-study was presented separately. For the FAS, there were a total of 52 paediatric patients in the micafungin group and 54 in the Ambisome group (41 and 42, respectively in the PPS). All age groups were well represented in both treatment arms (infants 0 to 4 weeks old: 15.4% and 16.7% of patients in the micafungin and Ambisome groups, respectively; infants 4 weeks to < 2 years old: 38.5% and 44.4% of patients, respectively; children 2 to 11 years old: 32.7% and 33.3% of patients, respectively; and children 12 to 15 years old: 13.5% and 5.6% of patients, respectively). Almost all children included in this sub-study had candidaemia. A higher proportion of children needed a dose increase (21.2% and 22.2% in the micafungin and Ambisome group) as compared to adults. The rates of treatment success were high in both groups in FAS analysis: an overall success rate of 69.2% in the micafungin arm and 74.1% in the Ambisome arm. In the PPS, the overall success rate was 85.4% in the micafungin arm and 88% in the Ambisome arm. The primary evidence to support this indication for paediatric patients is from the main study, which included a total of 531 adult patients. The FG-463-21-08 paediatric sub-study further supports the paediatric indication.

Study 03-0-192 was a multicentre, double blind, randomised comparative study. The study assessed the efficacy and safety of two dose levels (100 mg/day and 150 mg/day) of IV micafungin versus IV caspofungin in the treatment of patients with confirmed invasive candidiasis or candidaemia. A total of 611 patients were enrolled. Subjects were adult patients (≥18 years old) with candidaemia or invasive candidiasis, as documented by at least one typical clinical sign or symptom and confirmed by fungal culture and/or histology.

Subjects were randomised (1:1:1) to receive micafungin 100 mg qd, micafungin 150 mg qd, or caspofungin 70 mg qd on day 1 and 50 mg qd thereafter. The minimum treatment duration (IV therapy alone or IV therapy followed by oral fluconazole) was 14 days. The maximum duration was 4 weeks, except for pre-defined patients with chronic disseminated candidiasis or *Candida* endophthalmitis, for whom the use of IV therapy could have been prolonged to a maximum of 8 weeks.

The primary efficacy endpoint was treatment success at the end of blinded IV therapy. Success was defined as a positive clinical response (complete or partial) and a positive mycological response (eradication or presumed eradication) as assessed by the investigator at the end of blinded IV therapy. Patients who died during blinded IV therapy were counted as treatment failures. Additionally, if a clinical or mycological response was not assessed at the end of blinded IV therapy, the patient was counted as a treatment failure. A total of 147/199 (73.9%), 142/202 (70.3%), and 137/192 (71.4%) patients in the micafungin 100 mg, micafungin 150 mg, and caspofungin groups, respectively, were assessed by the investigator as treatment successes at the end of blinded therapy. The 95% CI for the difference between micafungin 100 mg and caspofungin was [-5.9%, 11.0%]. The 95% CI for the comparison of micafungin 150 mg to caspofungin was [-9.3%, 7.8%]. The lower bound of 95% CIs for the treatment differences (experimental regimen, caspofungin) were > -15%, indicating both micafungin regimens (100 mg qd and 150 mg qd) were non-inferior to caspofungin for the primary endpoint.

Oesophageal candidiasis

Pivotal studies: Studies 03-7-005 and Study 03-7-008 were pivotal Phase III studies submitted to support IV micafungin for the treatment of oesophageal candidiasis.

Study 03-7-005 was a Phase III, randomised, double-blind, comparative trial to determine the efficacy and safety of IV micafungin versus IV fluconazole for the treatment of oesophageal candidiasis. Subjects were patients ≥ 16 years with a diagnosis of oesophageal candidiasis confirmed by endoscopy and documented by typical clinical symptoms. A total of 518 patients were enrolled. Subjects were randomised (1:1) to receive micafungin (150 mg IV once daily) or fluconazole (200 mg IV once daily). The majority of patients in both treatment groups had HIV, either suspected or confirmed. Treatment duration was a minimum of 14 days or for 7 days after resolution of all clinical symptoms of oesophageal candidiasis. The maximum treatment duration was 42 days.

The primary efficacy endpoint was treatment success (endoscopic cure rate), which was defined as an oesophageal mucosal grade of 0 (zero) at the EOT. There were many secondary endpoints (see attached extract from the CER). A two-sided 95% CI was constructed for the difference in the success rates (micafungin minus fluconazole) using the normal approximation method. If the lower bound of the 95% CI exceeded -0.10, micafungin was considered non-inferior to fluconazole.

The FAS is the primary set for efficacy analysis which included 260 patients in micafungin group and 258 in fluconazole group. The endoscopic cure rate was 87.7% in micafungin group compared to 88.0% in fluconazole group. The difference was -0.3% with a 95% CI of [-5.9%, 5.3%]. Since the -5.9% lower bound was greater than -10%, micafungin was considered non-inferior to fluconazole. In both groups, most treatment failures were due to non-evaluable patients. Only 2.7% of micafungin patients and 3.9% of fluconazole patients had persistent lesions. Although the endoscopic cure rate for patients with HIV as a primary underlying disease was similar between the micafungin (216/245, 88.2%) and fluconazole group (217/241, 90.0%), the endoscopic cure rate for patients without HIV was numerically higher in patients that received micafungin (12/15, 80.0%) compared to those that received fluconazole (10/17, 58.8%). In addition, although the endoscopic cure rate for patients with *C. albicans* infections was similar between the two groups, the endoscopic cure rate for patients with infections due to non-*C. albicans* was numerically

higher for patients that received micafungin (10/12, 83.3%) compared to those that received fluconazole (8/13, 61.5%). In HIV patients with a baseline CD4 (T lymphocyte) count ≥ 100 , the odds of endoscopic cure was approximately 2.6 times higher than the odds in HIV patients with a baseline CD4 count < 100 .

Study 03-7-008 was a Phase III, randomized, double-blind, comparative trial. The primary objective was to determine the efficacy and safety of daily doses of IV micafungin versus IV caspofungin for the treatment of oesophageal candidiasis. The secondary objective was to determine if alternate day dosing of micafungin is as effective as daily dosing of micafungin and/or caspofungin. Study drug, either 150 mg micafungin qd, 50 mg caspofungin qd, or 300 mg micafungin qod alternating with placebo, was administered IV in a blinded manner. Study drug was administered for a minimum of 14 days or for 7 days after the resolution of clinical symptoms of oesophageal candidiasis, whichever was longer. The maximum length of therapy was 28 days. The study subjects were adult patients with oesophageal candidiasis confirmed by endoscopy and culture and documented by typical clinical signs and symptoms. A total of 454 patients were enrolled.

The primary efficacy endpoint was endoscopic cure (mucosal grade of 0) at the end of therapy. The primary comparison was micafungin 150 mg qd versus caspofungin qd. A secondary comparison was micafungin 300 mg qod versus caspofungin 50 mg qd. There were many secondary efficacy parameters as discussed in the CER. Using the FAS, a 95% two-sided CI was constructed for the difference in success rates between micafungin 150 mg qd and caspofungin 50 mg qd. If the lower bound of the CI was greater than -0.15, the micafungin 150 mg qd was considered non-inferior to caspofungin 50 mg qd. If the lower bound of the CI exceeds 0, then micafungin 150 mg qd was considered superior to caspofungin 50 mg qd. The difference in success rates between micafungin 300 mg qod and caspofungin 50 mg qd was compared similarly as a secondary analysis. An additional analysis of the success rates between micafungin 300 mg qod and micafungin 150 mg qd was also performed.

The FAS (primary analysis for efficacy analysis) consisted of 151 patients in micafungin 150 mg qd group and 152 patients in caspofungin 50 mg qd group. At end of therapy, treatment success was 92.1% (139/151) in micafungin 150 mg group and 91.4% (139/152) caspofungin group, with a difference of 0.6% (95% CI: -5.6%, 6.8%). Micafungin 150 mg qd was considered non-inferior to caspofungin 50 mg qd based on this result. The analyses in the modified FAS and PPS supported this conclusion. The 95% CI for the difference in treatment success at the end of therapy was (-2.5%, 8.9%) for micafungin 300 mg qod versus caspofungin 50 mg qd and was (-3.1%, 8.2%) for micafungin 300 mg qod versus micafungin 150 mg qd. These results indicate that micafungin 300 mg qod was non-inferior to caspofungin 50 mg qd and comparable to micafungin 150 mg qd.

Prophylaxis of candidiasis

Pivotal study: Study 98-0-050 was a Phase III, randomised, double-blind, comparative trial of micafungin versus fluconazole for prophylaxis of fungal infections in adults and paediatric patients (greater than 6 months) undergoing a HSCT. Randomised treatment was initiated at the time the transplant-conditioning regimen was initiated or within 48 hours post-initiation. The primary efficacy endpoint was treatment success, defined as the absence of a proven, probable, or suspected systemic fungal infection through the EOT and the absence of a proven or probable systemic fungal infection through the end of the 4 week post-treatment period. Both criteria had to be met in order for the patient to be considered a treatment success. A large sample normal approximation of the binomial distribution was used to construct a 2-sided 95% CI for the difference. If the lower limit of the CI was $\geq -10\%$, then micafungin was considered to be non-inferior to fluconazole. If the lower limit of the CI exceeded 0%, then micafungin was considered to be statistically superior to fluconazole.

A total of 1267 patients were screened and 889 were randomized (1:1) into the study (426 micafungin, 463 fluconazole). One micafungin patient and six fluconazole patients were randomized but never received study drug and were excluded from the FAS. A total of 28/425 (6.6%) micafungin and 24/457 (5.3%) fluconazole FAS patients did not meet the classification criteria and were not included in the PPS. The study included 84 paediatric patients (<16 years) and 56 elderly patients (≥ 65 years). The micafungin and fluconazole treatment groups were well balanced in terms of demographic and baseline disease characteristics.

In the FAS, the overall success rate in the micafungin group was significantly higher than that in the fluconazole group (80.0% versus 73.5%). The treatment difference was +6.5% (95% CI: 0.9%, 12.0%). The Kaplan-Meier estimate of treatment success was significantly different between the two groups ($p=0.025$). This difference was consistent in patients who underwent an allogeneic (+3.0%) or autologous (+9.1%) transplant. The treatment benefit of micafungin was consistent across all subgroups analyzed, including the PPS which required an ANC <200 cells/mm³.

Treatment differences were consistently in favour of micafungin when data were stratified for graft versus host disease (GVHD), age, gender or colonisation, and particularly notable for children and patients ≥ 65 years of age. There were a total of 84 paediatric patients (<16 years), and treatment success was 69.2% for the paediatric patients treated with micafungin and 53.3% for the paediatric patients treated with fluconazole.

Table 11. Treatment success in subgroups of patients

	Micafungin (N = 425)	Fluconazole (N = 457)	Treatment Difference †	[95% CI]
Graft versus Host Disease				
GVHD Present	65/96 (67.7%)	58/102 (56.9%)	+10.8%	[-2.6%, 24.3%]
GVHD Absent	275/329 (83.6%)	278/355 (78.3%)	+5.3%	[-0.6%, 11.1%]
Patient Age				
< 16 Years	27/39 (69.2%)	24/45 (53.3%)	+15.9%	[-4.7%, 36.4%]
≥ 16 Years	313/386 (81.1%)	312/412 (75.7%)	+5.4%	[-0.3%, 11.1%]
≥ 65 Years	32/33 (97.0%)	16/23 (69.6%)	+27.4%	[7.7%, 47.1%]
< 65 Years	308/392 (78.6%)	320/434 (73.7%)	+4.9%	[-1.0%, 10.6%]

The overall incidence of proven or probable systemic fungal infections was 1.6% in the micafungin group and 2.4% in the fluconazole group based on a blinded review of the cases using the protocol-specified diagnostic criteria. Both drugs were effective in preventing candidiasis with an incidence of 0.9% in the micafungin arm and 0.4% in the fluconazole arm.

Clinical safety

Information on safety was available from the clinical development program as well as post-marketing experience.

Guidance on study design for the clinical evaluation of antifungal agents is provided by the Guideline EMEA CHMP/EWP/1343/01. This notes that the evaluation of the safety of anti-fungal agents is not straightforward due to factors such as serious underlying diseases in the majority of patients with IFD, large numbers of concomitant medications, and, in many cases, the considerable potential for clinically significant drug-drug interactions to occur.

Safety information from the clinical development program

The safety database in the clinical development program comprised of 5102 subjects who were enrolled and received at least one dose of study drug in 41 clinical studies. Of these, 3584 subjects, including 3083 patients and 501 volunteers, received at least one dose of

micafungin. A total of 82.8% of the 3083 patients who received at least one dose of micafungin had ≥ 10 days of treatment with a mean duration of treatment of 20 days.

Adverse events: in the clinical development program, the most frequently reported AEs irrespective of causality were diarrhoea, nausea, vomiting, and pyrexia. A treatment-related AE was experienced by 32.2% of patients. The most frequently reported AEs assessed by the investigator as having at least a possible relationship to micafungin ($\geq 1\%$, MedDRA preferred term) in the clinical database or in a pivotal study were the hepatic AEs (AST increased, ALT increased, ALP increased, LFT abnormal and hyperbilirubinemia); the haematological AEs (leukopenia, neutropenia and anaemia); the electrolyte disturbances (hypokalemia, hypocalcemia and hypomagnesemia); the allergic like/histamine-related AEs (rash and rigors); the injection-site reaction phlebitis; as well as headache, nausea, vomiting, diarrhoea, pyrexia, thrombocytopenia, abdominal pain, pruritus, blood creatinine increased, blood bilirubin increased, blood urea increased, blood LDH increased, hypertension, hypophosphataemia, renal impairment, cholestasis and infusion site inflammation. Treatment-related haemolytic AEs were rare.

Serious adverse events: a total of 28.3% (873/3083) of micafungin-treated patients had a serious treatment-emergent adverse event during study participation. Serious treatment-emergent adverse events considered to be related to study drug by the investigators were reported in 3.6% (111/3083) of micafungin-treated patients. The most frequent serious treatment-emergent adverse events in micafungin-treated patients, regardless of relationship to study drug, were respiratory failure (3.1%), sepsis (2.8%), septic shock (1.7%), hypotension (1.4%), pneumonia (1.2%), and multi-organ failure (1.2%), and respiratory distress (1.0%).

Deaths: death occurred in 671 of 3083 (21.8%) of micafungin-treated patients: 134 (4.3%) deaths occurred in patients during study drug treatment, and 537 (17.4%) deaths occurred during the post treatment period. The most common primary causes of death that were reported for micafungin-treated patients were: septic shock (1.6% [50/3083]), sepsis NOS (1.6% [48/3083]), respiratory failure (1.6% [50/3083]), and multiorgan failure (1.3% [40/3083]).

Safety in special populations: in the paediatric population, the incidence of some AEs in the clinical study database was higher than adult patients, such as thrombocytopenia, tachycardia, hypertension, hypotension, hyperbilirubinemia, hepatomegaly, acute renal failure, and blood urea increased. Additionally, paediatric patients < 1 year of age experienced about two times more often an increase in ALT, AST and ALP than older paediatric patients. No clinically meaningful differences in the safety profile could otherwise be discerned.

Discontinuation due to adverse events: a total of 13.3% (409/3083) of all micafungin-treated patients were withdrawn from study drug due to adverse events, regardless of causality. In all micafungin-treated patients, the most frequent adverse events leading to drug withdrawal, regardless of relationship to study drug, were septic shock (0.9%), sepsis (0.8%), respiratory failure (0.8%), and multiorgan failure (0.8%).

Immunological events: no significant immunological events were identified.

Safety related to drug-drug interactions and other interactions: no significant issues were identified.

Post-marketing safety information

Since the original micafungin approval in Japan, two revisions to the Company Core Data Sheet (CCDS) were made based upon assessment of post-marketing reports. In October 2010, a Signal Evaluation Report (SER) was generated to document the Company's review of serious cutaneous adverse reactions and their potential association to the use of micafungin. Based on a cumulative review of all cases a causal association between

micafungin and the events of erythema multiforme, SJS and TEN was supported. The CCDS was amended and local prescribing information was revised to harmonise with the CCDS. A signal for disseminated intravascular coagulation (DIC) was identified and assessed. A SER was finalised in November 2010. Although no data supports the fact that micafungin directly induces DIC, the data indicate that micafungin may lower the threshold for the development of DIC in patients who were already at high risk.

Risk management plan

A RMP provided by the sponsor (Version 1, dated March 2012) has been reviewed by the TGA OPR. Of note, the RMP evaluator recommends the inclusion of SJS and TEN reported in the *Precaution* section of the PI to adequately inform prescribers of this possibility. The sponsor has accepted this recommendation. The OPR evaluator recommended the following requirement as the condition of registration:

- Implement the most updated AU-RMP and any future updates.
- Post marketing reports are to be provided in line with the current published list of EU reference dates and frequency until the period covered by such reports is not less than 3 years from the date of approval. The reports are to meet the requirements in accordance with ICH E2C (R2) guideline on Periodic Benefit-Risk Evaluation Reports and Module VII of the EMA Guideline on Good Pharmacovigilance (GPV) Practices relating to PSURs. Submission of the report must be within the 70 days of the data lock point for PSURs covering intervals up to and including 12 months and within 90 days of the data lock point for PSURs covering intervals in excess of 12 months. The submission may be made up of two PSURs each covering six months.

Risk-benefit analysis

Delegate considerations

This application separately addressed three different indications: invasive candidiasis, oesophageal candidiasis and prophylaxis of invasive fungal infection. For invasive candidiasis, non-inferiority of micafungin was demonstrated against Ambisome and caspofungin. For oesophageal candidiasis, non-inferiority of micafungin was demonstrated against fluconazole. For prophylaxis of invasive fungal infection, non-inferiority of micafungin was demonstrated against fluconazole.

It is noted that the clinical trials supporting oesophageal candidiasis were predominantly conducted in HIV positive patients, who made up over 90% of the study population. While there appears to be little doubt that micafungin will be efficacious in non HIV positive subjects with this indication, this should be stated in the PI.

No pivotal study was provided that assessed efficacy in only paediatric patients, although some studies did include paediatric patients. The guideline EMEA CHMP/EWP/1343/01 notes that in general, factors that predispose to invasive fungal diseases in children are similar to those in adults and the range of fungal pathogens encountered is also the same. Therefore, a demonstration of efficacy in specific circumstances in adults may be extrapolated to use in the same circumstances in children. Information provided in the clinical development program supported this extrapolation.

Micafungin is a new antifungal agent of a relatively new class of the echinocandins with broad antifungal activity and it has a low potential to interact with other medications (for example, via CYP450). Furthermore, micafungin demonstrated fungicide activity against *Candida*, and this is of importance especially in the immunocompromised patient

populations. Mycamine was more effective than fluconazole in preventing fungal infection in patients undergoing a bone marrow transplant (see Study 98-0-050).

The safety profile of micafungin appears to be comparable to other antifungal agents in the submitted studies. Overall, a relatively higher percentage of children than adults received a treatment of more than 28 days. The total hepatic AEs were slightly more frequent in paediatric patients (23.6%) than in non-elderly adults (20.6%) or elderly (16.3%). Important identified risks include hepatic reactions (elevated liver enzymes), allergic-like reactions, haemolytic reactions and renal AEs. An important potential risk is the risk for the development of liver tumours, as micafungin induced irreversible FAH and liver tumours in rat after treatment for 3 month and longer. The mechanism for FAH and tumour development has not been elucidated. It is noted the EU SmPC has include the following statement in the *Indications* section:

The decision to use Mycamine should take into account a potential risk for the development of liver tumours. Mycamine should therefore only be used if other antifungals are not appropriate

The updated RMP (version 1.1, January 2013) submitted by the sponsor indicates that an observational study to assess the safety of micafungin in the treatment and prophylaxis of candidiasis in comparison with other antifungal agents is proposed. This study aims to evaluate the risk of hepatotoxicity for micafungin, to exclude certain levels of risk of hepatocellular carcinoma, and to evaluate other AEs of special interest such as renal events. Follow-up questionnaires on allergic-like and haemolytic events are used to obtain further information to better characterise these two identified risks. In the submitted RMP, the sponsor indicates that they will continue to monitor the resistance development and will includes the collection of isolates from Europe, USA and the rest of the world. No Australia-specific microbiological surveillance program has been proposed.

Safety concerns and planned pharmacovigilance actions are summarised in the updated Australian RMP as follows:

Table 12. RMP: Safety concerns and planned pharmacovigilance

Risk classification	Safety concern (AE)	Planned action(s)
Important identified risks	Allergic-like/possible histamine-mediated	Specific standardized follow-up questionnaire (Annex 1) and routine pharmacovigilance
	Hemolytic	
	Hepatic	Observational study and routine pharmacovigilance
	Renal	Routine pharmacovigilance. Observational study
	Echinocandin cross-hypersensitivity	Routine pharmacovigilance
	Steven-Johnson syndrome and TEN	Routine pharmacovigilance
	Disseminated intravascular coagulation	Routine pharmacovigilance
Important potential risks	Pancytopenia	Routine pharmacovigilance
	Relevance in humans of the development of liver tumors in rats	Routine pharmacovigilance Observational study.
	Effects on the male reproductive tract	Routine pharmacovigilance
	Development of resistant strains	Routine pharmacovigilance Propose susceptibility breakpoints in a microsurveillance study protocol (see section 2.8)
Important missing information	Use in pregnant/lactating women	Routine pharmacovigilance
	Reproductive and developmental toxicity	Routine pharmacovigilance

Given the high morbidity and mortality associated with the three proposed indications, there are obvious benefits to the introduction of micafungin treatment, especially for

patients who suffer from infections due to resistant fungal strains, patients who have multiple co-medications due to multimorbidity, and patients who are resistant or unable to tolerate treatments with azole products. With the proper RMP, the benefits of micafungin for the proposed indications outweigh the risks in the intended population.

Product Information

The proposed PI has been reviewed by the evaluators from Pharmaceutical and Chemistry, non-clinical, clinical, and RMP evaluation areas. A draft PI incorporating recommended changes¹⁶ should be submitted. Further changes to the PI may be required following the Advisory Committee on Prescription Medicines (ACPM) discussion on this application.

Proposed action

Pending the advice from ACPM, the Delegate proposed to approve the registration of micafungin (Mycamine) powder for IV infusion for the following indications:

Adults, adolescents ≥ 16 years of age and the elderly:

- treatment of invasive candidiasis
- treatment of oesophageal candidiasis in patients for whom IV therapy is appropriate
- prophylaxis of *Candida* infection in patients undergoing allogeneic haematopoietic stem cell transplantation or patients who are expected to have neutropenia (absolute neutrophil count < 500 cells/ μL) for 10 or more days.

Children (including neonates) and adolescents < 16 years of age:

- treatment of invasive candidiasis
- prophylaxis of *Candida* infection in patients undergoing allogeneic haematopoietic stem cell transplantation or patients who are expected to have neutropenia (absolute neutrophil count < 500 cells/ μL) for 10 or more days.

The proposed dosages and treatment durations for the respective indications are also supported.

The conditions of registration include:

- Implementing the Australian Risk Management Plan (RMP) Version 1.1, January 2013, and subsequent updates to the RMP.
- Providing post marketing reports at the intervals specified by the OPR.

Request for ACPM advice

The Delegate proposed to seek general advice on this application from the ACPM, and requested advice and comment specifically with regards to the following issues:

- What is the view of the ACPM regarding the overall benefit and risk balance of micafungin treatment for the proposed three indications?
- What is the ACPM view on the clinical relevance of the comparators and primary endpoints used in the pivotal trials?
- Should the following statement be included in the PI to caution about the potential risk of liver tumour?

“The decision to use Mycamine should take into account a potential risk for the development of liver tumours. Mycamine should therefore only be used if other antifungals are not appropriate.”

¹⁶ Details of recommended revisions to the PI are beyond the scope of the AusPAR.

- Should the following statements be included in the PI to instruct on the proper use of Mycamine?

“Specimens for fungal culture and other relevant laboratory studies should be obtained prior to therapy to isolate and identify causative organism(s). Therapy may be instituted before the results of the cultures and other laboratory studies are known. However, once these results become available, antifungal therapy should be adjusted accordingly.”

- The sponsor states that they will continue to monitor the resistance development and will include the collection of isolates from Europe, USA and the rest of the world, however, no Australia-specific microbiological surveillance program has been proposed. The ACPM is asked to comment on the acceptability of not conducting Australia-specific microbiological surveillance program/s.

Response from sponsor

The sponsor’s comments on matters raised in the Delegate’s overview were as follows:

Delegate’s overview: Should the following statement be included in the PI to caution about the potential risk of liver tumour?

“The decision to use Mycamine should take into account a potential risk for the development of liver tumours. Mycamine should therefore only be used if other antifungals are not appropriate.”

Sponsor’s comments:

Based on the evidences explain as follow, the risk that Mycamine promotes FAH development or chronic hepatic injury in patients is considered minimal if Mycamine treatment is appropriately discontinued in patients who indicate significant and persistent abnormalities in liver function associated with the use of micafungin.

In dogs, the effect on the liver consisted of increased weight and centrilobular hypertrophy, without degenerative changes of hepatocytes at dose of 32 mg/kg (corresponding to 3 times the human exposure (as AUC) at the highest recommended clinical dose of 200 mg/day) [Report No GLR970118; Report No. GLR970292; Report No. GLR000510]. The plasma exposure at 10 mg/kg, the dose level where these effects in the dog did not occur (NOAEL), was in the same range as encountered during clinical use.

In rats, hepatotoxicity was indicated by increased liver enzymes (ALT, AST, ALP and total bilirubin), single cell necrosis, cellular and nuclear hypertrophy, vacuolation, acidophilic bodies in hepatocytes and pigmentation of Kupffer cells [Report No. GLR010334; Report No. GLR010153; Report No. GLR010732]. This was observed at doses of 32 mg/kg (corresponding to 6 times the exposure (as AUC) at highest recommended clinical dose of 200 mg/day). The plasma exposure at the dose level where these effects did not occur (NOAEL, 10 mg/kg) was in the same range as encountered during clinical use.

In the rat repeated dose studies of 13 weeks or longer, FAH were observed at a dose known to cause hepatotoxicity (32 mg/kg/day). FAH were shown to persist in these studies after a 13 week withdrawal period. There was no indication of micafungin- related development of FAH at lower doses, and the NOAEL was identified as 10 mg/kg/day [Report No, GLR010153].

Two follow-up studies to evaluate the reversibility of altered hepatocellular foci induced in rats treated with micafungin were conducted. Female rats were given IV micafungin of 20 and 32 mg/kg/day for 13 weeks with a follow-up of 20 months (MGC0600514) or 26 weeks with 18 month follow-up (MGC0600515). At 20 mg/kg/day, FAH was detected only at the end of 26- week treatment, but not at the end of the 13- week treatment. At 32 mg/kg, there was a significant increase in the incidence of hepatocellular adenoma and

hepatocellular carcinoma compared to the control group at the end of 18 and 20 months recovery period. Also of note is that the control animals had FAH in these 2 studies, although the occurrence was significantly higher than control in the micafungin groups (20 and 32 mg/kg).

The mean AUC in rats at steady state (mean of values observed at 13 and 26 weeks) was 834.5 µg.h/mL at 20 mg/kg and 1307.1 µg.h/mL at 32 mg/kg (GLR050858). Based on the maximum recommended dose in human of 200 mg/day (AUC₂₄=210.6 µg.h/mL at steady state), which is indicated for invasive candidiasis when the patient's response is inadequate with 100 mg micafungin, these correspond to safety factors of approximately 4.0 and 6.2, respectively.

Quantitative evaluation of micafungin-induced FAH by morphometry, using Glutathione S-transferase placental form (GST-P) immunohistochemical staining, demonstrated that development of FAH was depended on the treatment duration [Report No. GLR020517; Report No. GLR020518]. There was a higher number/cm² as well as a larger area/cm² of GST-P-positive FAH after a 26-week treatment with micafungin at 32 mg/kg/day as compared to a 13-week treatment.

Micafungin (100 mg/day or 2 mg/kg/day) was as effective as and better tolerated than liposomal amphotericin B (3 mg/kg) as first-line treatment of candidaemia and invasive candidiasis in a randomised, double-blind, multinational, non-inferiority study. Median duration of micafungin dosing was 15 days (range 4 to 42 days in adults and 12 to 42 days in children) [Report No. FG463-21-08].

The dosing duration which rats caused FAH was much longer than the clinical use. In addition, after extensive use of micafungin on a worldwide base, no corresponding clinical signal was observed in post-marketing safety surveillance. It can be said the risk is considered minimal if Mycamine treatment is appropriately discontinued in patients who indicate significant and persistent abnormalities in liver function associated with the use of micafungin.

The sponsor believes that the precautions for hepatic effects in the Australian PI are sufficient to carefully monitor them, and no further attention will be needed.

Delegate's comment: Should the following statements be included in the PI to instruct the proper use of Mycamine?

"Specimens for fungal culture and other relevant laboratory studies should be obtained prior to therapy to isolate and identify causative organism(s). Therapy may be instituted before the results of the cultures and other laboratory studies are known. However, once these results become available, antifungal therapy should be adjusted accordingly."

Sponsor's comments:

Astellas does not consider the requested addition to be relevant to the intent of the prescribing information. The suggested statement regarding obtaining a fungal culture and other laboratory studies prior to therapy to isolate and identify the organism relates to the physician's direct care of the patient and not how micafungin should be used. In general, the prescribing information is to focus on providing details related to ensuring proper use and understanding of the medicinal product rather than to instruct the physician on the proper management of their patients. The sponsor also notes that this type of statement does not appear to be standard across systemic antifungals now on the market in Australia, such as Diflucan (fluconazole), Cancidas (caspofungin), Vfem (voriconazole) or Eraxis (anidulagungin).

Delegate's comment: The sponsor states that they will continue to monitor the resistance development and will include the collection of isolates from Europe, US and the rest of the

world, however, no Australia specific microbiological surveillance program has been proposed. ACPM is asked to comment on the acceptability of not conducting Australia specific microbiological surveillance program.

Sponsor's comments:

Astellas has been participating in a global microbiological surveillance program including Australia in order to monitor the resistance development. This is currently under the management of JMI Laboratories, Inc., North Liberty, Iowa, USA. An international group of sites contribute clinical isolates to this program.

As our proposed AU-RMP "*Study To Look At Development Of Resistant Strains*" describes, Astellas commits to continue with monitoring the resistance development in the global surveillance program. Astellas has also explained, in a response to the TGA's request for information, that Australian isolates have been included in this surveillance, and they will be collected in further surveillance and the potential emergence of resistance will be reported in the future PSURs.

There is no necessity to implement Australia-specific surveillance, as Australian data is included in the global program.

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 quality, efficacy, safety and, agreed with the Delegate and considered these products to have an overall positive benefit-risk profile for the proposed streamlined indication;

- *Treatment of invasive candidiasis in children and adults*
- *Treatment of oesophageal candidiasis in adults, adolescents ≥ 16 years of age and the elderly patients for whom intravenous therapy is appropriate*
- *Prophylaxis of Candida infection in children and adult patients undergoing allogeneic haematopoietic stem cell transplantation or patients who are expected to have neutropenia (absolute neutrophil count < 500 cells/ μ L) for 10 or more days.*

The ACPM agreed with the Delegate that the proposed dosage and treatment duration for the respective indications are supported by the evidence provided.

The ACPM was concerned at the possible safety signal of liver tumours and advised that, despite the intended short duration of exposure and low dose in the proposed treatment, given the lack of long term follow up of patients, routine clinical monitoring of liver function should be conducted and may be sufficient to identify potential safety concerns.

The ACPM acknowledged the international effort to monitor the emergence of resistant strains but was concerned that the international updates are infrequent and slow to appear and encouraged the sponsor to support a local group to accumulate data between international data updates.

Proposed PI/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:

- A strengthening of the statement in the *Precautions* section about risk of hepatic tumours, including;
 - that liver function should be carefully monitored during Mycamine treatment

- early discontinuation in the presence of significant and persistent elevation of ALT/AST is recommended

Proposed conditions of registration:

The ACPM agreed with the Delegate on the proposed conditions of registration.

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 Mycamine micafungin (as sodium) 50 mg powder for injection vial and Mycamine micafungin (as sodium) 100 mg powder for injection vial indicated for:

Mycamine is indicated for:

- Treatment of invasive candidiasis in children and adults
- Treatment of oesophageal candidiasis in adults, adolescents ≥ 16 years of age and the elderly patients for whom IV therapy is appropriate
- Prophylaxis of Candida infection in children and adult patients undergoing allogeneic haematopoietic stem cell transplantation or patients who are expected to have neutropenia (absolute neutrophil count < 500 cells/ μ L) for 10 or more days

Specific conditions applying to these therapeutic goods

The implementation in Australia of the micafungin (as sodium) powder for injection Risk Management Plan for Australia version 1, March 2012 included with submission PM-2011-04271-3-2, and any subsequent revisions, as agreed with the TGA and its Office of Product Review.

Other conditions of registration were those applicable to most new chemical entities.

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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