



European Medicines Agency
Evaluation of Medicines for Human Use

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ASSESSMENT REPORT

FOR

Mycamine

International Nonproprietary Name: mycafungin

Procedure No. EMEA/H/C/000734

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

TABLE OF CONTENTS

1.	BACKGROUND INFORMATION ON THE PROCEDURE	3
1.1	Submission of the dossier	3
1.2	Steps taken for the assessment of the product.....	3
2	SCIENTIFIC DISCUSSION	4
2.1	Introduction.....	4
2.2	Quality aspects.....	6
2.3	Non-clinical aspects	10
2.4	Clinical aspects	19
2.5	Pharmacovigilance.....	46
2.6	Overall conclusions, risk/benefit assessment and recommendation	47

1. BACKGROUND INFORMATION ON THE PROCEDURE

1.1 Submission of the dossier

The applicant Astellas Pharma GmbH submitted on 11 April 2006 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Mycamine, through the centralised procedure under Article 3 (2)(a) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 17 November 2005 and re-confirmed on 14 December 2005.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC, as amended - complete and independent application

The application submitted is a complete dossier:

composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies)

Scientific Advice:

The applicant received Scientific Advice from the CHMP on 31 May 2001, 30 May 2002, 22 April 2005 and 29 April 2005. The Scientific Advice pertained to clinical aspects of the dossier.

Licensing status:

Mycamine has been given a Marketing Authorisation in Japan on 08/10/02, USA on 16/03/05, Jordan on 23/02/05, China on 12/05/06, Taiwan on 28/08/06, Korea on 26/10/06, Hong Kong on 06/01/07, Canada on 22/05/07, Macau on 05/07/07, Syria on 23/08/07 and Kuwait on 30/10/07.

A new application was filed in the following countries: Saudi Arabia, Lebanon, Oman, United Arab Emirates, Bahrain, Thailand and Philippines.

Applications were withdrawn in the EU on 01/09/04 and in Switzerland on 02/12/04.

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Karl Broich

Co-Rapporteur: Bruno Flamion

1.2 Steps taken for the assessment of the product

- The application was received by the EMA on 11 April 2006.
- The procedure started on 24 May 2006.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 18 August 2006. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 23 August 2006.
- During the meeting on 18-21 September 2006, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 21 September 2006.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 13 July 2007.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 3 September 2007.
- During the CHMP meeting on 17-20 September 2007, the CHMP agreed on a list of outstanding issues to be addressed in writing and/or in an oral explanation by the applicant.

- The applicant submitted the responses to the CHMP list of outstanding issues on 12 December 2007.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the list of outstanding issues to all CHMP members on 8 January 2008.
- During the CHMP meeting on 21-24 January 2008, outstanding issues were addressed by the applicant during an oral explanation before the CHMP.
- During the meeting on 18-21 February 2008, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Mycamine on 21 February 2008. The applicant provided the letter of undertaking on the follow-up measures to be fulfilled post-authorisation on 20 February 2008.

2 SCIENTIFIC DISCUSSION

2.1 Introduction

Invasive fungal infections

Invasive fungal infections (IFIs) are a frequent cause of morbidity and mortality in high-risk patients, such as immunocompromised patients. The number of such patients has increased in recent years due to increases in the use of intensive cancer chemotherapy as well as immunosuppressive regimens for autoimmune disease, the occurrence of solid organ and bone marrow transplantation, and the incidence of individuals with diseases of the immune system such as AIDS.

Candida is currently the predominant fungal pathogen in these patient populations. However, invasive aspergillosis has been increasing in incidence and *Aspergillus* is a significant fungal pathogen in bone marrow transplant recipients. Organisms belonging to both genera are associated with significant morbidity and a high mortality. Current therapies are not sufficient and treatment alternatives for this indication are urgently needed.

About the product

Micafungin (FK463), manufactured by Astellas Pharma Co., Ltd., is a water-soluble semisynthetic compound belonging to the new class of antifungal agents, the echinocandin lipopeptides. It is synthesised through the chemical modification of a fermentation product from *Coleophoma empetri* F-11899. It acts by selectively inhibiting 1,3-beta-D-glucan synthase, which is required for fungal cell wall synthesis. Other antifungals such as polyenes and azoles interfere with the cell wall structure itself. Mammalian cells do not contain 1,3-beta-D-glucan polymers, indicating a lack of mechanism-based toxicity, which may at least partially account for the good tolerability of the echinocandins. Micafungin has potent *in vitro* and experimental *in vivo* activity against a variety of pathogenic *Candida* species (yeasts) and *Aspergillus* species (filamentous fungus), grouped as yeast-like organisms, which are the most common pathogens responsible for invasive fungal infections.

Two other echinocandins, caspofungin and anidulafungin, have already obtained a marketing authorization in the European Union. Caspofungin is indicated for the treatment of invasive aspergillosis in adult patients who are refractory to, or intolerant of, other antifungal therapies, for the treatment of invasive candidiasis in adult patients, and for empirical therapy for presumed fungal infections (such as *Candida* or *Aspergillus*) in febrile, neutropenic adult patients. Anidulafungin is indicated for treatment of invasive candidiasis in adult non-neutropenic patients.

So far, all echinocandins have to be used through the intravenous route.

Micafungin has already been licensed in Japan (2002), in the USA (2005) and in other countries.

The applied indication is:

Mycamine (micafungin) is an echinocandin and has broad spectrum activity against *Candida* and *Aspergillus* species. Mycamine is indicated as follows:

- Treatment of invasive candidiasis.
- Treatment of oesophageal candidiasis.
- Prophylaxis of *Candida* and *Aspergillus* 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.

The approved indication is:

Mycamine is indicated for:

Adults, adolescents \geq 16 years of age and 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.

The decision to use Mycamine should take into account a potential risk for the development of liver tumours (see section 4.4). Mycamine should therefore only be used if other antifungals are not appropriate.

The dose regimen of Mycamine depends on the body weight of the patient as given in the following tables:

Use in adults, adolescents \geq 16 years of age and elderly

<u>Indication</u>		
	Body weight > 40 kg	Body weight \leq 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 \leq 40 kg.

The treatment duration of *Candida* infection should be 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 should 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.

Use in children (including neonates) and adolescents < 16 years of age

<u>Indication</u>		
	Body weight > 40 kg	Body weight \leq 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.

The treatment duration of *Candida* infection should be 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 prophylaxis of *Candida* infection, Mycamine should be administered for at least one week after neutrophil recovery. Experience with Mycamine in patients less than 2 years of age is limited.

2.2 Quality aspects

Introduction

Micafungin, is a sterile powder for solution for infusion, available in two strengths, 50 mg and 100 mg. The drug substance is micafungin sodium, a semi-synthetic, novel drug substance with antifungal activity that belongs to the echinocandin family of antifungal agents. Echinocandin lipopeptides selectively inhibit the synthesis of 1,3-β-D-glucan, an essential component of the fungal cell wall, which is not present in mammalian cells. Each vial contains 50 mg or 100 mg micafungin (equivalent to 50.86 mg or 101.73 mg micafungin sodium), 200 mg lactose as stabiliser, and citric acid and/or sodium hydroxide for pH adjustment. Recommended diluents for the reconstitution of the powder in the vial and further dilution in infusion bags are 0.9% sodium chloride solution for injection or 5 % glucose solution.

Active Substance

The chemical name corresponding to micafungin sodium is sodium 5-[(1*S*,2*S*)-2-[(3*S*,6*S*,9*S*,11*R*,15*S*,18*S*,20*R*,21*R*,24*S*,25*S*,26*S*)-3-[(*R*)-2-carbamoyl-1-hydroxyethyl]-11,20,21,25-tetrahydroxy-15-[(*R*)-1-hydroxyethyl]-26-methyl-2,5,8,14,17,23-hexaoxo-18-[4-[5-(4-pentyloxyphenyl)isoxazol-3-yl]benzoylamino]-1,4,7,13,16,22-hexaaza-tricyclo-[22.3.0.09,13]heptacos-6-yl]-1,2-dihydroxyethyl]-2-hydroxyphenylsulphate. Its molecular formula and weight are C₅₆H₇₀N₉NaO₂₃S and 1292.26 respectively

Micafungin sodium is a white, amorphous and highly hygroscopic powder. It is freely soluble in water and isotonic sodium chloride solution, slightly soluble in methanol and practically insoluble in ethanol (95%).

The pH of its aqueous solution is between 6.2 and 6.9 (10% aqueous solution). The dissociation constant (pKa) and partition coefficient (log P) are 9.15 and -0.39 (pH 7), respectively.

- **Manufacture**

Micafungin sodium is produced in three steps – fermentation, enzymatic deacylation and purification, and finally, synthesis and purification. Detailed description is presented in the confidential annex to the restricted part of the EDMF.

The manufacturing method of micafungin was modified to improve the micafungin filtration process during the development. The previous method and the current method are abbreviated as method I and method II, respectively. The latter is used for the manufacture of commercial scale batches. Batch analysis data confirm that there is no significant difference in the quality of micafungin produced by either of the two methods.

- **Specification**

The specifications for the control of the drug substance include tests for description (visual), identification (UV-PhEur, IR-PhEur, NMR- PhEur, flame coloration test for sodium), specific rotation $[\alpha]_D^{20}$ -PhEur, pH-PhEur, heavy metals, residue on ignition, related substances (HPLC), residual solvents (GC), water (PhEur), bacterial endotoxins (PhEur), microbial limit test (PhEur), and assay (HPLC).

The selected test parameters and acceptance criteria are considered as appropriate to control the quality of the drug substance micafungin sodium. The levels for the specified related substances have been qualified by toxicological studies.

Batch analyses results are provided for twelve batches of the drug substance. The older batches were produced according to the previous manufacturing method I. Five pilot scaled batches and three consecutive commercial scaled batches were manufactured by the current manufacturing method II. By comparing not only the batch analysis data but also the stability test results of micafungin obtained from method II with those of method I, equivalency in the quality has been confirmed.

The five pilot batches and three production batches were tested using the current specification requirements. Results comply with the set specifications.

- **Stability**

The manufacturing method of the drug substance has been changed from “Method I” to “Method II”. “Method II” was adopted as manufacturing method to be used for commercial production. Nevertheless, stability studies on three batches manufactured by “Method I” were provided as supportive data. There is no difference in the results of the stability studies of the drug substance obtained from either manufacturing method.

Stability studies on three primary pilot scale batches and three production batches manufactured at the commercial production site, under long term conditions (5°C) over 39 and 36 months respectively and under accelerated conditions (25°C/60%) over 6 months were conducted according to the requirements of the ICH guideline “Note for Guidance on Stability Testing: Stability Testing of New Drug Substances and Products (CPMP/ICH/2736/99)”.

The results of the long term stability studies are within specification. Under long term conditions a slightly increase of two related substances has been observed, but the results are within specification. No significant changes of the other parameters compared to the initial values have been detected. All results are within specification after 39 respectively 36 months at 5°C.

At accelerated conditions the same two related substances were increased. After 3 months the level of one of them was out of specification, however, the assay was within specification over 6 months.

In addition, one pilot scale batch was tested at stress conditions (40°C after 12 weeks, 25°C/82% RH after 4 weeks, xenon lamp/30,000 lux after 40 h). These studies reveal that the active substance is sensitive to high temperature, high humidity and exposure to light.

The stability studies of the pilot and production scale batches are in compliance with the requirements of the current ICH guideline. The stability results are acceptable and support the proposed re-test period under the proposed storage conditions.

Medicinal Product

- **Pharmaceutical Development**

Micafungin can only be manufactured as an amorphous powder, which shows poor flowability and has undesirable physicochemical characteristics for a powder filling operation. Therefore, a lyophilisation process has been employed to manufacture the drug product. The results of micafungin stability in aqueous solution clearly indicate that the micafungin drug product could not be developed as a liquid dosage form. Based upon these results, a lyophilised/sterile powder formulation of Micafungin for concentration for solution for infusion was selected for further development.

A stabiliser was considered necessary for the drug product since it has been observed that the lyophilised amorphous powder of micafungin is unstable in the absence of excipients. Several standard excipients were tested as possible stabilising agents. The lyophilised product formulation containing lactose monohydrate was the most stable among all the drug products evaluated and therefore lactose monohydrate was selected as stabiliser while the amount of lactose monohydrate was optimised with subsequent studies.

The effects of the pH of the lyophilised product on its stability were investigated and an acceptable pH range was established.

The photostability of the drug product in vials with and without a transparent UV-resistant film was evaluated. The results clearly indicate the necessity of light protection for the product. Therefore, the vials will be wrapped with an UV-resistant film, which protects the product sufficiently from light.

Finally, the compatibility of the solution reconstituted and diluted with saline or 5% dextrose was investigated. The stability of the drug product solution was studied under fluorescent light (1000 lux) for up to 24 hours at room temperature with or without light protection. The results show no significant decrease in the potency in any of the drug product solutions up to 24 hours at room temperature either with or without light resistant sleeves regardless the type of diluent. However, the related substances increased with elapsed time in the drug product solution without a light-resistant sleeve; the increase being more evident in the lower concentration on the drug product solution. Therefore, it is recommended to protect the transfusion bag from light exposure with a light-resistant sleeve.

- Adventitious Agents

A TSE statement of the active drug substance manufacturer was provided confirming that no materials of animal origin are used during the manufacturing process of micafungin sodium. In addition, lactose monohydrate is in compliance with guideline EMEA/410/01 rev 2.

- Manufacture of the Product

The manufacture of Mycamine is a standard process comprising basically the following steps:

- Preparation of the solution containing micafungin sodium and lactose monohydrate
- Pre-filtration of the solution
- Vial and Stopper processing
- Final sterile filtration
- Filling
- Lyophilisation
- Stoppering and Flip-off capping
- Shrink-wrapping, labelling and packaging

The data gathered during process validation and the provided batch analyses on three consecutive validation batches per strength demonstrate that the manufacturing process is robust and consistently yields drug product, which meets the predetermined quality characteristics. The chosen in-process controls have been shown to be suitable for monitoring the manufacturing process.

- Product Specification

The specification for batch release and shelf-life include the following tests: appearance (visual), identification (UV and HPLC), pH (PhEur), colour and clarity (visual), related substances (HPLC), water (Karl Fisher), bacterial endotoxins (PhEur), content uniformity (PhEur), foreign insoluble matter (PhEur), particulate matter (PhEur), sterility (PhEur) and assay (HPLC).

Regarding the 50 mg presentation, batch analysis results of four clinical batches manufactured by method I, three batches for clinical and stability studies manufactured by method II and one scale up and three commercial batches manufactured by method II were presented. Regarding the 100 mg presentation, batch analysis results of three pilot and three full scale batches produced with method II at two different plants, including three batches produced at the commercial manufacturing site, were presented. The results comply with the specification and confirm consistency of the product.

- Stability of the Product

Three primary stability and three production scale batches of micafungin 50 mg powder for solution for infusion have been stored for up to 39 and up to 42 months respectively under long-term 25°C/60% RH, and up to 6 months under accelerated conditions (40°C/75%RH). Another three pilot scale batches of micafungin 100 mg powder for solution for infusion have been placed in a formal stability study under long-term conditions for up to 36 months and up to 6 months under accelerated conditions.

The composition and the manufacturing process of the primary stability batches as well as those of the production scale batches are the same as that proposed for marketing. However, the UV protecting

shrink film material and the lubricant formulation of the rubber stoppers of these batches are slightly different from the commercial presentation of the product.

Therefore, three additional production batches of each strength manufactured at the commercial manufacturing site using the same container closure system as proposed for commercial use, have been placed in a formal long-term stability study and in an accelerated conditions study in order to confirm the available stability data. So far, data up to 24 months (50 mg) and 18 months (100 mg) in normal and up to 6 months in accelerated are available and presented but studies are on-going. Although different materials for the UV protecting film have been utilised, the proposed shelf life is considered justified, because the equivalency between the two shrink film materials has been proven. The product has shown a tendency to degrade under stress testing at 60°C for three months and/or under xenon lamp emission. However, no changes were observed when vials were wrapped in a light resistant packaging.

All stability results of the primary and production scale batches stored under long-term conditions and under accelerated conditions met the requirements of the shelf-life specification over the studied period and therefore confirm the proposed shelf-life. As seen from the photo-stability study the proposed over-wrapping material assures sufficient light protection. Therefore no storage precaution is required.

In-use studies on reconstituted solutions in vial and in transfusions bag

Several in-use stability studies have been performed on the 50 mg after reconstitution of the powder and further dilution with the recommended diluents (0.9% sodium chloride solution for injection and 5% glucose solution). For the 100 mg formulation no further in-use stability tests have been conducted. The results of the different studies demonstrate that there is no difference between the low concentration and the high concentration in the recommended diluents. Furthermore, the results confirm that there is no difference in the stability profile of the reconstituted and the diluted solution in a transfusion bag after 96 hours compared to the results obtained in the reconstitution study where the reconstituted solution was first stored for 48 hours in a vial and then further diluted in a transfusion bag and stored for additional 72 hours. No changes in description, osmolality, pH, potency and related substances were observed both in 0.9% sodium chloride solution for injection and 5% glucose solution up to 96 hours when stored at room temperature with a light-resistant sleeve under 1,000 lux.

In addition, the microbiological in-use stability has been demonstrated for 96 hours at 25°C in the diluted infusion solution.

Based on the results of the different studies, the storage precautions as given in the SPC are considered appropriate.

Discussion on chemical, pharmaceutical and biological aspects

The quality of Mycamine powder for solution for infusion is adequately established. In general, sufficient chemical and pharmaceutical documentation relating to development, manufacture and control of the drug substance and drug product has been presented. There are no major deviations from EU and ICH requirements. The results of tests carried out indicate satisfactory consistency and uniformity of all the important product quality characteristics. At the time of the CHMP opinion, there were a number of minor unresolved quality issues having no impact on the Benefit/Risk ratio of the product. The applicant submitted a Letter of Undertaking dated on 20 February 2008 and committed to resolve these as Follow Up Measures after the opinion, within an agreed timeframe.

Stability tests indicate that the product under ICH guidelines conditions is chemically stable for the shelf life.

It can be safely concluded that the product should have a satisfactory and uniform performance in the clinic.

2.3 Non-clinical aspects

Introduction

The potential efficacy and safety of micafungin in clinical use were evaluated in a comprehensive nonclinical development programme. The applicant has provided a reasonable package on pharmacology studies to characterise the pharmacological profile of micafungin. Nonclinical studies were conducted with micafungin drug substance (micafungin sodium) dissolved in physiological saline. The commercial product, which was also used in clinical studies, is a lyophilised formulation containing micafungin sodium and lactose monohydrate as stabiliser as well as anhydrous citric acid and sodium hydroxide for pH adjustment. All excipients of the formulation are well known and comply with the European Pharmacopoeia.

The antifungal spectrum and activity of micafungin was established using *in vitro* microbiological methods as well as mouse models of fungal infections. In addition, safety pharmacology data were generated.

Pharmacokinetic studies were conducted in animal species that were also used for pharmacological (mice) and toxicological assessments (mice, rats, rabbits and dogs). A relationship between exposure and toxicity in animals was established. The pharmacokinetic programme also included *in vitro* and *in vivo* (human) drug-drug interaction studies.

The toxicological development programme included single-dose and repeat-dose toxicity studies in rats (including juveniles) and dogs, reproductive toxicity studies in rats and rabbits, standard genotoxicity tests as well as additional toxicological assessments such as studies in juvenile animals (rats and dogs), local tolerance, antigenicity and studies to establish the safety of impurities and photodegraded drug product. Standard carcinogenicity studies have not been performed. In order to assess a carcinogenic potential of micafungin, repeat-dose toxicity studies including recovery periods which approximately cover the life span were conducted in rats. Together with the safety pharmacology data, the programme was appropriate to characterise the toxicological profile of micafungin.

GLP aspects

Standard safety pharmacology tests were conducted in compliance with GLP and are in accordance with the requirements in ICH S7A for safety pharmacology studies.

The pharmacokinetic studies were performed in Japan, where they are required to satisfy “Reliability Criteria” as stated in Article 18-4-3 of the “Pharmaceutical Affairs Law, Enforcement Ordinance and Enforcement Regulations”. Therefore, the quality of the pharmacokinetic studies can be considered equivalent to that of GLP studies.

Toxicokinetic measurements were integrated in repeat-dose toxicity studies. With the exception of two non-pivotal studies, all toxicity studies were conducted in compliance with GLP regulations.

Pharmacology

- Primary pharmacodynamics

The exact mechanism of action of micafungin and other echinocandin lipopeptides upon glucan synthase activity remains to be elucidated. However, data from standard biochemical assays and morphological techniques provided clear evidence that micafungin is a selective inhibitor of cell wall 1,3-β-D-glucan polymer synthesis.

In vitro susceptibility studies of yeast and filamentous fungi (standard strains and clinical isolates), were performed, with modifications according to the Clinical and Laboratory Standards Institute

(CLSI) methods M27-A2 (*Candida* species) and M38-A (*Aspergillus* species), and in comparison to reference antifungal drugs.

In vitro Micafungin displayed a broad spectrum and potent activity against *Candida* and *Aspergillus* species. In particular:

Against *Candida* species:

- The MICs were higher in *C. krusei*, *C. parapsilosis* and *C. guilliermondii* as compared to *C. albicans* species.
- Micafungin was fungicidal against most *Candida* species at concentrations of the MIC or above. This activity was time-dependent, but not concentration-dependent.
- *In vitro* no resistance development could be induced in *C. albicans*.
- No cross-resistances to micafungin were observed in azole-resistant *Candida* strains.

Against *Aspergillus* species:

- Micafungin inhibited conidial growth, germ tube emergence and hyphal growth, but was not fungicidal at concentrations of the MIC or above.

MICs measured with human serum or in the presence of human serum albumin were 64- to 128-times higher than those measured without them, reflecting the high protein binding rate of micafungin.

Micafungin was inactive against *Cryptococcus neoformans*, *Trichosporon* spp., *Fusarium solani*, *Pseudallescheria boydii* and zygomycetes.

***In Vivo* efficacy of micafungin in mouse models**

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, disseminated and pulmonary aspergillosis in immunocompetent and in immunocompromised mice, which represent the most common infections in immunocompromised patients (including HIV patients) or in patients immunosuppressed as a result of underlying diseases or medications.

Mice were immunocompetent, neutropenic or corticosteroid-immunosuppressed. Neutropenia and corticosteroid immunosuppression in these models, however, may be considered transient. Particularly in later stages of the experimental period of survival tests micafungin and host defence mechanisms may act in concert. For the oropharyngeal/oesophageal candidiasis model a congenitally immunodeficient mouse strain was used.

It was evident from these studies that micafungin is highly effective in both the treatment and prevention of disseminated candidiasis and disseminated and pulmonary aspergillosis.

In particular the studies indicate:

With regard to *Candida* species infections:

- Micafungin was highly effective in the treatment of disseminated candidiasis.
- The efficacy of micafungin in the survival model was not obviously influenced by the immune status of the host and the time of treatment start.
- Comparative efficacy studies of survival demonstrated that higher doses are required for non-albicans *Candida* species like *C. krusei*, *C. parapsilosis*, and *C. guilliermondii* than for *C. albicans*, *C. glabrata* and *C. tropicalis*.
- Micafungin was highly effective against azole-resistant and amphotericin B-resistant *Candida* species.
- Against oropharyngeal and oesophageal candidiasis (*C. albicans* infected) in the immunodeficient mouse an eradicated effect of micafungin was suggested, which provided further support for a fungicidal activity of micafungin against *C. albicans* species.

With regard to *Aspergillus* species infections:

- Micafungin proved highly effective in mouse models of disseminated and pulmonary aspergillosis.
- Micafungin was effective against both azole and amphotericin B resistant *Aspergillus* species.
- The efficacy of micafungin was comparable to amphotericin B.
- Micafungin was superior or similar in efficacy as compared to caspofungin.
- Particularly in the case of pulmonary aspergillosis the type of immunosuppression appears to be important for the dosing regimen. In comparative efficacy studies it was found that the ED₅₀ of micafungin was similar to that of AMPH-B in mice immunosuppressed with cyclophosphamide or 5-fluorouracil. However, in mice immunosuppressed with hydrocortisone the efficacy of micafungin was inferior to that of AMPH-B.
- In addition, in the case of *Aspergillus* infections, ED₅₀s of micafungin were higher when the treatment start was at 24 hours after infection than at a treatment start at 1 hour after infection. Thus, for prophylactic treatment lower doses may be necessary than for treatment against probable or proven aspergillosis.

Resistance induction

Fifteen serial transfers of a typical *C. albicans* isolate on subinhibitory concentrations of micafungin did not substantially change its MIC value. *In vivo* studies further indicated a low potential of micafungin for resistance development. No resistance induction was observed in *C. albicans* isolates obtained from patients with oesophageal candidiasis. Cultures persistently positive during treatment with micafungin showed similar sensitivities against micafungin on day 0 and 29. In addition, no clinical isolates with acquired resistance to micafungin have been identified against *Aspergillus* spp. In patients that had persistent positive cultures for *Aspergillus* spp. (*A. fumigatus*, *A. terreus*) no change was noted in the MIC before, during (29th day) or after (1-4 days) the treatment.

- Secondary pharmacodynamics and Safety pharmacology

In standard **safety pharmacology** tests effects of micafungin upon cardiovascular and blood systems were evident.

Haemolysis was observed *in vitro* (rabbit blood) at concentrations of 500 µg/ml micafungin. In rats in repeat-dose toxicity studies signs of haemolytic anaemia were observed. After the repeated daily bolus injection of high doses of micafungin haemolytic plasma concentrations might have been reached (at C_{max}). In dogs in repeat-dose toxicity studies micafungin was infused which yielded much lower plasma concentrations. No haemolytic anaemia was observed under these conditions. As the risk of micafungin-induced haemolytic anaemia cannot be excluded a warning concerning this matter is included in the SPC (Section 4.4 Special warnings and precautions for use).

In standard safety pharmacology tests cardiovascular and histamine releasing effects of micafungin were evident at high doses (32 and 100 mg/kg i.v. bolus) and appeared to be time above threshold dependent. Prolongation of infusion time reducing the plasma concentration peak appeared to abolish these effects. However, safety margins for histamine-mediated effects are low (2-3) and can also occur in patients. A warning has been included in the SPC (4.4) that during administration of micafungin, anaphylactoid reactions including shock may occur.

In vitro and *in vivo* investigations to assess the potential for QT interval prolongations were generally negative, so it can be considered that there is no preclinical evidence of risk of prolonging the QT interval for micafungin.

Urinary excretion of electrolytes was increased in rats receiving 100 mg/kg micafungin suggesting an effect upon reabsorption of water and electrolytes. In a rat 26 week repeat-dose toxicity study at 32 mg/kg/day, in parallel, increases in urinary excretion of sodium, potassium and chloride were noted, but these findings were not accompanied by changes in serum electrolytes.

- Pharmacodynamic drug interactions

***In Vitro* interactions**

In vitro interactions between micafungin and relevant antifungal agents were evaluated by using a checkerboard method based on the standard broth microdilution method M27-A recommended by the NCCLS.

A combination of micafungin with amphotericin B (AMPH-B), fluconazole (FLCZ) and itraconazole (ITCZ) had additive effects against *C. albicans* isolates. In addition, additive interaction was prevalently seen on *A. fumigatus* for the combination with AMPH-B and ITCZ. No antagonism was observed in any combination for *C. albicans* and *A. fumigatus*.

While micafungin alone was reported to be inactive against *C. neoformans* strong synergistic or additive interaction was observed when combined with AMPH-B. Combination with ITCZ, however, displayed antagonistic effects on *C. neoformans*. The interaction of micafungin and FLCZ was indifferent for all the isolates of *C. neoformans* tested.

***In Vivo* interactions**

In order to validate *in vitro* positive interactions of combined treatment with micafungin and AMPH-B *in vivo* efficacy was evaluated against pulmonary aspergillosis induced by intranasal challenge with *A. fumigatus* IFM40836 in hydrocortisone immunosuppressed mice.

Six days after infection treatment with low doses of micafungin or AMPH-B alone had no effect on fungal burden in lungs. However, combined treatment of the two drugs at low doses resulted in a significant decrease in colony counts as compared to control values.

At higher doses single treatment of both micafungin and AMPH-B reduced colony counts significantly. Further significant reductions were obtained with higher doses at the combined treatment.

Pharmacokinetics

Plasma concentration profiles of micafungin were determined in mice, rats and dogs in single-dose and repeat-dose studies at doses of 0.32 to 3.2 mg/kg and 3.2 to 32 mg/kg, respectively. Micafungin is protein bound in these species to more than 99%, similar to humans. Protein binding was concentration-independent over a range of 10-100 µg/ml.

In the single-dose studies pharmacokinetic parameters were linear within the dose range 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 suggesting the saturation of metabolising or saturation processes. In dogs, similar to humans, there was no evidence of accumulation of micafungin.

Micafungin was rapidly distributed into the organs/tissues with the highest concentration at common sites of fungal infections (kidney, liver, and lungs). 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. Micafungin was not extensively taken up by blood cells. The blood/plasma partition ratio at concentration between 0.1-10 µg/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 this concentration range.

Disposition studies with ¹⁴C-labelled micafungin suggested that metabolites were slowly formed and slowly eliminated from the plasma of rats and dogs.

Qualitatively the same metabolites were found in rats, dogs and humans. Major metabolites were M-1, M-2 and M-5. The metabolites M-1 and M-2 were found in various tissues. M-1 formation was slower in humans as compared to rats. M-5 was the main metabolite found in rat and human plasma. This metabolite was demonstrated to be formed by multiple CYP isoenzymes (CYP1A2, 2B6, 2C and 3A4). In dogs, M4 (a sulfoconjugate of M5) is the major metabolite and this metabolite is dog-specific.

In vitro susceptibility tests demonstrated that M-1 exhibited an activity against *Candida* and *Aspergillus* species which was 4-16 times lower than that of micafungin and had moderate activity against *C. neoformans* and *T. cutaneum* (strains that were not inhibited by micafungin). The *in vitro* spectrum and activity of M-2 was similar to micafungin. M-5 was 128 times less active than micafungin. The "metabolite" M-3 (or related substance 6) is the ring-opened form of micafungin. It is formed in solutions under neutral or basic conditions and supposed to form a covalent adduct with proteins. Acidified micafungin solutions were shown to minimise this degradation. *In vivo* studies demonstrated little covalent binding and the amount of covalent binding did not increase with time.

The biliary-faecal route was found to be the major excretion route in animals and humans. In rats and dogs, the excretion reached approximately 95% after 144 hours. Micafungin was able to cross the placenta and was secreted into the milk of lactating rats.

There was no interaction with other protein-bound drugs. Further interaction studies with CYP3A4 substrates indicated that interactions are most unlikely to occur. Micafungin didn't inhibit P-glycoprotein.

Toxicology

The toxicological development programme included single-dose and repeat-dose toxicity studies in rats and dogs, reproductive toxicity studies in rats and rabbits, standard genotoxicity tests as well as additional toxicological assessments such as studies in juvenile animals (rats and dogs), local tolerance, antigenicity and studies to establish the safety of impurities and photodegraded drug product. In order to assess a carcinogenic potential of micafungin, repeat-dose toxicity studies including recovery periods which approximately cover the life span were conducted in rats.

- Single dose toxicity

Single-dose studies in two mammalian species were conducted in accordance with the EU guideline 3BS1a on single-dose toxicity. Micafungin was administered to rats (62.5, 125 and 250 mg/kg) and dogs (100 and 200 mg/kg) using intravenous bolus injection.

The minimum lethal dose of Mycamine is 125 mg/kg in rats and above 200 in dogs, equivalent to about respectively 5 and 25 times the maximum recommended human clinical dose based on body surface area comparisons.

Clinical signs prior to death in rats included decreased spontaneous movement, clonic convulsions, prone position, oligopnoea, dark red ear auricles and extremities, and swelling of the face. These symptoms may be at least partly related to endogenous histamine release. In dogs, toxic symptoms suggestive of histamine release were observed in the high dose group. Abnormal haematological and clinical chemistry parameters indicated haemolytic anaemia and hepatic injury.

- Repeat dose toxicity (with toxicokinetics)

In the rat toxic changes were occasionally observed at a daily dose of 3.2 mg/kg. Changes were consistently found at the highest dose administered (32 mg/kg) and their incidence and severity generally increased with time. The primary target organs of micafungin toxicity are the liver (in rats and dogs) and the urinary tract (in rats) at a dose of 32 mg/kg/day.

Liver (rat)

In the rat indices of hepatic injury were increased activity of serum ALT and AST. Histologically, hepatic injury was indicated by degenerative changes and necrosis of hepatocytes and its subsequent adaptive changes (e.g. mitosis, in addition, in the 13- and 26-week studies: multinucleated hepatocytes and foci of cellular alterations). Foci in the 26-week study were clearly treatment-related and females were more affected than males. Although blood parameters (AST/ALT) returned to normal during a 4 or 13 week recovery period in the 26-week study and most of the hepatic changes showed evidence for regression, the incidence of females affected with foci, the number, size and type of foci were essentially the same as at the end of the treatment. There was neither a regression nor progression. Persistence of foci could suggest a preneoplastic process.

After the occurrence of foci of altered hepatocytes (FAH) which were not reversible even after a recovery period of 4 to 13 weeks had been identified as a concern in the first licensing procedure, the applicant conducted new studies (13-week treatment with 6, 12 and 21 months recovery, respectively; 26-week-treatment with 6, 12 and 18 months recovery, respectively). These studies showed that part of the FAH are not reversible and persist or develop into tumours after a long recovery period. Regarding the size of FAH a progression was found with increasing time (recovery) and at least at the highest dosage (32 mg/kg) significantly increased tumour rates were induced in both studies.

After 6 months of treatment, 20 mg/kg micafungin clearly induces (statistically significant) FAH and increased tumour rates were observed at the end of a 12 month recovery period (not statistically significant). Even if the increase in tumour rate at 20 mg/kg is not statistically significant, it is to be considered biologically relevant in view of the complete data available. Therefore, the NOAEL for both effects (induction of FAH and tumours) is unknown but less than 20 mg/kg. Both, the AUC_{0-24h} in female rat at 10 mg/kg and the AUC_{0-24h} in humans at the intended max. human therapeutic dose is approximately 200 µg/ml. Thus, there is no reliable safety margin to the intended therapeutic exposure.

In order to support the assumption that tumour development in rat is based on a non-genotoxic mode of action the applicant has conducted an *in vitro* study on unscheduled DNA synthesis (UDS) in primary female rat hepatocyte cultures. This study demonstrated that micafungin (at concentrations which produced no or weak cytotoxicity) does not induce unscheduled DNA synthesis in female rat hepatocytes. Calculation of equivalent plasma concentrations in patients and rats showed that the concentration ranges applied in the UDS trials covered and exceeded those determined in repeat dose toxicity studies in rats and those determined in patients at therapeutic doses. Thus, the non-genotoxic mode of action for FAH development and subsequent tumour formation in the rat liver is further confirmed and supported.

The mechanism for FAH and tumour development has not been elucidated. Based on the NOAEL for FAH development the threshold for tumour development is assumed to be at 10 mg/kg/day, which is approximately in the therapeutic range. At this threshold for tumour development, the AUC in female rats is in the range of human AUCs at therapeutic doses, i.e. there aren't any safety margins at least for the high therapeutic doses (safety factor for adult patients at the 150 mg/day dose: **1.2**). Especially in paediatric patients the safety margin at a dose of 4 mg/kg is < 1 (0.7).

Liver (dog)

In the dog liver enlargement and discoloration of the liver indicated hepatotoxicity. Histologically centrilobular hypertrophy of hepatocytes was noted. The proliferation of the endoplasmatic reticulum might indicate an induction of microsomal enzymes. Abnormal laboratory parameters indicating hepatic injury, however, were not noted in any repeat dose study in dogs. The NOAEL for hepatic injury in the dog was established at 10 mg/kg/day.

Blood

Dose-dependent signs of haemolysis were observed in rats at 10 and 32 mg/kg/day administered as a bolus injection. Signs of haemolytic anaemia were present in all repeat-dose studies at doses of 10 and 32 mg/kg/day. 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. The NOAEL for the induction of haemolysis in rat was 3.2 mg/kg/day. The haemolytic effect of micafungin *in vivo* is suggested to be based on C_{max} values reached in the blood and/or the time spent above a threshold concentration. Although signs of haemolytic anaemia were observed in dogs following single administration of 200 mg/kg, there were no abnormal haematological parameters indicating haemolysis in the repeat-dose studies. As the risk of micafungin-induced haemolytic anaemia can not be excluded a warning concerning this matter is included in the SPC (Section 4.4 Special warnings and precaution for use).

Urinary tract (rat)

Changes in the urinary tract consisted of vacuolation of the renal pelvic epithelium and mucosal epithelium of the urinary bladder after 32 mg/kg were noted after 4-week treatment. The changes were reversible on cessation of the treatment. In a first 26-week study, histological changes included haemosiderin deposition in the proximal tubular epithelium, dilatation and swelling of the collecting duct epithelium, vacuolation of the renal pelvic epithelium as well as vacuolation and thickening (hyperplasia) of the bladder epithelium at a dose of 32 mg/kg. Slight to mild vacuolation of the renal pelvic epithelium occurred in 7/14 males and 5/14 females, while hyperplasia of transitional cells in the urinary bladder as well as mild vacuolation of the bladder epithelium (14/14 males, 14/14 females) was observed at 32 mg/kg/day. The reversibility of the changes was not assessed. Abnormal urinalysis findings consisting of increased urine volume, decreased urine pH and increased excretion of electrolytes, mainly sodium and chloride, were noted in the 26-week study. These changes were accompanied by an increase in water intake. Small increases in blood urea nitrogen, but no increase in creatinine was recorded. Increased urinary excretion of electrolytes (sodium, chloride, potassium) was also observed in the safety pharmacology study. However, decreased serum electrolytes as a potential consequence of electrolyte loss via the urine were not found in repeat-dose studies. In a more recent 26-week study, only 3 out of 20 animals showed vacuolation of the renal pelvic epithelium and hyperplasia of transitional cells in the urinary bladder at a dose of 32 mg/kg and these changes showed to be reversible after 18 months.

Male genital tract

In male dogs, dose-dependent testicular toxicity was observed in the 39-week toxicity study at 10 and 32 mg/kg/day. The reversibility of the findings was not assessed. The Applicant refers to literature to substantiate that the effects on germ cells observed are probably reversible. Although this appears acceptable, with respect to the changes in the Sertoli cells reversibility is less certain. The applicant has provided a further discussion on the reversibility of testicular findings. He supposes that Sertoli cell vacuolation is a secondary event due to phagocytosis of degenerate germ cells and therefore reversible after withdrawal of the compound. However, a final conclusion on the reversibility of this finding can not be drawn. Given the fact that the NOAEL for male genital toxicity leads to AUC levels which are in the therapeutic range this issue is addressed in the labelling under section 4.6.

In rats, reduced sperm count and vacuolation of epithelial cells in the epididymides were observed at 32 mg/kg/day in the study on fertility and early embryonic development. In repeat-dose studies in rats, micafungin did not affect male reproductive organs although the treatment duration was longer than in the fertility study (up to 26 weeks versus 9 weeks). The NOAEL with respect to toxicity to the male genital tract was 10 mg/kg/day in rats, and 3.2 mg/kg/day in dogs. Taken together, the findings indicated that micafungin may have the potential to affect male fertility in humans

A study in juvenile dogs was performed to evaluate testis toxicity after 39-week micafungin treatment (including a recovery period of 13 weeks in mid-dose and high-dose animals) and to compare the testis toxicity in juvenile dogs with that in adult dogs. Segmental seminiferous tubular hypoplasia (minimal)

was observed in 3/4 animals of the 10 mg/kg group. This change was not observed in the animals of the 32 mg/kg group, and was noted in animals of both recovery groups. Based on historical control data for the years 2002 until 2006 it can be acknowledged that “Segmental hypoplasia of seminiferous tubule” may occur spontaneously in beagle dogs, but unfortunately only historical control values from one study are available for the 13-months age group (which is the age group of the recovery animals at the time of histopathology) showing no spontaneously occurring effects.

As testicular toxicity had been observed in two animal species and reversibility of these effects had not been proven sufficiently, a statement has included in the SPC (Section 4.6 Pregnancy and lactation; Section 5.3 Preclinical safety data) that micafungin may affect male fertility in humans.

- Genotoxicity

Micafungin was tested in standard ICH battery of *in vitro* and *in vivo* genotoxicity tests according to ICHS2B without evidence for genotoxicity.

Table 1: Overview of genotoxicity studies

Type of test Study No	Test system	Concentrations/ Metabolising system	Results
Gene mutations in bacteria	Salmonella strains TA 100, 98, 1535, 1537 <i>Escherichia coli</i> WP2 uvrA	+/- S9: 156, 313, 625, 1250, 2500, 5000 µg/plate	negative
Chromosomal aberrations <i>in vitro</i>	Chinese Hamster Lung Cells	Direct method: 24/48 h Treatment: 40, 80, 160 µg/ml (-S9) Metabolic activation method: 6 h (- S9) 1250, 2500, 5000 µg/ml 6 h (+ S9) 625, 1250, 2500 µg/ml	negative
Chromosomal aberrations <i>in vivo</i>	ICR strain mice (5 males per group). Micronuclei in bone marrow	1x i.v.: 25, 50 or 100 mg/kg sampling 24, 48 72 h after dos. Plasmalevel at 100 mg/kg: C _{5min} = 532 µg/ml AUC ₀₋₂₄ = 2763 µg hr/ml	negative
Unscheduled DNA Synthesis (UDS) <i>in vitro</i>	Female rat hepatocytes	Cytotoxicity: 0.5 µg/ml to 5790 µg/ml UDS: 0.06 µg/ml to 12.4 µg/ml	negative

- Carcinogenicity

No standard carcinogenicity studies were conducted in either rats or mice with micafungin.

- Reproduction Toxicity

The effects of micafungin on reproduction were assessed using a 3-study design. In studies in rats, decreased body weight gain and impaired liver function (increase in plasma ALT) were observed at 32 mg/kg, the highest dose tested (HD), in adult male and/or female animals. In HD males, effects on reproductive organs and sperms were detected. Although treatment-related effects on male reproductive organs (testes and epididymidis) and sperm cell count have not been observed in a 26-week toxicity study in rats, similar effects have been noted in the 39-week toxicity study in dogs. This issue has been addressed in the SPC sections 4.6 and 5.3.

In rats and rabbits no treatment-related effects on embryo/foetal development had been observed up to the highest dose tested. Reduced pup birth weights and a possibly related delay in the time of opening of the eyelids and cleavage of the balanopreputia were the only effects observed in the HD F1-generation in the course of the prenatal and postnatal developmental study in rats. As body weights

were comparable to control values on postnatal days 14 and 21 this is of minor concern. Micafungin crossed the placenta of pregnant rats and was excreted into the milk of lactating rats.

Juvenile animals

A 2-week and a 4-week repeated dose toxicity studies has been performed in newborn/juvenile rats toxic effects seen in the liver, kidney, urinary bladder, red blood cells (4-week study), and organ weights were restricted to high dose animals. Differences in the severity of these effects seem to be dependent on treatment duration. While in the 2-week study liver effects were more pronounced compared to the results of the 4-week study, treatment with micafungin for 28 consecutive days revealed more toxic effects in the kidneys (high dose males and females), urinary bladder (high dose males and females), and red blood cells (haemolysis, high dose males only). Toxicokinetic investigations had been done in the course of the 4-week study (at the end of treatment week 2 and 4). C_{max} as well as AUC_{0-24} values were comparable at the end of treatment week 2 and 4. Based on effects observed in the liver, kidneys, urinary bladder and red blood cells the NOAEL has to be set at 10 mg/kg/d. Corresponding C_{max} (~ 21 µg/ml) and AUC_{0-24} (~ 190 µg*h/ml) values were just in the range of those achieved in adult patients at a dose of 200 mg/d (C_{max} 22.6 µg/ml, AUC_{0-24} 210 µg*h/ml) and was similar to the one measured in one 10-years old child who had received 6 mg micafungin/kg/d for 56 days for treatment of deep mycosis. Regarding premature infants a small sample size of 23 infants had been treated with single doses of 0.75, 1.5, or 3.0 mg/kg, respectively. The maximum dose level of 3 mg/kg/d revealed exposure levels (C_{max} : 9.3 µg/ml, AUC_{0-24} : 59.5 µg*h/ml) well below those obtained in newborn/juvenile animals at a dose of 10 mg/kg/d, but it has to be kept in mind that only single dose kinetics had been investigated in this patient group. Toxic changes in the liver, kidneys, and urinary bladder remain a safety problem as only low safety margins can be established.

In general toxic effects were seen in animals at exposure levels which were approximately in the same range as compared to clinical exposure levels. Consequently, all toxic effects observed can be expected in human clinical use of micafungin.

- Local tolerance

Local tolerance studies were designed to assess the perivenous and intra-arterial tolerance of micafungin following a single injection in adult New Zealand White rabbits. At concentrations ranging from 0.5 to 4.0 mg/ml, micafungin did not produce any dose-related local tissue reactions. In the 4-week rat study following intravenous bolus injection, dose-dependent increase of vascular lesions at the injection site was observed at all doses. In a 4-week rat study using 1-hour infusion, the incidence of injection site reactions was comparable between controls and micafungin treated rats (10 and 32 mg/kg/day). The highest micafungin concentration administered via 1-hour intravenous infusion was 1.6 mg/ml (32 mg/kg/day). In the SPC, Section 6.6 (Instruction for use and handling), final micafungin concentrations in the infusion solutions are 2.0 mg/ml at the maximum clinical dose of 200 mg/day. Thus the micafungin concentrations administered in the 4-week rat study using 1-hour infusion do not reach the micafungin concentrations at the maximum clinical dose of 200 mg/day. Injection site reactions are reported in the Section 4.8 of the SPC (Undesirable effects).

- Other toxicity studies

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

In toxicological, clinical and commercial batches, five impurities (RS6, RS7+8, RS9 and RS10) were found at levels > 0.2%. Additional toxicity studies using repeated dosing for 4 and 13 weeks were performed to establish the safety of these impurities. A batch micafungin drug substance containing a high level of impurities was specifically manufactured for this purpose. From the results of the studies, the toxicity of micafungin drug substance with a high level of impurities was considered to be not higher than that of pure micafungin.

Ecotoxicity/environmental risk assessment

The applicant has used the guideline on the environmental risk assessment of medicinal products for human use (CHMP/SWP/4447/00 draft) from January 2005. The PEC was above the threshold specified in the final guideline (EMEA/CHMP/SWP/4447/00) of 2006. However the MAA was submitted before this guideline came into effect.

2.4 Clinical aspects

Introduction

Micafungin (FK463) is a water-soluble lipopeptide compound (echinocandin) synthesized by chemical modification of a fermentation product of *Coleophoma empetri* F-11899. Micafungin belongs to a new class of antifungal drugs, the echinocandins.

A total of 41 human pharmacology studies have been conducted as part of the development program for micafungin. 14 studies used human biomaterials and 31 clinical pharmacokinetic (PK) studies.

The main clinical programme to support the indication consisted of:

- One phase III, multicentre, randomised (1:1), active controlled, double blind, parallel group study in adult and paediatric patients with confirmed candidaemia or invasive candidiasis (IC);
- One phase III multicentre, randomised (1:1:1), double blind, parallel group non inferiority study to assess the efficacy and safety of micafungin compared to fluconazole in adult patients with oesophageal candidiasis (EC);
- One phase III multicentre, randomised (1:1), double blind, parallel group non inferiority study comparing micafungin to caspofungin in adult patients with EC;
- One phase III randomised (1:1) double blind study in adult and paediatric patients haematopoietic stem cell transplant recipients, comparing micafungin to fluconazole in the prophylaxis of invasive fungal infections (IFI).

Micafungin is to be administered as an intravenous infusion over approximately 1 hour at a daily dose of 100 mg (body weight > 40 kg) and 2 mg/kg (body weight ≤ 40 kg) for the treatment of invasive candidiasis in adults and paediatrics. Dose may be increased to 200 mg/day respective 4 mg/kg/day, if the patient's response is inadequate.

For the treatment of oesophageal candidiasis in adults the daily dose is 150 mg (body weight > 40 kg) and 3 mg/kg (body weight ≤ 40 kg).

The daily dose of micafungin for prophylaxis of *Candida* and *Aspergillus* infection in adults and paediatrics is 50 mg (body weight > 40 kg) and 1 mg/kg (body weight ≤ 40 kg).

GCP

The applicant stated GCP compliance and accordance with ethical standards of Directive 2001/20/EC.

Pharmacokinetics

In summary the PK of micafungin in adults is consistent across studies. Studies with both healthy subjects and patients showed a biexponential decline in micafungin concentrations, a mean half-life values of approximately 15 hours which remained constant with increases in dose, no evidence of systemic accumulation with repeated administration, increases in systemic exposure (AUC and C_{max}) proportional to increases in dose and steady-state reached by Day 7 after daily repeated administration.

- Methods

Analytical Methods

Micafungin and its metabolites M-1, M-2 and M-5 were measured by two separate HPLC systems that were used for the separation of 1) M-5 and 2) micafungin, M-1, and M-2. Separation on both systems was achieved on a TSK gel ODS -80 TM (15 cm x 4.6 mm ID, Tosoh) column using a mobile phase consisting of acetonitrile/20 mM potassium dihydrogenphosphate. Gradient elution was used for the separation of M-5. Fluorescence detection was used to detect micafungin and its metabolites.

The same chromatographic conditions were used for the measurements of micafungin and its metabolites M-1, M-2, and M-5 in human urine as those described above for human plasma.

Plasma protein binding was studied using the ultrafiltration method. In principle, micafungin in human plasma or plasma ultrafiltrate was assayed by HPLC with fluorescence detection. The chromatographic conditions were the same as those described above for human plasma.

The precision and accuracy of the methods were high, and show that the analytical method used in each study was valid for the determination of micafungin.

Pharmacokinetic data analysis

PK analysis was performed model-independently using WinNonlin and standard procedures. In some cases, a two-compartment model was used.

Statistical analysis

T-tests and ANOVA were used, depending on needs.

- Absorption/ Bioavailability

Micafungin is intended for intravenous use only.

The pharmacokinetics of micafungin administered once daily as a 1-h infusion, or even as a 30-min or a 2-h infusion in early clinical studies, is quite reproducible and is well described by a linear two-compartment model over a wide range of doses (certainly 25 to 150 mg/day, or 0.5 to 3 mg/kg body weight in children). Linear pharmacokinetics was demonstrated in healthy volunteers up to 150 mg/day, as well as in adult and paediatric patients, some of them received even much higher doses. There is no dose- or time-dependency, although very high doses (8 mg/kg in adults and 4 mg/kg in children) may result in some accumulation, as suggested by comparison of trough concentrations. However, comparison of dose normalized AUC from adults and paediatric patients (less than 5 years group and greater than 5 years group) revealed no accumulation.

In healthy volunteers, C_{max} range from 2 µg/ml after a 25-mg dose to 15 µg/ml after a 150-mg dose. Trough concentrations at steady state with a 75-mg/day regimen were around 2.4 µg/ml, i.e. ~2 µM.

Exposure steady state is reached after 4 days, however no earlier time points were tested. The plasma concentrations of micafungin at steady state (C_{max} , AUC, trough concentrations) are approximately 40–60% higher than after a single dose. This is explained by the long elimination time (~15 h; see below). Steady state is reached at a similar rate in cancer patients and neutropenic children.

Micafungin was infused at single doses of 25, 50, 75 or 150 mg or daily at 75 mg for 7 days, administered as a 30-60 minute infusion. After a single infusion of micafungin, $t_{1/2}$, CL_t , Vd_{ss} and Vd_{β} were independent of the dose administered, and AUC_{0-inf} increased in proportion to dose ($r = 0.989$, $n = 23$) from 34 to 216 µg*h/ml. After repeated daily infusions of 75 mg micafungin, steady-state was reached by Day 4 ($AUC_{0-inf} = 108$ µg*h/ml). Values for $t_{1/2}$, CL_t , Vd_{ss} , and Vd_{β} were similar after a single dose of micafungin compared with values after repeated doses. M-1 and M-2 levels were very low. Micafungin was extensively bound to plasma proteins: $99.83 \pm 0.01\%$ on Day 1 and $99.82 \pm 0.01\%$ on Day 7. Micafungin (unchanged drug) in urine was $0.74 \pm 0.10\%$ of the administered dose. Urinary recovery of M-1 was $0.15 \pm 0.02\%$ and M-2 measurements were below the LOQ in all subjects.

- Distribution

Following intravenous infusion, there is a rapid and extensive biotransformation process as micafungin distributes into the tissues. The apparent volume of distribution of 0.2 l/kg is larger than the volume of the interstitial fluid, but it does not increase when going from steady state to pseudodistribution equilibrium, which means that equilibrium between plasma and tissue is reached rapidly.

The percent of micafungin transferred into human red blood cells is approximately 35%. Based on *in vitro* studies with human biomaterials, micafungin is highly protein bound (> 99%), primarily to albumin and, to a lesser extent, to alpha-1-acid glycoprotein.

A high level of covalent binding to albumin and other proteins was demonstrated (24% at 24 h, based on radiolabeled FK463). Covalent adducts with cysteine and lysine, but not with glutathione, have been found. This raises the possibility that micafungin may induce allergic or immunological reactions (cf. the haemolysis and hepatotoxicity problems). An *in vitro* test for haemolysis at high concentrations of micafungin (500 µg/ml) was negative, but the predictive value of this test for immune-mediated haemolysis is probably very low.

Micafungin does not displace albumin-bound bilirubin at clinically relevant concentrations (and therefore would not be expected to cause kernicterus) and is not an inhibitor of P-glycoprotein (and therefore would not be expected to alter P glycoprotein mediated drug transport activity). Micafungin may form covalent adducts with HSA via cysteine and lysine residues.

- Metabolism

Micafungin undergoes oxidative hepatic metabolism depending on several CYP isoforms. At least 12 metabolites were detected in animals by HPLC. Qualitatively the five metabolites detected in humans (M-5, M-1, M-2 in plasma and M-3, M-11 in faeces and urine) were also found in rats and dogs. *In vitro*, 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). Given the minimal concentrations of M-1 and M-2 in plasma in both volunteers and HSCT patients and the biological inertness of M-5, it is unlikely that metabolites in plasma contribute to the activity of micafungin. The enzymes involved in the synthesis of M-1 and M-2 have not been defined. The contribution of M-1 and M-2 metabolites to the tissue actions of micafungin is unknown.

In vitro, the metabolism of micafungin involves multiple CYP isoenzymes including CYP1A2, 2B6, 2C and 3A4. Concentration-dependent inhibition of CYP3A4 was observed *in vitro*, with no effect at 5 µM and 80% inhibition at 50 µM, which is equivalent to a C_{max} of 60 µg/ml (observed with a dose of 8 mg/kg in patients). However, no clinically relevant interaction was observed in this regard.

The role of the liver in micafungin overall metabolism appears minor, and cannot be qualified as “extensive” despite several involved isoenzymes. Therefore, a single dose study, although performed in 8 patients with a 7-9 Child-Pugh score, is considered acceptable at the present time.

- Elimination

After intravenous infusion, micafungin concentrations decline in a biexponential manner with a terminal half-life of 14 to 15 h (mean: 14.7 h) that is dose-independent up to 150 mg. Total clearance, which is about 0.2 ml/min/kg, is also independent of dose, supporting the lack of accumulation that has been observed in repeated dose studies in healthy volunteers.

Renal clearance is <10% of total clearance. The main elimination pathway is faecal (90%), but the excretion of all micafungin compounds is very slow ($t_{1/2}$ ~300 h in the radioactive study). By Day 28, approximately 82.5% of the radioactive dose was recovered with a further 4.9% extrapolated as being excreted between Days 29 to 55. During prolonged treatment, it has been observed some accumulation of M-1 (4 % at Day 7) and M-2 (0.8 %) metabolites, which however do not reach clinically significant levels.

- Inter-individual variability

The effect of age, gender and race on pharmacokinetics of micafungin is minimal. No adjustment of dose is needed in elderly patients. It has been observed a slightly higher exposure of micafungin in Mulatto as compared to Caucasian and Black at day 1 and the EOT. Comparative data on Asians are missing.

- Special populations

The pharmacokinetics of micafungin has been examined in a small (n=9) group of patients with severe renal insufficiency, and no significant difference was seen with a group of normal volunteers. For hepatic insufficiency, a single-dose study has shown that moderate hepatic impairment (Child-Pugh score 7-9) slightly decreases exposure to micafungin, partly due to a faster clearance. This does not require dose adjustment.

Children

PK parameters were obtained:

- in premature infants, where clearance was approximately 2- to 6-fold greater than in adults with doses of 0.75 mg/kg, 1.5 mg/kg and 3.0 mg/kg as a single 30-minute infusion;
- in paediatric patients 29 days to 15 years old with deep mycoses, where systemic exposure as assessed by C_{max} and C_{min} but not by full PK profiles or AUCs increased with increases in dose (daily infusions of 1, 2, 3 or 6 mg/kg micafungin), indicating clear accumulation;
- in febrile neutropenic patients 2 to 17 years old, as a once daily 1-hour infusion of 0.5 to 4.0 mg/kg. CL , V_{ss} , and $t_{1/2}$ remained constant with increasing doses and did not change appreciably with repeated administration. Plasma metabolite levels remained low.

The applicant committed to provide the results of US paediatric studies once finalized.

- Pharmacokinetic interaction studies

In vitro studies did not suggest any potential interaction with micafungin.

Fourteen (14) studies in healthy volunteers were conducted to evaluate the potential for interaction between micafungin and drugs commonly used in the target patient populations, including CYP3A substrates, inhibitors and inducers. Mycophenolate mofetil (MMF), ciclosporin, tacrolimus, prednisolone, sirolimus, nifedipine, fluconazole, voriconazole, itraconazole, amphotericin B, ritonavir (a potent inhibitor of CYP3A4) and rifampicin (a potent inducer of CYP3A4) were evaluated. In these studies, no interaction altering micafungin PK was observed. There was also no effect of single-dose or steady-state micafungin on MMF, ciclosporin, tacrolimus, prednisolone, fluconazole voriconazole, ritonavir or rifampicin PK. Increases in exposure (AUC) with sirolimus (total exposure AUC_{0-72} by 21%), nifedipine (total exposure AUC_{0-inf} and C_{max} by 42%), amphotericin B (by 30%) and itraconazole (by 22%) in the presence of steady-state micafungin were observed. It is thus, that patients receiving sirolimus, amphotericin B or itraconazole should be monitored. As increases in exposure (AUC) with sirolimus (by 15%), nifedipine (by 18%) amphotericin B (by 30%) and itraconazole (by 22%) in the presence of steady-state micafungin were small, a requirement for dose adjustments is not anticipated.

Pharmacodynamics

- Mechanism of action

Please see the non-clinical part of this report.

- Primary and Secondary pharmacology

Please see the non-clinical part of this report.

Clinical efficacy

Introduction

The clinical evidence of efficacy in the invasive candidiasis indication has been demonstrated by a large double-blind comparative study of micafungin versus Ambisome[®] (Study FG-463-21-08).

For the oesophageal candidiasis indication, a double-blind comparative trial of micafungin versus fluconazole (Study 03-7-005), and a double-blind comparative trial of two dose regimens of micafungin versus caspofungin (Study 03-7-008) were conducted.

Concerning the prophylaxis indication the submitted pivotal study has been reviewed taking into account some concerns such as the choice of the comparator fluconazole, the choice of the pre-engraftment period as the treatment period, the choice of the primary and secondary endpoints, and the targeted population for this indication.

Analysis sets were common to all studies, as follows:

- Full analysis set (FAS [safety population and secondary efficacy population]): Patients who were randomised and received at least a single dose of study drug.
- Modified full analysis set (mFAS [secondary efficacy population]): Patients who had a confirmed diagnosis of IC or candidaemia or EC and received at least a single dose of study drug.
- Per protocol set (PPS [primary efficacy population]): Patients who had a confirmed diagnosis of candidaemia or IC or EC at baseline, for whom the investigator's assessment of overall treatment success at EOT was available, who received at least 5 doses of study drug, and who did not have any further major protocol violations.

Table 2: Dose-response and main studies:

Protocol	Objective	Design/ Control	Product/ Dose/Route	No. of Subjects	Subjects/ Diagnosis	Treatment Duration (micafungin)
FG-463-21-09	Dose response, safety / PK	Double-blind, randomised (1:1:1:1), comparative micafungin versus fluconazole	1-hr infusion daily of micafungin (50 mg or 100 mg or 150 mg) or 1-hr infusion daily of fluconazole (200 mg).	Micafungin 185 Fluconazole 60	Adult HIV-positive patients with oesophageal candidiasis	14 days minimum, extension to 21 days possible if endoscopic clearance not achieved by 14 days.
FG-463-21-08	Efficacy Safety PK Main study	Phase III Double-blind, comparative, randomised (1:1) Micafungin versus AmBisome	1-hr IV infusion daily Micafungin: 100 mg/day (2 mg/kg/day ≤40kg) with a possible increase up to 200 mg/day (4 mg/kg/day ≥40 kg) AmBisome: 3 mg/kg/day, with a possible increase up to 5 mg/kg/day	Micafungin 264 adults 52 paediatrics AmBisome 267 adults 54 paediatrics	Neutropenic or nonneutropenic adult and paediatric patients with confirmed candidaemia or invasive candidiasis	Minimum of 2 weeks; maximum of 4 weeks. Possible extension to 8 weeks for pre-defined patients
03-7-005	Efficacy, safety Main study	Phase III Double-blind, randomised (1:1), comparative,	1-hr IV infusion 1x daily micafungin (150 mg) or 1-hr IV infusion 1x daily	Micafungin 260 Fluconazole 258	Patients ≥ 16 years with confirmed oesophageal candidiasis	14 days minimum or 7 days after resolution of clinical signs and symptoms,

		parallel-group Miconazole versus fluconazole	fluconazole (200 mg)			maximum 42 days
03-7-008	Efficacy, safety, PK Main study	Phase III Double-blind, comparative, randomised (1:1:1), parallel-group Miconazole versus caspofungin	1 hr IV infusion 1x daily miconazole (150 mg), 1-hr IV infusion 1x daily caspofungin (50 mg) or 1 hr IV infusion miconazole (300 mg) every second day	Miconazole 150 mg 151 300 mg 149 Caspofungin 152	Patients ≥ 16 years with confirmed oesophageal candidiasis	14 days minimum or 7 days after resolution of clinical signs and symptoms
98-0-050	Efficacy, safety of miconazole versus fluconazole Main study	Phase III Double-blind randomised (1:1) Miconazole versus fluconazole	1-hr infusion 1x daily miconazole: 50 mg/day (1 mg/kg/day <50 kg); fluconazole: 400 mg/day (8 mg/kg/day <50 kg)	miconazole 425 fluconazole 457	Adult and paediatric patients undergoing hematopoietic stem cell transplant	Treatment started at time transplant conditioning regimen was initiated or within 48 hours postinitiation; treated until neutrophil recovery or up to 5 days post recovery (up to maximum of 42 days post transplant)

- Dose response studies

The **study FG-463-21-09** was aimed to investigate the dose-response of miconazole relating to 3 different dose levels (50 mg/day, 100 mg/day and 150 mg/day) compared with 200 mg/day fluconazole in HIV positive patients with confirmed EC. As a result, the PK observed in this population of adult HIV patients with EC is similar to those observed in earlier studies with healthy adult volunteers. Miconazole exhibited linear PK over the dose range investigated (50, 100 and 150 mg/day). Steady-state was reached between Days 3 and 7. There was no accumulation of miconazole following repeated daily dosing for 14 or 21 days.

Patients who did not respond to therapy had a lower systemic exposure compared with those who responded. The non-responders had a systemic exposure similar to the 50 mg group and the responders a similar systemic exposure to the 100 and 150 mg groups, suggesting that a daily dose of between 100 and 150 mg is necessary to achieve the optimal exposure associated with a therapeutic response against EC in this patient population.

Thus, a daily dose of between 100 and 150 mg would appear necessary to achieve the optimal exposure associated with a therapeutic response in EC.

The **study 03-7-008** was aimed to determine the efficacy and safety of daily doses of intravenous miconazole versus intravenous caspofungin for the treatment of patients with EC. The patients received miconazole (at a dose of either 150 mg/day or 300 mg every other day alternating with placebo [qod]) or caspofungin (50 mg/day). Study drug was infused over a period of 1 hour. The treatment period was a minimum of 14 days or 7 days after the resolution of clinical symptoms of EC, whichever was longer. The maximum duration of study drug therapy was 28 days. A subgroup of patients, 20 per treatment group, was to be selected for participation in the PK aspect of this study. Samples for PK profiles were obtained from these patients over a 48-hour period starting on Days 1 and 11. As a result, Miconazole exhibited linear PK over the dose range investigated (150 and 300 mg/day). Steady-state miconazole PK profiles were similar for both dosing regimens, particularly with regards to systemic exposure (AUC), average concentration over the dosing interval (C_{avg}), half-life ($t_{1/2}$), and clearance (CL_{ss}).

These studies showed that miconazole should be applied for treatment of oesophageal candidiasis in a dose of 150 mg/day or 300 mg every other day.

In patients who received a daily dose of 50 mg miconazole treatment was not as effective as in patients receiving a daily dose of 150 mg.

- Main studies

1. *Invasive candidiasis (IC) and candidaemia*

Study FG-463-21-08

This is a phase III, randomized, active-controlled, parallel grouped non inferiority study, comparing micafungin and Ambisome[®] (liposomal amphotericin B) the treatment of patients with candidaemia and other IC.

Study participants

Five hundred and thirty-one (531) patients were enrolled and randomized to micafungin (n=264, 100 mg up to 200 mg/day) and to Ambisome (n=267, 3 mg up to 5 mg/kg/day). The patients had to have candidaemia or IC caused by *Candida Albicans* or a non-*albicans Candida* species. The diagnosis was confirmed by fungal culture or histology, no more than 4 days prior the first planned dose of study drug.

Main exclusion criteria were:

- patients who were nursing or pregnant,;
- patients with a known hypersensitivity to echinocandins, Ambisome[®] or any product containing amphotericin B;
- patients with evidence of liver disease, defined by a) serum glutamic oxaloacetic transaminase (SGOT)/aspartate transaminase (AST) or serum glutamic pyruvic transaminase (SGPT)/alanine transaminase (ALT >10 times the upper limit of normal (ULN) or b) total bilirubin >5 times ULN;
- patients with a yeast or mold-like systemic fungal infection other than candidaemia or IC;
- patients who received more than 3 days of systemic antifungal therapy within 1 week before planned study.

Treatments

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 administered at a daily dose of 3 mg/kg (dose increase to 5 mg/kg permitted).

A dose decrease of 50% for Ambisome was indicated in the protocol for drug-related nephrotoxicity. Study drug was administered as 1-hour infusion in a blinded manner.

The minimum duration of therapy was 14 days. The maximum treatment period was 4 weeks, except for patients with chronic disseminated (hepatosplenic) candidiasis, *Candida* osteomyelitis or *Candida* endocarditis, for whom administration of study drug could be prolonged up to a maximum of 8 weeks.

Dosing could be interrupted for a maximum of 2 days without withdrawal of the patient from the treatment phase of the study. Investigators were instructed to interrupt therapy for significant abnormal liver function test (LFT) values (increase of ≥ 10-fold the upper limit of normal [ULN] when the baseline value was > 5-fold the ULN or an increase of ≥ 2-fold when the baseline value was 5- to 10-fold higher than the ULN); and for any severe or life-threatening AE suspected of being at least possibly related to the study drug.

Objectives

The study was powered to demonstrate non-inferiority of micafungin to Ambisome in adult patients with a non-inferiority limit of 15%. Ambisome was chosen as an appropriate reference therapy since it combines the broad spectrum of conventional amphotericin B with an improved safety profile and the possibility of allowing appropriate blinding of the study. This choice was agreed upon by the CHMP earlier during the scientific advice of May 2002. It was allowed to have a dose increase in both treatment arms for persistence of fungal infection and this occurred in 9.8% and 6.7% of the patients in the micafungin and Ambisome group, respectively.

Outcomes/endpoints

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 the end of treatment (EOT).

Secondary efficacy endpoints included clinical response, mycological response, emergent fungal infections, recurrence of fungal infections and the independent data review board (IDRB) assessment of overall success. Predefined key safety endpoints were estimated glomerular filtration rate (GFR) and infusion-related reactions.

- Sample size

The protocol indicated an enrolment number of 500 patients 16 years of age or older. Patients were recruited from around 200 centres worldwide, with each centre recruiting a maximum of 28 patients.

- Randomisation

Randomization was 1:1 stratified by centre and neutropenic status. Centres with only adult patients were assigned 1 unique block of sequentially ordered patient numbers, for neutropenic patients and non-neutropenic patients. Centres with paediatric and adult patients were assigned 2 unique blocks of sequentially ordered patient numbers to allow stratification by neutropenic status and age group.

- Blinding (masking)

The study was double-blinded.

- Statistical methods

The primary endpoint was analysed using a 1-sided 97.5% confidence interval (CI) (based on normal approximation) for the difference in the proportions adjusted for neutropenia (yes/no) based on the PPS. The lower CI limit exceeding -0.15 indicates micafungin non-inferiority to Ambisome. The lower limit of the CI lying above -0.15 and above zero, indicates evidence of superiority for micafungin. To this respect, a statistical test for superiority (the P value calculated based on normal approximation) was planned to confirm results. For a superiority interpretation, the robustness of the result in the FAS is considered to be essential. To assess the robustness of the result of the non-inferiority test, the non-inferiority test was also conducted on the FAS and the mFAS.

Additionally, the difference in the proportions adjusted for neutropenia (yes/no) and Apache II score (≤ 20 and > 20) and the corresponding 1-sided 97.5% CI and P value were calculated.

Patient survival was analysed using Kaplan-Meier survival estimates for the treatment phase and for the whole study phase. The log-rank test was used to assess the difference between treatment groups with respect to patient survival.

RESULTS

Participant flow

The planned number of adult patients for the PPS was 320, 160 per treatment group (500 planned for enrolment). Study Population Analysis Sets, Adult Population were as follows:

	Micafungin	Ambisome
Full analysis set	264	267
Modified full analysis set	247	247
Per protocol set	202	190

Patient Disposition:

Overall 264 and 267 patients were included in the FAS for the micafungin and Ambisome groups, respectively. The PPS (the primary efficacy population) included 202 and 190 patients, respectively. A summary of discontinuations during the treatment phase (FAS) is presented in table 3.

Table 3: Treatment Discontinuation, Adult Patients . No. Patients (%)

	Micafungin N=264	Ambisome N=267
Completed treatment	162 (61.4)	159 (59.6)
Discontinued treatment	102 (38.6)	108 (40.4)
Discontinued treatment (but entered study follow-up)	31 (11.7)	48 (18.0)
Non-compliance	1 (0.4)	0
Prohibited medication	0	4 (1.5)
Adverse event	14 (5.3)	25 (9.4)
Lack of efficacy	5 (1.9)	6 (2.2)
Other reason	11 (4.2)	13 (4.9)
Discontinued treatment (and did not enter follow-up)	71 (26.9)	60 (22.5)
Non-confirmed invasive candidiasis or candidaemia	12 (4.5)	7 (2.6)
Withdrawal of consent	10 (3.8)	7 (2.6)
Lost to follow-up	1 (0.4)	0
Death	47 (17.8)	46 (17.2)
Other reason	1 (0.4)	0

Patient base (full analysis set): patients who received at least 1 dose of study drug.

Source: Table 13.1.3.1.

Overa

ll, 5/264 (1.9%) and 6/267 (2.2%) in the micafungin and Ambisome groups, respectively, discontinued treatment due to lack of efficacy, 0/264 and 4/267 (1.5%) due to prohibited medication.

Baseline data

In the adult population, the treatment groups were well balanced with regard to demographic and baseline characteristics.

Neutropenia (absolute neutrophil count [ANC] < 500 cells/μL) was present at baseline for 12.9% and 10.5% of patients in micafungin and Ambisome groups, respectively.

Underlying conditions were heterogeneous; the most frequently reported categories (≥ 10%) being haematological disorder (18.6% and 13.5%, respectively), solid organ tumour (13.6% and 20.2%) and diabetes mellitus (11.7% and 11.6%). The mean ± SD Apache II score (for patients 18 years and older) was 15.8 ± 8.4 for patients in the micafungin group (N = 240) and 15.6 ± 8.1 for patients in the Ambisome group (N = 233).

Treatment groups were well balanced with regard to type and the primary site of *Candida* infection.

In both treatment groups, fluconazole was the most frequently used systemic prior antifungal agent (FAS: 35.2% in the micafungin group, 41.6% in the ambisome group), followed by amphotericin B, voriconazole, itraconazole, caspofungin and ketoconazole.

Concomitant non-systemic antifungal medications were received by 46/264 (17.4%) adult patients in the micafungin group and 45/267 (16.9%) in the Ambisome group (FAS)

Administration of a systemic antifungal therapy other than the study drug was grounds for discontinuation from the treatment phase.

Treatment groups were well balanced with regard to administration of medications other than Anti-fungal Therapy. During the pre-treatment phase (the 4 weeks preceding the study), systemic antibiotics were received by 97.0% and 97.4% of patients in the micafungin and Ambisome groups, respectively; systemic corticosteroids by 37.1% and 36.7% of patients, respectively; and antineoplastic and immunomodulating agents by 17.8% and 16.1% of patients, respectively (FAS). Administration of these special interest medications remained high during the treatment phase of the study.

Table 4: Overall Treatment Success in the Per Protocol Set, FG-463-21-08

	Micafungin		Liposomal Amphotericin B		% Difference [95% CI]
	N	n (%)	N	n (%)	
Adult Patients					
Overall Treatment Success	202	181 (89.6)	190	170 (89.5)	0.1 [-5.9, 6.1] †
Overall Treatment Success by Neutropenic Status					
Neutropenia at baseline	24	18 (75.0)	15	12 (80.0)	0.7 [-5.3, 6.7] ‡
No neutropenia at baseline	178	163 (91.6)	175	158 (90.3)	
Paediatric Patients					
Overall Treatment Success	48	35 (72.9)	50	38 (76.0)	-2.7% [-17.3, 11.9] §
< 2 years old	26	21 (80.8)	31	24 (77.4)	
Premature Infants	10	7 (70.0)	9	6 (66.7)	
Neonates (0 days to < 4 weeks)	7	7 (100)	5	4 (80%)	
2 to 15 years old	22	14 (63.6)	19	14 (73.7)	
Adults and Children Combined, Overall Treatment Success by <i>Candida</i> Species					
<i>Candida albicans</i>	102	91 (89.2)	98	89 (90.8)	
Non- <i>albicans</i> species ¶: all	151	133 (88.1)	140	123 (87.9)	
<i>C. tropicalis</i>	59	54 (91.5)	51	49 (96.1)	
<i>C. parapsilosis</i>	48	41 (85.4)	44	35 (79.5)	
<i>C. glabrata</i>	23	19 (82.6)	17	14 (82.4)	
<i>C. krusei</i>	9	8 (88.9)	7	6 (85.7)	

For the paediatric patients, the descriptive results are presented on the full analysis set.

† Micafungin rate minus the liposomal amphotericin B rate, and 2-sided 95% confidence interval for the difference in overall success rate based on large sample normal approximation.

‡ Adjusted for neutropenic status; primary endpoint.

§ The paediatric population was not sized to test for non-inferiority.

¶ Clinical efficacy was also observed (< 5 patients) in the following *Candida* species: *C. guilliermondii*, *C. famata*, *C. lusitanae*, *C. utilis*, *C. inconspicua* and *C. dubliniensis*.

Treatment success (PPS) for micafungin was 89.6% (181/202), Ambisome 89.5% (170/190). Mortality was similar in the micafungin group (3/21, 14.3%) compared with the Ambisome group (7/24, 29.2%). Consistent results of non-inferiority were seen for the full analysis set (overall response rates of 71.6% versus 68.2%) and the modified full analysis set (overall treatment success of 74.1% and 69.6%) where the overall success rates were lower than in the per protocol set as could be expected. Treatment success was also stratified by neutropenic status and was lower in patients who were neutropenic than in those who were not (75% and 80% for neutropenic versus 91.6% and 90.3% for non-neutropenic patients in the micafungin and Ambisome group, respectively, PPS). Nevertheless, the lower bound of the 97.5%CI adjusted for neutropenic status at the baseline [-5.3%, 100%] was above the pre-defined non-inferiority margin of -15%. Although the absolute number of neutropenic patients remains limited (34 patients in the micafungin and 28 patients in the Ambisome group, FAS) it would be very difficult to include more patients since the risk to develop an IC in neutropenic patients has decreased significantly during the last decade as a result of antifungal prophylaxis.

Stratification by Apache II score revealed similar success rates, although patients with an Apache II score of >20 treated with micafungin showed lower success rates than those treated with Ambisome (79.5% versus 89% in the PPS). Success rates were somewhat higher for candidaemia than IC, but there were no treatment differences. In patients with candidaemia, baseline catheter status had no apparent influence on the overall success rate. In addition, overall treatment success was similar whether candidaemia patients had their catheter removed or replaced or not. Both micafungin and Ambisome were effective in treating systemic infections caused by *C. albicans* (88.4% and 89.3%, respectively) and non-*C. albicans* species (89.7% and 89.3%).

An independent data review board also did assessment of overall success. Findings from this IDRb analysis were considered descriptive but were consistent with a non-inferiority interpretation. Their assessment can be considered as more stringent since treatment success was consistently lower when

assessed by the IDRB as compared to the investigators. For instance, in the IDRB PPS, treatment success was experienced by 81.4% and 80.4% of patients in the micafungin and Ambisome groups, respectively, which is approximately a 10% lower response rate than in the primary analysis as assessed by the investigators. There was also a discrepancy between the number of proven emergent and proven recurrent fungal infections in the micafungin group when assessed by the IDRB or the investigators. The microbiological documentation of the *Candida* isolates was properly done with strict criteria used for confirmation of IC. The response rates by *Candida* species were similar for both micafungin and Ambisome with no apparent differences between both treatments, taking into account that for the more rare species the data were too limited to draw any robust conclusion. There was no evidence of resistance development against micafungin. Unfortunately, the data did not allow for establishment of breakpoint MIC determinations for the treatment of IC.

Ancillary analysis

- Paediatric population

Results for children were presented separately in a paediatric substudy, and were considered solely supportive and descriptive. 52 patients in the Micafungin and 54 patients in the Ambisome group have been included in the FAS (41 and 42, respectively in the PP set).

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).

Although demographics and baseline characteristics were similar between treatment groups, a significantly higher percentage of paediatric patients was neutropenic in the Ambisome group (13/54; 24.1%) as compared to the micafungin group (only 7/52; 13.5%). Almost all children included in this substudy 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, which might be related to the higher clearance seen in young children in comparison to adult patients (please see the pharmacokinetic section).

The rates of treatment success were high in both groups: an overall success rate of 69.2% in the micafungin arm was shown as compared to 74.1% in the Ambisome arm (FAS) (85.4% versus 88% treatment success, respectively in the PPS).

2. Oesophageal candidiasis (EC)

Study 03-7-005:

This is a phase III, randomized, active controlled, multicentre, multinational, double-blind, parallel group, non-inferiority study comparing micafungin versus fluconazole for the treatment of oesophageal candidiasis (OE).

Study participants

Five hundred and eighteen patients (518) were enrolled and randomized (1:1) to micafungin (n=260, 150 mg/day) and fluconazole (n=258, 200 mg/day). Patients received at least a single dose of study drug (full analysis set [FAS] = safety set = primary analysis set for efficacy analysis).

Patients \geq 16 years old with a confirmed diagnosis of EC were eligible for enrolment. For a confirmed diagnosis of EC, the patient had to have a mucosal grade > 0 ; a positive histology or both a positive cytology and a positive *Candida* fungal culture; and 1 or more clinical symptoms of EC (dysphagia, odynophagia or retrosternal pain). Treatment was completed by 232/260 (89.2%) patients in micafungin group and by 234/258 (90.7%) patients in the fluconazole group.

Main exclusion criteria were:

- Pregnancy or lactation. Females of childbearing potential were to avoid becoming pregnant while receiving study drug
- History of anaphylaxis attributed to azole compounds or the echinocandin class of antifungals.
- Evidence of liver disease, as defined by a) aspartate aminotransferase (AST), alanine aminotransferase (ALT) or alkaline phosphatase >10 times the upper limit of normal (ULN) or b) total bilirubin >5 times ULN.

- Presence of another active opportunistic fungal infection and/or receiving acute systemic therapy for an opportunistic fungal infection.
- Concomitant oesophagitis caused by herpes simplex virus or cytomegalovirus.
- Receipt of an oral, non-absorbable (topical) antifungal agent within 48 hours or a systemic antifungal agent within 72 hours prior to the first dose of study drug.

Treatments

The study consisted of two treatment arms: micafungin 150 mg or fluconazole 200 mg administered intravenously once daily for a minimum of 14 days or for 7 days after resolution of all clinical symptoms of the oesophageal candidiasis. The maximum allowed length of study drug administration was 42 days.

Dose adjustments based on the intensity of the adverse event were allowed at the discretion of the investigator if the patient experienced a toxicity considered to be related to the study drug. The National Cancer Institute Common Toxicity Criteria (NCI-CTC) were provided for use as a guideline.

Objectives

The objective of the study was to determine the efficacy and safety of intravenous micafungin versus intravenous fluconazole in the treatment of patients with oesophageal candidiasis.

Outcomes/endpoints

Primary Endpoint

The primary endpoint was treatment success (i.e., endoscopic cure rate), which was defined as a mucosal grade of 0 (zero) at the end of therapy.

Secondary Endpoints

The secondary endpoints were as follows:

- Clinical response at the end of therapy, with success defined as cleared or improved
- Mucosal response at the end of therapy, with success defined as cleared or improved
- Overall therapeutic response at the end of therapy
- Incidence of relapse at 2 weeks and 4 weeks posttreatment
- Changes in the endoscopic assessment of oesophageal candidiasis (mucosal grade) at the end of therapy compared to baseline
- Changes in clinical symptoms of oesophageal candidiasis at the end of therapy compared to baseline
- Changes in clinical signs and symptoms of oropharyngeal candidiasis at the end of therapy compared to baseline

• Sample size

230 enrolled patients were planned in order to ensure that at least 201 treated patients would have confirmed oesophageal candidiasis at baseline. This was based on the results of Study FG-463-21-09, in which approximately 11% of the patients did not receive study drug or had non-confirmatory endoscopic results at baseline.

• Randomisation

Patients were randomly assigned to receive micafungin or fluconazole using a 1:1 randomization schedule generated by the Research Data Operations Department at FHI.

• Blinding (masking)

The study was double blinded.

- Statistical methods

Unless otherwise indicated, all statistical analyses were to be performed using two-sided tests with a significance level of $\alpha=0.05$. For the purpose of stratified or subset analyses, centers enrolling 10 or fewer patients were pooled together by country.

Primary Endpoint: A two-sided 95% confidence interval (95% CI) was constructed for the difference in the success rates of micafungin and fluconazole (micafungin minus fluconazole) using the normal approximation method. If the lower bound of the 95% CI exceeded -0.10, then micafungin would be considered non-inferior to fluconazole. If the lower bound of the 95% CI exceeded 0, then micafungin would be considered superior to fluconazole.

Secondary Endpoint: The primary analysis used for endoscopic cure rate was repeated for clinical response (cleared or improved), mucosal response (cleared or improved), and overall therapeutic response. The 95% CI was used to evaluate non-inferiority.

RESULTS

Participant flow

A total of 776 patients were screened in order to obtain the 523 patients who were randomized into the study. The primary reasons for failure to enroll 253 screened patients were lack of confirmation of oesophageal candidiasis based on endoscopy and clinical symptoms and concomitant medical conditions that might have resulted in an unacceptable additional risk if subjects had been enrolled. Criteria for diagnosis of EC were correctly defined, based on endoscopy, histology or culture and clinical symptoms.

The patients disposition was the following:

	Micafungin	Fluconazole
All randomized patients	265 (100%)	258 (100%)
Full analysis set	260	258
Modified full analysis set	220	215
Per protocol set	189	192

The treatment consisted in a minimum of 14 days or for 7 days after resolution of all clinical symptoms of EC (maximum 42 days). The post-treatment follow-up period was 4 weeks.

The reasons for treatment discontinuation are summarized in Table 5.

Table 5: Reasons for Treatment Discontinuation

Reason	Treatment Group	
	Micafungin (n=260)	Fluconazole (n=258)
Completed Therapy	232 (89.2%)	234 (90.7%)
Adverse Event	17 (6.5%)	12 (4.7%)
Treatment-related Adverse Event	6 (2.3%)	1 (0.4%)
Adverse Event Resulting in Death	10 (3.8%)	9 (3.5%)
Withdrew Consent	2 (0.8%)	0 (0.0%)
Non-Compliance with Protocol		
Baseline Infection Not Confirmed	1 (0.4%)	0 (0.0%)
Did Not Return for Medication	3 (1.2%)	1 (0.4%)
Other	1 (0.4%)	3 (1.2%)
Lack of Efficacy	2 (0.8%)	6 (2.3%)
Other	2 (0.8%)	2 (0.8%)

Patient base: all randomized patients who received at least one dose of study drug (Full Analysis Set).

n=total number of patients in each treatment group.

Other: includes herpes virus infection (1 micafungin patient), non-compliance (1 micafungin patient), concomitant esophagitis caused by herpes virus (1 fluconazole patient), and patient too ill to participate (1 fluconazole patient).

Baseline data

The treatment groups were well balanced with regard to demographic and baseline characteristics, and distribution of the different *Candida* species was comparable in both groups.

The main underlying condition was HIV 486/518 (93.8%) in both treatment arms. Among them, approximately 60% had CD4 cell counts of <100/ml, and of which only 8.5% in the micafungin group and 11.6% in the fluconazole group received antiretroviral therapy. The remaining 32 patients had other underlying conditions of immunosuppression of which malignancy was the most frequent one in both groups. A majority of patients in both treatment groups (>86%) did not have a prior history of oesophageal candidiasis. As could be expected, most patients (>88%) presenting with EC also had oropharyngeal candidiasis.

Approximately 10% of patients in each treatment group had negative culture results. Among patients with positive culture results, *C. albicans* was the predominant fungal organism at baseline (98.3 %). Concomitant use of non-systemic antifungal medications was noted for 1/260 (0.4%) micafungin patient and 3/258 (1.2%) fluconazole patients.

Few patients in either treatment group had a history of receiving antifungal therapy, fluconazole being the most frequently reported prior therapy. Systemic antifungal medications were administered to only 4.2% of micafungin patients and 2.7% of fluconazole patients. Similarly, non-systemic antifungal medications were administered to 3.8% of micafungin patients and 6.2% of fluconazole patients.

The classes of non-antifungal medications that were commonly administered concomitant with study drug included drugs for functional gastrointestinal disorders, vitamins, systemic antibacterials, antimycobacterials, antipruritics, anti-inflammatory and antirheumatic drugs, analgesics, psycholeptics, and antihistamines.

At all times, antiviral medications were not commonly administered to patients in either treatment group.

Outcomes and estimation

The study was completed by 232/260 (89.2%) patients in micafungin group and by 234/258 (90.7%) patients in the fluconazole group.

Table 6: Outcomes of study 03-07-005

Treatment Outcome	Treatment		Treatment Difference	95% CI for the Difference
	Micafungin	Fluconazole		
Full Analysis Set	n=260	n=258		
Success	228 (87.7%)	227 (88.0%)	-0.3%	[-5.9%, 5.3%]
Failure	32 (12.3%)	31 (12.0%)		
Mucosal Grade >0	7 (2.7%)	10 (3.9%)		
Not Evaluable	25 (9.6%)	21 (8.1%)		
Modified Full Analysis Set	n=220	n=215		
Success	191 (86.8%)	188 (87.4%)	-0.6%	[-6.9%, 5.7%]
Failure	29 (13.2%)	27 (12.6%)		
Mucosal Grade >0	6 (2.7%)	10 (4.7%)		
Not Evaluable	23 (10.5%)	17 (7.9%)		
Per Protocol Set	n=189	n=192		
Success	183 (96.8%)	182 (94.8%)	2.0%	[-2.0%, 6.0%]
Failure	6 (3.2%)	10 (5.2%)		
Mucosal Grade >0	6 (3.2%)	10 (5.2%)		

Patient base:

Full Analysis Set: all randomized patients who received at least one dose of study drug.

Modified Full Analysis Set: all randomized patients who received at least one dose of study drug and had a positive histology or cytology at baseline.

Per Protocol Set: all randomized patients who received at least 10 doses of study drug, who had confirmed esophageal candidiasis at baseline, who had a baseline and end of therapy endoscopy performed, and who did not have major protocol deviations.

Endoscopic cure: mucosal grade=0 at end of therapy.

n=total number of patients in each treatment group in each analysis set.

95% Confidence Interval: the 95% CI for the difference in success is based on the large sample normal approximation.

The primary endpoint was treatment success (endoscopic cure), which was defined as an oesophageal mucosal grade of 0 at EOT.

Endoscopic cure at EOT (the primary endpoint) was experienced by 228/260 (87.7%) patients in the micafungin group and 227/258 (88.0%) patients in the fluconazole group (95% CI for difference: [-5.9%, 5.3%]) FAS (the primary population for efficacy and safety analyses).

Micafungin can be considered as effective as fluconazole in the treatment of invasive candidiasis, because the lower limit of the 95% CI is above the predefined non-inferiority margin of -10%. Non-inferiority was confirmed for the mFAS (patients who received at least a single dose of study drug and had positive histology or cytology at baseline) and the PPS (patients who received at least 10 doses of study drug, had confirmed EC at baseline, had a baseline and EOT endoscopy performed and did not have major protocol violations).

Findings for secondary efficacy endpoints at EOT were consistent with the primary endpoint. Success rates of 94.2% and 94.6% for the micafungin and fluconazole group, respectively, were observed for clinical response; 87.3% and 87.2%, respectively for overall therapeutic response; and 68.8% and 73.3%, respectively, for mycological response.

The rate of relapse for patients who had experienced overall therapeutic success at EOT was low for both treatment groups, with 15.2% (30/198) and 11.3% (22/195) patients in the micafungin and fluconazole groups, respectively, having experienced relapse during the 4-week post-treatment period ($P = 0.257$, CMH χ^2 test controlling for pooled centre).

Study 03-7-008

This is a phase III, randomized, multicentre, multinational, double-blind, parallel group, non-inferiority study comparing micafungin versus caspofungin for the treatment of oesophageal candidiasis (OE).

Study Participants

Patients ≥ 16 years old with a confirmed diagnosis of EC, within 5 days prior to first dose of study drug were eligible for enrolment. For a confirmed diagnosis of EC, the patient had to have a mucosal grade > 0 ; a positive histology or both a positive cytology and a positive *Candida* fungal culture; and

at least 1 clinical symptom of EC (dysphagia, odynophagia or retrosternal pain). A total of 450 patients were planned. In total, 452 patients received at least 1 dose of study drug (FAS = safety set = primary analysis set for efficacy analysis). The study was completed by 126/149 (84.6%) patients in micafungin 300 mg qod group, 136/151 (90.1%) patients in the micafungin 150 mg/day group and by 134/152 (88.2%) patients in the caspofungin group.

Main exclusion criteria were: (i) patient pregnant or nursing; (ii) patient had evidence of liver disease; (iii) patient had an opportunistic infection other than oesophageal candidiasis; (iv) patient received an oral, non-absorbable (topical) antifungal agent.

Treatments

Patients received micafungin (at a dose of either 150 mg/day or 300 mg every other day alternating with placebo [qod]) or caspofungin (50 mg/day). Study drug was infused over a period of 1 hour. The treatment period was a minimum of 14 days or 7 days after the resolution of clinical symptoms of EC. The primary comparison for assessment of non-inferiority was micafungin 150 mg/day versus caspofungin 50 mg/day.

Objectives

The primary objective of this study was to determine the efficacy and safety of daily doses of intravenous micafungin versus intravenous caspofungin for the treatment of patients with oesophageal candidiasis.

The secondary objective of this study was to determine if alternate day dosing of micafungin is as effective as daily dosing of micafungin and/or caspofungin.

Outcomes/endpoints

The primary efficacy endpoint was endoscopic cure (mucosal grade of 0 - no evidence of oesophageal candidiasis associated with plaques) at the end of therapy. The primary comparison was micafungin 150 mg /day versus caspofungin 50 mg/day.

Overall therapeutic response was calculated based on the clinical symptoms and oesophageal mucosal grade at the end of therapy (EOT) as compared to baseline. A positive overall therapeutic response was defined as a clinical response of cleared or improved and an endoscopic response of cleared or improved by at least 2 grades at the end of therapy.

Relapse was defined as the recurrence or worsening of oesophageal candidiasis at the 2 week and/or 4 week post-treatment visit as assessed by clinical symptoms and endoscopic evaluation for any patient with a cured or improved overall therapeutic response at the end of therapy.

Secondary efficacy endpoints included clinical, mucosal, mycological and oropharyngeal response at EOT, overall therapeutic response, incidence of relapse at 2 and 4 weeks post treatment, changes in clinical symptoms of oesophageal and oropharyngeal candidiasis at EOT compared to baseline, changes in endoscopic assessment of EC at EOT compared to baseline, changes in clinical symptoms of candidiasis at the end of therapy compared to baseline and time to complete resolution of clinical symptoms of oesophageal candidiasis.

- Sample size

A total of approximately 450 patients were planned for enrolment in a 1:1:1 ratio into one of three treatment groups, resulting in 150 patients per treatment group.

- Randomisation

The study was designed to enroll oesophageal candidiasis patients on a 1:1:1 basis into one of three treatment arms: micafungin 150 mg qd, micafungin 300 mg qod, or caspofungin 50 mg qd.

- Blinding (masking)

Study drug assignment remained blinded to all staff members with the exception of the hospital pharmacist or designee.

- Statistical methods

To assess the robustness of the primary analysis results, the primary analysis was repeated using the modified full analysis set and the per protocol set. For the primary comparison of micafungin 150 mg qd versus caspofungin 50 mg qd, treatment success was also analyzed using the Cochran-Mantel-Haenszel (CMH) test adjusted for study site. The Breslow-Day test was used to assess the consistency of the results across study sites.

An analysis of covariance (ANCOVA) test, with baseline value as a covariate, was performed on the following secondary efficacy endpoints: (i) changes in endoscopic assessment of EC at EOT compared to baseline, (ii) changes in clinical symptoms of EC at EOT compared to baseline, and (iii) changes in clinical symptoms of oropharyngeal candidiasis at EOT compared to baseline (for patients with oropharyngeal candidiasis at baseline).

Results

- Participant flow

Table 7: Summary of patient population and disposition

Data Set	Micafungin 300 mg qod	Micafungin 150 mg qd	Caspofungin 50 mg qd	Total
All Randomized Patients	150 (100.0%)	152 (100.0%)	152 (100.0%)	454 (100.0%)
Full Analysis Set	149 (99.3%)	151 (99.3%)	152 (100.0%)	452 (99.6%)
Safety Set	149 (99.3%)	151 (99.3%)	152 (100.0%)	452 (99.6%)
Modified Full Analysis Set	144 (96.0%)	149 (98.0%)	152 (100.0%)	445 (98.0%)
Per Protocol Set	132 (88.0%)	138 (90.8%)	138 (90.8%)	408 (89.9%)
Pharmacokinetic Set	20 (13.3%)	23 (15.1%)	0	43 (9.5%)
Final Disposition				
Completed Study	126 (84.0%)	136 (89.5%)	134 (88.2%)	396 (87.2%)
Death	16 (10.7%)	10 (6.6%)	12 (7.9%)	38 (8.4%)
Lost to Follow-up	6 (4.0%)	2 (1.3%)	4 (2.6%)	12 (2.6%)
Other†	2 (1.3%)	4 (2.6%)	2 (1.3%)	8 (1.8%)

Patient base: All randomized patients.

Full analysis set: All randomized patients who received at least one dose of study drug (efficacy analyses).

Safety set: All randomized patients who received at least one dose of study drug (safety analyses). Modified

full analysis set: All randomized patients who received at least one dose of study drug and had a positive histology or cytology result at baseline. Per protocol set: All randomized patients who received at least ten doses of study drug, had confirmed esophageal candidiasis at baseline, had baseline and end-of-therapy endoscopies performed, and did not have major protocol deviations. Pharmacokinetic set: All randomized patients who received at least one dose of study drug and provided sufficient data to calculate the primary pharmacokinetic parameters.

†Other: Discontinued due to adverse event (3 patients); withdrew consent (2 patients); randomized but never received study drug (2 patients); and, non-compliant with protocol (1 patient).

qd: Once daily. qod: Once every other day.

Most of the protocol deviations noted in this study were minor and did not affect the overall results of the study. A total of 46/454 patients (10.1%) were excluded from the per protocol set due to major protocol deviations and/or not fulfilling the criteria for the per protocol set.

Baseline data

There were no statistically significant differences in demographics across treatment groups for patients included in the full analysis set. The vast majority of patients in the full analysis set (> 90%) had HIV as their primary underlying disease and, of patients with HIV, > 60% had CD4 counts of < 100

cells/mcl. Furthermore, the proportion of patients using concomitant anti-retroviral medication(s) was similar across the three treatment groups (< 10% patients/treatment group).

There were no statistically significant differences among treatment groups in terms of oesophageal/oropharyngeal candidiasis characteristics at baseline. Over 85% of the patients in each treatment group were being treated for oesophageal candidiasis for the first time. More than 90% of patients in each treatment group received study drug therapy from 10 to 20 days. Consistent with the study design, mean and median treatment durations for each treatment group were approximately 14 days. Baseline fungal cultures were positive for approximately 95% of randomized patients, with *Candida albicans* being the most commonly isolated fungal organism.

The treatment groups were well balanced with respect to oesophageal/oropharyngeal candidiasis characteristics

Outcomes and estimation

The primary efficacy endpoint was endoscopic cure (success) at EOT. Using the FAS, a 95% 2-sided CI was constructed for the difference in success rates between micafungin 150 mg/day and caspofungin 50 mg/day using normal approximation. If the lower bound of the CI was greater than -0.15, the micafungin 150 mg/day would be considered non-inferior to caspofungin 50 mg/day. In total, 452 patients received at least a single dose of study drug (FAS, the primary population for efficacy and safety analyses). The study was completed by 126/149 (84.6%) patients in the micafungin 300 mg qod group, 136/151 (90.1%) patients in the micafungin 150 mg/day group and by 134/152 (88.2%) patients in the caspofungin group.

Table 8: Summary of treatment success (mucosal grade = 0) at the EOT

Analysis Set	Outcome	Micafungin 150 mg/day	Caspofungin 50 mg/day	Treatment Difference†	95% CI for Difference‡
FAS	Success	139 (92.1%)	139 (91.4%)	0.6%	(-5.6%, 6.8%)
	Failure	12 (7.9%)	13 (8.6%)		
mFAS	Success	138 (92.6%)	139 (91.4%)	1.2%	(-4.9%, 7.3%)
	Failure	11 (7.4%)	13 (8.6%)		
PPS	Success	136 (98.6%)	133 (96.4%)	2.2%	(-1.5%, 5.9%)
	Failure	2 (1.4%)	5 (3.6%)		

Patient base: Full analysis set (FAS): all randomised patients who received at least 1 dose of study drug; Modified full analysis set (mFAS): all randomized patients who received at least one dose of study drug and had a positive histology or cytology result at the baseline. Per protocol set (PPS): all randomized patients who received at least 10 doses of study drug, had confirmed EC at the baseline, had baseline and EOT endoscopies performed, and did not have major protocol deviations.

† Treatment difference: micafungin 150 mg/day minus caspofungin 50 mg/day.

‡ 95% confidence interval for the difference in success based on large sample normal approximation.

Success: Mucosal grade = 0; Failure: Mucosal grade > 0; Not evaluable: No end-of-therapy endoscopy performed or samples were not obtained from end-of-therapy endoscopy. CI: Confidence interval.

The FAS had a median and mean duration of study drug exposure of 14 days for all 3 treatment groups. Cure (success, mucosal grade = 0) at EOT was experienced endoscopically by 92.1% (139/151) patients in the micafungin 150/day group and 91.4% (139/152) of patients in the caspofungin group. The treatment difference between the micafungin 150 mg/day and caspofungin 50 mg/day treatment groups was 0.6%, with a 95% CI of [-5.6%, 6.8%].

Basing on the pre-defined non-inferiority limit of 15% (FAS), these data indicate micafungin 150 mg/day was as effective as caspofungin 50 mg/day. Non-inferiority was confirmed for the mFAS (patients who received at least a single dose of study drug and had positive histology or cytology at baseline) and the PPS (patients who received at least 10 doses of study drug, had confirmed EC at baseline, had a baseline and EOT endoscopy performed and did not have major protocol violations).

The micafungin 300 mg qod group showed similar results, with a success rate of 141 (94.6%) patients. The treatment difference was 2.6% (95% CI: [-3.1%, 8.2%]) for micafungin 300 mg qod *minus* micafungin 150 mg/day; and 3.2% (95% CI: [-2.5%, 8.9%]) for micafungin 300 mg qod *minus* caspofungin 50 mg/day.

Mycological eradication was observed for 124/149 (83.2%), 120/151 (79.5%) and 119/152 (78.3%) patients in the in micafungin 300 mg qod group, micafungin 150 mg/day group and caspofungin group.

The relapse rate through the 4-week follow-up for patients who had overall therapeutic success at EOT (excluding missing values) was 22/129 (17.1%) for the micafungin 150 mg/day group and 27/129 (20.9%) for the caspofungin group (difference for micafungin *minus* caspofungin: -3.9%; 95% CI for difference: [-13.4%, 5.7%]). In the micafungin 300 mg/every other day group, 19/128 (14.8%) patients experienced relapse through the 4-week follow-up period

3. *Prophylaxis indication*

Study 98-0-050

This was a phase III, randomised (1:1), comparative trial of micafungin versus fluconazole for prophylaxis of fungal infections in patients undergoing haematopoietic stem cell transplantation (HSTC).

Study participants

Adult and paediatric patients (≥6 months old) scheduled to undergo an autologous or syngeneic (for haematologic malignancies) or allogeneic HSCT were considered for study entry. The number of patients planned for inclusion was 800 (400 in each treatment arm). Patients were collected from 72 sites in the USA and Canada.

Treatments

Patients received either micafungin, 50 mg per day (1 mg/kg per day for patients weighing <50 kg), or fluconazole 400 mg/day (8 mg/kg/day for patients weighing <50 kg), once daily as a 1-hour infusion. Randomized treatment was initiated at the time the transplant-conditioning regimen was initiated or within 48 hours post-initiation. Treatment was to continue until one of following occurred: the patient experienced neutrophil recovery to a post nadir ANC of ≥500 cells/mm³ (study drug could be continued for up to 5 days post-neutrophil recovery at the investigator's discretion); the patient developed a proven, probable, or suspected fungal infection; the patient developed unacceptable toxicity;

Objectives

The study was aimed to demonstrate non inferiority of micafungin to fluconazole in preventing invasive fungal infection in patients undergoing a haematopoietic stem cell transplant.

Outcomes/endpoints

The primary efficacy endpoint was treatment success, defined as the absence of a proven, probable, or suspected systemic fungal infection through the end of therapy, and the absence of a proven or probable systemic fungal infection through the end of the 4-week posttreatment period.

- **Sample size**

Based on prior multicenter, randomized prophylactic trials with fluconazole in adult bone marrow transplant patients, the rate of treatment success for fluconazole was estimated to be 40%. Therefore, 400 patients per treatment group would provide at least 80% power at a one-sided 2.5% significance level to demonstrate that mycamine is not inferior to fluconazole over a difference of 10%.

- Randomisation

The study was randomised 1:1 and stratified by centre, age, type of transplant and risk for transplant-related mortality

- Blinding (masking)

The study was double-blinded.

- Statistical methods

The primary analysis focused on the efficacy of micafungin and fluconazole based upon the primary endpoint, treatment success at the end of the study. The rates of treatment success were calculated as the ratio of the total number of treatment successes to the total number of patients treated across all centers and strata (age group and transplant type). A 2-sided 95% confidence interval (CI) for the difference in the true success rates was constructed using a large sample normal approximation of the binomial distribution. Mycamine was considered not statistically inferior to fluconazole if the lower confidence bound was $\geq -10\%$, and statistically superior if the lower confidence bound was $>0\%$.

RESULTS

Participant flow

- Study population

Table 9: Summary of patient population and disposition

Data set	FK463	Fluconazole
All Randomized Patients	426	463
Full Analysis Set	425 (99.8%)	457 (98.7%)
Per Protocol Set	397 (93.2%)	433 (93.5%)
Final disposition		
Completed Study	402 (94.4%)	428 (92.4%)
Death	18 (4.2%)	27 (5.8%)
Lost to Follow-Up	5 (1.2%)	3 (0.6%)
Other	1 (0.2%)	5 (1.1%)

Patient base: all randomized patients irrespective of whether study drug was administered (all randomized patients); all patients who received at least 1 dose of study drug (full analysis set); patients who received at least 1 dose of study drug and who were deemed evaluable following patient classification (per protocol set).

A total of 1267 patients were screened from 70 sites in the USA and Canada (2 sites were initiated but never enrolled patients), and 889 were randomized 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 full analysis set.

A total of 28/425 (6.6%) micafungin and 24/457 (5.3%) fluconazole full analysis set patients did not meet the classification criteria and were not included in the per protocol set. A patient could have had more than one reason for exclusion. The 2 main reasons for exclusion were an absolute neutrophil count which was never below 200 cells/mm³, and the use of systemic antifungal therapy prior to enrolment.

The study included 84/882 (9.5%) paediatric patients (<16 years of age) and 56/882 (6.3%) elderly patients (≥65 years of age).

Baseline data

The micafungin (N = 425) and fluconazole (N = 457) treatment groups were well balanced in terms of gender, race, age and weight as well as status of underlying disease, type of transplant received and risk of transplant related mortality.

Outcomes and estimation

Table 10: Efficacy findings for the primary endpoint, study 98-0-050

	Micafungin (N=425)	Fluconazole (N=457)	Treatment Difference †
Overall	340 (80.0%)	336 (73.5%)	+6.5% 95% CI: [0.9%, 12%]
Allogeneic HSCT	157/220 (71.4%)	175/256 (68.4%)	+ 3.0%; 95% CI: [-5.3%, 11.3%]
Autologous HSCT	181/203 (89.2%)	161/201 (80.1%)	+ 9.1%; 95% CI: [2.1%, 16.0%]
No HSCT	2/2 (100%)	0	N/A

Patient base (full analysis set): all patients who received at least a single dose of study drug.

Treatment success: absence of proven, probable, or suspected systemic fungal infection through the end of therapy and absence of proven or probable systemic fungal infection through the end of study. † Micafungin rate *minus* the fluconazole rate; CI: confidence interval; N/A: not applicable; HSCT: haematopoietic stem cell transplant.

In adult patients, the mean duration of therapy was similar between the two treatment arms and the median duration was 18 days in both arms.

In the full analysis set, the overall success rate for micafungin 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 success rates in the per protocol set, which required an ANC <200 cells/mm³, were 81.1% (322/397) for micafungin versus 74.1% (321/433) for fluconazole. The treatment difference was +7.0% (95% CI: 1.3%, 12.6%). Overall, treatment differences were consistent, in favour of micafungin, when data were stratified for GVHD, age, gender or fungal colonization.

Table 11: Proven or Probable Fungal Infections During the Study by Organism Based on Protocol-Specified Diagnostic Criteria

	FK463 (n=425)	Fluconazole (n=457)
Proven	6 (1.4%)	8 (1.8%)
<i>Aspergillus</i> species	0 (0.0%)	4 (0.9%)
<i>Candida</i> species	4 (0.9%)	2 (0.4%)
<i>Fusarium</i> species	1 (0.2%)	2 (0.4%)
<i>Zygomycetes</i> species	1 (0.2%)	0 (0.0%)
Probable	1 (0.2%)	3 (0.7%)
<i>Aspergillus</i> species	1 (0.2%)	3 (0.7%)

Patient base: all randomized patients who received at least 1 dose of study drug (full analysis set).

Proven: includes biopsy-proven (with or without culture) invasive or disseminated fungal infection

Probable: includes patients with the characteristic clinical or radiologic (chest x-ray, CT scan, other) picture of pulmonary aspergillosis plus a positive BAL specimen.

Ancillary analysis

- Special Populations

Paediatric patients

As discussed for study FG463-21-08 the efficacy of micafungin in paediatric patients was consistent with that of adults.

A total of 84/882 (9.5%) patients who received micafungin in the pivotal study 98-0-050 were paediatric patients. All but four of these patients (2 in each treatment arm) underwent an allogeneic HSCT. In this study micafungin was more effective than fluconazole (45/882) in preventing invasive fungal infections in paediatric patients (treatment success: micafungin 69.2%, fluconazole 53.3%). Of the four proven and probable breakthrough infections in paediatric patients in this trial, 1/39 (zygomycosis) occurred in the micafungin arm and 3/45 (2 proven aspergillosis, 1 *C. parapsilosis* candidaemia) occurred in the fluconazole arm.

Elderly patients

A total of 56 of the 882 patients (6.3%) who received study drug in the pivotal study 98-0-050 were elderly (≥ 65 years of age). Of these 56 patients, 33 were treated with micafungin and 23 were treated with fluconazole. In this study micafungin was more effective than fluconazole in preventing fungal infections in elderly patients (treatment success: micafungin 97.0%, fluconazole 69.6%).

Clinical safety

- Patient exposure

Data from 22 phase I studies, which included healthy volunteers and study participants of special interest, are included in this submission. In total, 501 study participants were exposed to at least a single dose of micafungin in a Phase I study. Overall, 433 (97.7%) completed the study. Treatment was discontinued for 10 subjects, 6 because of an AE (5 treatment-related).

A total of 3028 patients (patients who received at least a single dose of micafungin) were included in the updated safety database. Among them, 2732 were adults (2345: 16 to 64 years of age; 387: ≥ 65 years of age) and 296 were children (< 16 years of age).

The mean \pm SD age of patients was 39.6 ± 18.0 years; 265 (10.2%) patients were < 16 years old and 251 (9.7%) patients were ≥ 65 years old. The majority of patients (55.8%) were male. Race comprised 54.9% Caucasian, 28.5% black, 3.7% oriental, and 12.9% were of another race.

This population of patients had very morbid and often life-threatening conditions. Transplantation was a common underlying condition (774 [29.8%] patients overall – 448 [17.3%] allogeneic HSCT; 286 [11.0%] autologous HSCT and 37 [1.4%] solid organ transplant). Non-HSCT patients with a haematological malignancy accounted for a further 278 (10.7%) patients. HIV was also a common underlying condition (990 [38.2%] patients). Other conditions were represented by 423 (16.3%) patients. Overall, 289/2595 (11.1%) patients were neutropenic (ANC < 500 cells / μ L). The CD4 count for patients in the EC indication (most [95.9%] were HIV positive) was < 100 cells/ μ L for 607/1013 (59.9%) patients, indicating that the majority of HIV patients had advanced AIDS.

The 443 study participants in Phase I received a mean daily dose of 131.2 mg, with an overall mean of 6.5 doses in a Phase I study. A total of 210 subjects received a fixed dose of ≥ 150 mg. One-hundred-forty subjects received micafungin for a mean of 14 to 15 days.

A summary of treatment duration in patient days by micafungin daily dose is provided in table 12 for adult and paediatric **patients**.

Table 12: Treatment Duration by Micafungin Daily Dose, Clinical Efficacy and Safety Studies . No. Patients (%)

		Micafungin Daily Dose (mg) †				
Adults, overall		< 100	≥ 100 - < 150	≥ 150 - ≤ 200	> 200	Overall ‡
N		1172	780	912	230	2732
Patient Days	1 - 14	578 (49.3)	549 (70.4)	692 (75.9)	176 (76.5)	1616 (59.2)
	15 - 28	482 (41.1)	199 (25.5)	167 (18.3)	33 (14.3)	857 (31.4)
	29 - 42	63 (5.4)	20 (2.6)	21 (2.3)	8 (3.5)	141 (5.2)
	43 - 90	43 (3.7)	11 (1.4)	24 (2.6)	9 (3.9)	88 (3.2)
	> 90	6 (0.5)	1 (0.1)	8 (0.9)	4 (1.7)	30 (1.1)
Total patient days		20163	10302	14782	3232	48479
Mean patient days		17.2	13.2	16.2	14.1	17.7
		Micafungin Daily Dose (mg) †				
Adults, non-elderly		< 100	≥ 100 - < 150	≥ 150 - ≤ 200	> 200	Overall ‡
N		1042	579	814	226	2345
Patient Days	1 - 14	511 (49.0)	417 (72.0)	631 (77.5)	173 (76.5)	1406 (60.0)
	15 - 28	436 (41.8)	140 (24.2)	138 (17.0)	33 (14.6)	722 (30.8)
	29 - 42	57 (5.5)	16 (2.8)	16 (2.0)	7 (3.1)	121 (5.2)
	43 - 90	32 (3.1)	5 (0.9)	21 (2.6)	9 (4.0)	67 (2.9)
	> 90	6 (0.6)	1 (0.2)	8 (1.0)	4 (1.8)	29 (1.2)
Total patient days		17790	7566	13299	3175	41830
Mean patient days		17.1	13.1	16.3	14.0	17.8
		Micafungin Daily Dose (mg) †				
Adults, elderly		< 100	≥ 100 - < 150	≥ 150 - ≤ 200	> 200	Overall ‡
N		130	201	98	4	387
Patient Days	1 - 14	67 (51.5)	132 (65.7)	61 (62.2)	3 (75.0)	210 (54.3)
	15 - 28	46 (35.4)	59 (29.4)	29 (29.6)	-	135 (34.9)
	29 - 42	6 (4.6)	4 (2.0)	5 (5.1)	1 (25.0)	20 (5.2)
	43 - 90	11 (8.5)	6 (3.0)	3 (3.1)	-	21 (5.4)
	> 90	-	-	-	-	1 (0.3)
Total patient days		2373	2736	1483	57	6649
Mean patient days		18.3	13.6	15.1	14.3	17.2
		Micafungin Daily Dose (mg/kg) †				
Pediatric		< 2.0	≥ 2.0 - < 3.0	≥ 3.0 - ≤ 4.0	> 4.0	Overall ‡
N		224	95	46	22	296
Patient Days	1 - 14	129 (57.6)	57 (60.0)	37 (80.4)	7 (31.8)	145 (49.0)
	15 - 28	57 (25.4)	26 (27.4)	4 (8.7)	3 (13.6)	76 (25.7)
	29 - 42	18 (8.0)	5 (5.3)	1 (2.2)	2 (9.1)	33 (11.1)
	43 - 90	12 (5.4)	4 (4.2)	2 (4.3)	5 (22.7)	21 (7.1)
	> 90	8 (3.6)	3 (3.2)	2 (4.3)	5 (22.7)	21 (7.1)
Total patient days		4500	1722	940	1337	8499
Mean patient days		20.1	18.1	20.4	60.8	28.7

Patient base: all patients who received at least a single dose of micafungin.

Adult: ≥ 16 years of age; Adults, non-elderly, 16 to 64 years of age; Elderly: ≥ 65 years of age; Pediatric: < 16 years of age.

† Patients who received different daily doses during the study may be counted more than once in different daily dose categories.

‡ For all doses combined.

- Adverse Events

Table 13: Summary of Treatment-related Adverse Events by Maximal Micafungin Dose, Non-elderly Adult Patients 16 to 64 Years of Age, Clinical Efficacy and Safety Studies . No. Patients (%)

Selected MedDRA Preferred Terms †	Micafungin Dose (mg) ‡			
	< 100 N=1042	≥ 100 - <150 N=579	≥ 150 - ≤ 200 N=814	> 200 N=226
Neutropenia	17 (1.6)	5 (0.9)	10 (1.2)	3 (1.3)
Anemia NOS	11 (1.1)	1 (0.2)	8 (1.0)	8 (3.5)
Leukopenia NOS	20 (1.9)	7 (1.2)	18 (2.2)	10 (4.4)
Thrombocytopenia	8 (0.8)	4 (0.7)	4 (0.5)	2 (0.9)
Hypokalemia	12 (1.2)	17 (2.9)	12 (1.5)	4 (1.8)
Hypomagnesemia	18 (1.7)	8 (1.4)	3 (0.4)	1 (0.4)
Hypocalcemia	20 (1.9)	4 (0.7)	4 (0.5)	3 (1.3)
Hypophosphatemia	4 (0.4)	0	1 (0.1)	1 (0.4)
Headache NOS	20 (1.9)	6 (1.0)	18 (2.2)	6 (2.7)
Phlebitis NOS	8 (0.8)	2 (0.3)	33 (4.1)	22 (9.7)
Hypertension NOS	7 (0.7)	1 (0.2)	2 (0.2)	0
Diarrhea NOS	17 (1.6)	9 (1.6)	16 (2.0)	10 (4.4)
Vomiting NOS	33 (3.2)	17 (2.9)	8 (1.0)	4 (1.8)
Nausea	30 (2.9)	16 (2.8)	20 (2.5)	7 (3.1)
Abdominal pain NOS	7 (0.7)	6 (1.0)	7 (0.9)	2 (0.9)
Cholestasis	0	5 (0.9)	0	0
Hyperbilirubinemia	10 (1.0)	7 (1.2)	2 (0.2)	1 (0.4)
Rash NOS	18 (1.7)	3 (0.5)	25 (3.1)	7 (3.1)
Pruritus NOS	8 (0.8)	4 (0.7)	7 (0.9)	4 (1.8)
Renal impairment NOS	0	2 (0.3)	0	1 (0.4)
Pyrexia	18 (1.7)	22 (3.8)	8 (1.0)	3 (1.3)
Rigors	8 (0.8)	3 (0.5)	10 (1.2)	4 (1.8)
Infusion-site inflammation	0	0	4 (0.5)	0
AST increased	29 (2.8)	15 (2.6)	12 (1.5)	7 (3.1)
ALT increased	25 (2.4)	10 (1.7)	9 (1.1)	5 (2.2)
Liver function tests NOS abnormal	12 (1.2)	6 (1.0)	9 (1.1)	2 (0.9)
Blood bilirubin increased	5 (0.5)	5 (0.9)	1 (0.1)	2 (0.9)
Blood AP NOS increased	22 (2.1)	17 (2.9)	21 (2.6)	5 (2.2)
Blood LDH increased	3 (0.3)	7 (1.2)	3 (0.4)	1 (0.4)
Blood creatinine increased	9 (0.9)	6 (1.0)	4 (0.5)	0
Blood urea increased	6 (0.6)	4 (0.7)	1 (0.1)	0

Patient base: all patients who received at least a single dose of micafungin.

Related: assessed by investigator as at least possibly related to micafungin.

AP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; LDH: lactate dehydrogenase; LFT: liver function tests; MedDRA: Medical Dictionary for Regulatory Activities; NOS: not otherwise specified.

† MedDRA preferred terms (treatment-related) with an incidence of ≥ 1% in the pooled analysis; or ≥ 1% in study FG-463-21-08, 03-7-005 or 98-0-050.

‡ Maximum dose at time of onset of adverse event. Patients who received different daily doses during the study may be counted more than once in different daily dose categories.

Safety data in healthy volunteers (443 participants) were presented separately. The incidence of adverse events, irrespective of causality, was 64.6% (286/443 subjects), of which the majority (237 subjects) were mild in intensity, and 151 (34.1%) subjects had at least 1 event that was considered by the investigator to be related to micafungin. There were no serious AEs, and treatment-related AEs that led to discontinuation were seldom (5/443, 1.1%). Overall, 36/443 (8.1%) subjects had a treatment-related hepatic AE and none led to treatment discontinuation or was severe, 46/443 (10.4%) subjects had a treatment-related injection-site AE of which 1 led to treatment discontinuation (mild phlebitis) and 20/443 (4.5%) subjects had a treatment-related allergic-like AE of which 2 led to treatment discontinuation (mild rash; mild pruritus and erythema). Of note, treatment-related haemoglobinuria was reported in 2/443 (0.5%) subjects, which were neither serious nor led to treatment discontinuation.

Reflecting the severe morbidity of the underlying conditions represented in the patient database, most patients (91.1%, 2758/3028) experienced one or more AEs, and nearly a third of patients (28.1%, 850/3028) experienced a SAE at some time during a clinical study. The nature and incidence of AEs for the various patient groups were consistent with the nature and general morbidity associated with the underlying condition.

The most frequently reported AEs, irrespective of causality were diarrhoea (23.5%), nausea (22.0%), vomiting (22.3%), pyrexia (20.4%) and mucosal inflammation (16.8%).

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 updated clinical database (N = 3028) or in a pivotal study were the hepatic AEs AST increased (2.3%), ALT increased (2.0%), AP increased (2.7%), LFT abnormal (1.5%) and hyperbilirubinemia (1.0%); the hematological AEs leukopenia (1.9%), neutropenia (1.3%) and anaemia (1.0%); the electrolyte disturbances hypokalaemia (2.1%), hypocalcaemia (1.2%) and hypomagnesaemia (1.2%); the allergic-like /histamine-related AEs rash (1.9%) and rigors (1.1%); the injection-site reaction phlebitis (2.5%); as well as headache (1.8%), nausea (2.8%), vomiting (2.5%), diarrhoea (2.0%), pyrexia (2.1%), thrombocytopenia (0.9%), abdominal pain (0.9%), pruritus (0.8%), blood creatinine increased (0.7%), blood bilirubin increased (0.6%), blood urea increased (0.6%), blood LDH increased (0.6%), hypertension (0.6%), hypophosphataemia (0.3%), renal impairment (0.3%), cholestasis (0.2%) and infusion-site inflammation (0.1%).

Hepatic AEs were common with 8.6% of patients who had a treatment-related hepatic AE, the most frequently reported being AST (2.7%) and ALT (2.0%) increased, blood AP NOS increased (2.7%) and hyperbilirubinaemia (1.0%). There was a higher incidence of treatment-related hepatic AE in the micafungin group as compared to the Ambisome group in the comparative IC study FG-463-21-08, whereas the incidence was similar when compared to fluconazole or caspofungin in the other two pivotal comparative studies. Few patients (1.1%; 0.5% serious) discontinued treatment due to a hepatic AE.

Haematological AEs were also common, with 5.6% of patients having experienced a haematological AE that was suspected of being related to micafungin. The most frequently reported treatment-related AE comprised leucopenia, neutropenia and anaemia. There were no significant differences in the incidence of treatment-related haematological AEs between micafungin and any reference therapy (Ambisome, fluconazole or caspofungin), and the overall incidence of treatment-related haematological AEs that led to treatment discontinuation was low in these studies and also showed no treatment differences. There were 3 patients (0.1%) with a treatment-related haemolytic AE of which 2 were serious (only one of them led to treatment discontinuation).

Electrolyte disturbances such as hypokalaemia, hypomagnesaemia, hypocalcaemia, and hyponatraemia were frequently suspected by the investigator of being related to micafungin (2.1%, 1.2%, 1.2% and 0.5% of patients, respectively) but none of these events was treatment-limiting, and micafungin showed a significant safety advantage to Ambisome with regard to the incidence of electrolyte disturbances.

The clinical presentation of *allergic-like/histamine-related AEs* (5.4% of patients), is more consistent with histamine release than of an antibody-mediated response, the most frequently reported being rash and rigors. In study FG-463-21-08, micafungin demonstrated an overall lower incidence of allergic-like AEs and of rigors than Ambisome. On the other hand, at daily doses of micafungin of 150 mg and higher in EC/HIV patients, micafungin showed a higher overall incidence of allergic-like AEs, rigors and rash than fluconazole in study 03-7-005 and than caspofungin in study 03-7-008. These events were seldom treatment-limiting. Of the 7 infusion-related events that were serious or led to discontinuation (including the 2 described as anaphylactic/anaphylactoid reactions), 4 occurred during the first exposure with the study drug. None was life-threatening.

Treatment-related *injection-site AEs* were seen in 6.5% of patients, the most common being phlebitis, but none was treatment-limiting. There were no significant differences in the rate of treatment-related injection-site reactions between micafungin and any reference therapy (Ambisome, fluconazole or

casprofungin), however, there was a trend for a higher incidence for patients treated with micafungin. Nevertheless, phlebitis is considered not to warrant a large consideration in the assessment of benefit/risk since many patients receiving micafungin will do so through centrally placed catheters or port-a-caths.

Overall, 1.7% of patients experienced a treatment-related *renal AE* (most frequently blood creatinine and urea increased). In the comparative trials micafungin demonstrated a significantly lower incidence of treatment-related renal AEs than Ambisome, and a similar incidence compared with fluconazole and casprofungin. Few patients (4 patients, of whom 2 had serious events) discontinued treatment due to a renal AE that was suspected of being related to micafungin. Especially paediatric patients treated with micafungin experienced more often than adults renal adverse drug reactions (3.7% vs. 1.4% [acute renal failure (1.0 vs 0.1%), blood urea increased (1.7 vs 0.5%)]).

With respect to *cardiovascular AEs*, *in vitro* studies showed that micafungin does not have a potential for delayed ventricular repolarisation, and 12-lead ECG evaluations in clinical studies showed no evidence of prolongation of QT interval. Therefore, it seems that effects on ventricular repolarisation or QT interval are not anticipated with micafungin.

Regarding *genitourinary AEs*, data from toxicity studies in animals indicate that the male genital tract is one of the main toxicological target sites, in particular an inhibitory effect on the spermatogenesis was seen in dogs and rats. Although the Applicant claims that no cases with sexual dysfunction, fertility disorders and /or spermatogenesis disorders could be identified from the clinical or post-marketing databases, these disorders are difficult to trace and can only be detected through semen analyses which were not conducted. Without proper results of these analyses oligospermia/aspermia cannot be excluded as a side effect in male patients. As stated before this is of major importance for children and young adults who are treated with micafungin. An appropriate warning on testicular toxicity has been included in section 4.6 of SPC. Since the use of micafungin should be restricted as last-line indication at present no further studies concerning the potential risk of testicular toxicity is necessary.

- Serious adverse events/deaths/other significant events

A total of 850/3028 (28.1%) patients experienced 1 or more SAEs, irrespective of causality: 25.8% (604/2345) in non-elderly adults, 37.5% (145/387) in elderly adults, and 34.1% (101/296) in children. Overall, the most frequently reported SAEs, irrespective of causality, were respiratory failure (3.1%), sepsis NOS (2.7%, 82/3028), multiorgan failure (1.2%), septic shock (1.7% 50/3028) and pneumonia (1.1%, 34/3028).

In the updated database, a total of 3.5% (107/3028) patients had a SAE other than death that was suspected of being related to micafungin. There was no trend with regard to the incidence by age group. The SAEs included 21/3028 (0.7%) patients with a hepatic SAE of which 14 led to treatment discontinuation; 13/3028 (0.4%) patients with a renal SAE of which 4 led to treatment discontinuation; 12/3028 (0.4%) patients with an allergic-like or infusion-related SAE of which 8 led to treatment discontinuation; and 2/3028 patients with a haemolytic SAE of which 1 led to treatment discontinuation.

- Safety in special populations

Overall, the nature and incidence of AEs, irrespective of causality, were similar between paediatric and adult patients. Exceptions were leucopenia and phlebitis where adults showed a markedly higher incidence than children, whereas adults had a markedly lower incidence than children for vomiting, abdominal pain and pruritus. Also, children had a higher incidence of thrombocytopenia (1.7 vs. 0.8%), hyperbilirubinaemia (2.0 vs. 0.9%), hepatomegaly (1.4 vs. 0.0%), tachycardia (1.0 vs. 0.2%), hypertension (2% vs. 0.4%), hypotension (1.4 vs. 0.3%), and renal adverse drug reactions (3.7% vs. 1.4%) than adults. Additionally, in the paediatric population the frequency of increase in AST, ALT and bilirubin, each >2.5 x ULN is about doubled compared to the adult population. Furthermore, paediatrics below 1 year of age experienced about 2x more often treatment related increase in ALT,

AST and AP compared to older paediatrics. The most likely reason for these differences were different underlying conditions compared with adults or older paediatric patients observed in clinical studies. For treatment-related AEs, the trend for most selected AEs was a higher incidence in adults than children. For treatment-related special interest AE clusters, a higher incidence in adults than in children was observed for injection-site AEs and allergic-like AEs, which may be explained by the absence of paediatric patients in the EC set, who had a higher incidence of phlebitis and rash.

- Safety related to drug-drug interactions and other interactions

In vitro studies did not suggest any potential interaction with micafungin. Mycophenolate mofetil (MMF), ciclosporin, tacrolimus, prednisolone, sirolimus, nifedipine, fluconazole, voriconazole, itraconazole, amphotericin B, ritonavir (a potent inhibitor of CYP3A4) and rifampicin (a potent inducer of CYP3A4) were evaluated. In these studies, no interaction that altered the PK of micafungin was observed.

Patients receiving one of the following drugs should be monitored for the respective co-medication, because increases in exposure (AUC) with sirolimus (total exposure AUC₀₋₇₂ by 21%), nifedipine (total exposure AUC_{0-inf} and C_{max} by 42%), amphotericin B (by 30%) and itraconazole (by 22%) in the presence of steady-state micafungin were observed.

There was also no effect of single-dose or steady-state micafungin on MMF, ciclosporin, tacrolimus, prednisolone, fluconazole voriconazole, ritonavir or rifampicin PK. As increases in exposure (AUC) with sirolimus (by 15%), nifedipine (by 18%) amphotericin B (by 30%) and itraconazole (by 22%) in the presence of steady-state micafungin were small, a requirement for dose adjustments is not anticipated.

Micafungin treatment should be carefully monitored in patients receiving a concomitant therapy including hepatotoxic and/or genotoxic properties, having chronic liver diseases known to represent preneoplastic conditions (advanced liver fibrosis, cirrhosis) or in patients carrying viral infections of the liver with the potential of liver tumour initiating activity (HBV,HCV).

- Discontinuation due to adverse events

An AE led to treatment discontinuation, irrespective of causality, for a total of 395/3028 (13%) patients. The incidence of AEs that led to discontinuation was 285/2345 (12.2%) for non-elderly adult patients, 80/887 (20.7%) for elderly patients and 30/296 (10.1%) for paediatric patients. Overall, the most frequently reported AEs that led to treatment discontinuation were septic shock (0.9%, 28/3028) and sepsis NOS (0.8%, 24/3028).

A total of 102/3028 (3.4%) patients had a treatment-related AE that led to treatment discontinuation: 78/2345 (3.3%) for non-elderly adult patients, 17/887 (4.4%) for elderly patients and 7/296 (2.4%) for paediatric patients.

Treatment-related SAEs that led to treatment discontinuation included 14 hepatic AEs, 4 renal AEs, 8 allergic-like/infusion-related AEs and 1 haemolytic AE.

Non-serious treatment-related AEs that led to treatment discontinuation comprised 18/3028 patients with a hepatic AE, 2/3028 patients with a renal AE, and 18/3028 patients had an allergic-like or infusion-related AE.

Post marketing experience

296,194 patients in Japan, 19,505 in the USA and 202 patients in the EU have been exposed to Mycamine. Most post-marketing data are available from Japan, where micafungin has been marketed since 4.5 years. The reported adverse events seem to be in line with the known safety profile of micafungin to date (see SPC comments in section 4.8).

The hepatotoxic potential of micafungin is stressed by the majority of reports received for hepatic AEs (ca 25% of all AEs), including 20 fatal cases considered at least as possibly causal related to micafungin (1/3 of all fatal related AEs). Other AEs following in frequency belong to the SOCs 'blood and lymphatic system disorders', 'skin and subcutaneous tissue disorders', 'infections and infestations' and 'renal and urinary disorders'.

2.5 Pharmacovigilance

Detailed description of the Pharmacovigilance system

The CHMP considered that the Pharmacovigilance system has deficiencies that should be addressed as part of the follow up measures.

Risk Management Plan

The MAA submitted a risk management plan, which included a risk minimisation plan

Table Summary of the risk management plan

Safety concern	Pharmacovigilance activities	Risk minimization activities
Allergic-like/ possible histamine- mediated AEs	Specific standardized follow-up questionnaire	Warning in section 4.4 of the SPC 'Possible allergic-like symptoms' listed as an ADR in section 4.8 of the SPC Prescriber checklist
Haemolytic AEs	Specific standardized follow-up questionnaire	Warning in section 4.4 of the SPC 'Hemolytic reactions' listed as an ADR in section 4.8 of the SPC Prescriber checklist
Hepatic AEs	Enhanced pharmacovigilance Observational study Pharmacokinetic study in patients with severe hepatic dysfunction	Warning in section 4.4 of the SPC 'Hepatic adverse reactions' listed as an ADR in section 4.8 of the SPC Prescriber checklist Nurse administration and monitoring guide
Renal AEs	Routine pharmacovigilance Observational study (paediatric population)	Description of pre-clinical observations in section 5.3 of the SPC 'Renal and urinary disorders' listed as an ADR in section 4.8 of the SPC Prescriber checklist Nurse administration and monitoring guide
Pancytopenia	Routine pharmacovigilance	Listed as an ADR in section 4.8 of the SPC
Relevance in humans of the development of liver tumours in rats	Close monitoring Observational study	Description of pre-clinical observations in section 5.3 of the SPC Prescriber checklist Nurse administration and monitoring guide

Effects on the male reproductive tract	Routine pharmacovigilance	Description included in section 4.6 of the SPC
Development of resistant strains	Routine and enhanced pharmacovigilance Monitor resistance development Propose susceptibility breakpoints in a microsurveillance study protocol	Section 5.1 of the SPC
Reproductive and developmental toxicity	Routine pharmacovigilance	Description included in section 4.6 of the SPC Description of pre-clinical observations in section 5.3 of the SPC

The CHMP, having considered the data submitted in the MA application is of the opinion that the following risk minimisation activities are necessary for the safe and effective use of the medicinal product: see as detailed in section 2.3 of this CHMP Assessment Report

2.6 Overall conclusions, risk/benefit assessment and recommendation

Quality

The quality of the product is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product were investigated and are controlled in a satisfactory way. There are no unresolved quality issues, which have a negative impact on the Benefit Risk balance of the product.

Non-clinical pharmacology and toxicology

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 and a threshold has not been shown by experimental data. Based on the NOAEL for FAH development a threshold for tumour development is assumed to be at 10 mg/kg/day, which is in the therapeutic range. Possibly, the prevention of liver injury would prevent formation of liver tumours, however, a causal relationship between increased liver enzymes and tumour development could not be shown. Nevertheless, patients should be careful monitored for liver damage.

In order to minimise the risk for liver tumour formation in patients treated with micafungin the SPC sections 4.1, 4.2, 4.4 and 5.3 addresses this issue. To better evaluate the risk for the development of liver tumours in children the applicant committed to conduct a study in animals comparing juvenile and adult rats.

Efficacy

The efficacy of micafungin in adults has been demonstrated in phase III active controlled randomized clinical trials to be non-inferior to AmBisome in invasive candidiasis and non-inferior to fluconazole and caspofungin in oesophageal candidiasis. A total of n=1301 patients were treated with micafungin in those phase III studies. Micafungin was at least non-inferior to fluconazole in the 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.

In children (including neonates) and adolescents < 16 years of age the efficacy of micafungin has been demonstrated in phase III active controlled randomized clinical trials to be non-inferior to AmBisome in invasive candidiasis and at least non-inferior to Fluconazole in the 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.

Safety

3028 patients have been treated with micafungin in clinical studies: 2002 patients with *Candida* infections, 375 with invasive aspergillosis and 651 for prophylaxis of systemic fungal infections.

Overall 32.2 % of the patients experienced adverse drug reactions. The most frequently reported adverse reactions were nausea (2.8 %), blood alkaline phosphatase increased (2.7 %), phlebitis (2.5 %, primarily in HIV infected patients with peripheral lines), vomiting (2.5 %), and aspartate aminotransferase increased (2.3 %). No clinically significant differences were seen when the safety data were analysed by gender or race.

The overall incidence of hepatic adverse reactions in the patients treated with micafungin in clinical studies was 8.6 % (260/3028). The majority of hepatic adverse reactions were mild and moderate. Most frequent reactions were increase in AP (2.7 %), AST (2.3 %), ALT (2.0 %), blood bilirubin (1.6 %) and liver function test abnormal (1.5 %). Few patients (1.1 %; 0.4 % serious) discontinued treatment due to a hepatic event. Cases of serious hepatic dysfunction occurred uncommonly (see SPC section 4.8). Paediatric patients < 1 year of age might be more prone to liver injury (see also SPC section 4.8). There are insufficient data on the pharmacokinetics of micafungin in patients with severe hepatic impairment (see SPC section 5.2). Micafungin may cause kidney problems, renal failure, and abnormal renal function test. Patients should be closely monitored for worsening of renal function.

The incidence of some adverse events was higher in paediatric patients than in adult patients. Additionally, paediatric patients < 1 year of age experienced about two times more often an increase in ALT, AST and AP than older paediatric patients (see section 4.4 and 4.8). The most likely reason for these differences were different underlying conditions compared with adults or older paediatric patients observed in clinical studies. At the time of entering the study, the proportion of paediatric patients with neutropenia was several-fold higher than in adult patients (40.2 % and 7.3 % of children and adults, respectively), as well as allogeneic HSCT (29.4 % and 13.4 %, respectively) and haematological malignancy (29.1 % and 8.7 %, respectively).

In rats, the development of foci of altered hepatocytes (FAH) and hepatocellular tumours after a treatment period of 3 months or longer were observed. The assumed threshold for tumour development in rats is approximately in the range of clinical exposure. The relevance of this finding for the therapeutic use in patients can not be excluded. Liver function should be carefully monitored during micafungin treatment. To minimise the risk of adaptive regeneration and potentially subsequent liver tumour formation, early discontinuation in the presence of significant and persistent elevation of ALT/AST is recommended. Micafungin treatment should be conducted on a careful risk/benefit basis, particularly in patients having severe liver function impairment or chronic liver diseases known to represent preneoplastic conditions, such as advanced liver fibrosis, cirrhosis, viral hepatitis, neonatal liver disease or congenital enzyme defects, or receiving a concomitant therapy including hepatotoxic and/or genotoxic properties.

To evaluate the potential risk for the development of liver tumours in patients the applicant committed to conduct an observational database-assisted comparative cohort study with a long follow-up period.

From the safety database all the adverse reactions reported in clinical trials and post-marketing have been included in the Summary of Product Characteristics.

Having considered the safety concerns in the risk management plan, the CHMP considered that the activities described in section 3.5 adequately addressed these.

- User consultation

The applicant committed to perform a user consultation as soon as a final PI has been agreed upon.

Risk-benefit assessment

Clinical context

During the last decades an increase in fungal infections could be recognised worldwide. Although several antifungal agents have been marketed there is a high need for new antifungal substances especially for children, because more and more isolates of fungal species are reported to show resistance against these antifungal agents on the one hand and more primarily resistant fungal species are emerging on the other hand.

Benefits

Micafungin is a new antifungal agent of a relatively new class of the echinocandins with broad antifungal activity. Neither cross-resistance with other antifungal classes nor rapid development of resistance in fungal strains is expected. Therefore, patients suffering from infections due to resistant fungal strains (of different *Candida* species) could profit from treatment with micafungin. Furthermore, patients receiving micafungin for prophylaxis of invasive fungal infections seem to have a low risk to develop a fungal infection due to azole-resistant fungi (including *Candida* and *Aspergillus*).

Micafungin also has a low potential to interact with other medications (e.g. via CYP450).

At present, there are limited treatment options for paediatrics with invasive fungal infection. Only fluconazole is approved for the indications as applied for in this patient population, but due to resistance spectrum not effective in all cases. The 2nd azole, voriconazole, is approved for children > 2 years of age only for candidiasis. However, all azoles reveal a high interaction potential via CYP450. Therefore, a high number of patients due to multimorbidity may be excluded from azole antifungal treatment. Furthermore, micafungin demonstrated fungicide activity against *Candida*. This is of importance especially in the immunocompromised patient populations.

Risks

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. Based on the NOAEL for FAH development a threshold for tumour development is at 10 mg/kg/day, which is in the therapeutic range.

There were no apparent trends with regard to treatment duration for AEs, whether treatment-related or not. One exception are renal ADRs in the paediatric population whereas treatment related renal ADRs have only been observed in the long duration group (>90 days). Overall a relatively higher percentage of children than adults received a treatment of more than 28 days.

The mean treatment duration in paediatric patients in clinical studies on invasive candidiasis, including on prophylaxis (32 days in patients 4 weeks to <2 years) but mainly in clinical studies on invasive *Aspergillosis* was higher compared to adult patients. In clinical trials total hepatic adverse events were slightly more frequent in paediatric patients (23.6%) than in non-elderly adults (20.6%) or elderly (16.3%).

Important identified risks are 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.

Balance

There is no doubt about the need for new antifungal agents, including for the paediatric population, because of the development of fungal resistance as well as emerging fungal pathogens. Micafungin has shown to be effective in sufficient number of clinical studies including against azole-resistant *Candida* strains with more than 3000 patients including 296 children. Fluconazole shows fungistatic activity against *Candida* species. Micafungin demonstrated fungicidal activity against *Candida* strains. This is of importance especially in the immunocompromised patient populations. Therefore, micafungin would be approvable as a first-line treatment option for the claimed indications in all age groups if the risk for hepatocarcinogenicity could be excluded. As this risk however cannot be excluded for time being, the benefit/risk ratio of all other antifungals is “superior” in “uncomplicated” clinical situations (e.g. absence of: resistant strain, multiple co-medication, renal insufficiency). In other cases micafungin might be an adequate treatment option in life threatening situations despite this potential risk.

The overall B/R of mycamine is positive and can be recommended as a treatment option only when the use of other antifungals is not appropriate. A number of follow-up measures will be fulfilled by the applicant within agreed time limits.

A risk management plan was submitted. The CHMP, having considered the data submitted, was of the opinion that:

- pharmacovigilance activities in addition to the use of routine pharmacovigilance were needed to investigate further some of the safety concerns: see as detailed in section 2.5.
- the following additional risk minimisation activities were required: see as detailed in section 2.3

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the risk-benefit balance of Mycamine in the following indication:

Adults, adolescents \geq 16 years of age and 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.

The decision to use Mycamine should take into account a potential risk for the development of liver tumours (see section 4.4). Mycamine should therefore only be used if other antifungals are not appropriate.

was favourable and therefore recommended the granting of the marketing authorisation.