New drugs

Micafungin

Approved indication: invasive candidiasis

Mycamine (Astellas)

vials containing 50 mg or 100 mg powder for reconstitution

Australian Medicines Handbook section 5.2

Like anidulafungin and caspofungin, micafungin is an echinocandin antifungal drug. It selectively inhibits an enzyme, glucan synthase, required for fungal cell wall synthesis. Micafungin has in vitro activity against *Candida albicans*, *C. tropicalis*, *C. glabrata*, *C. krusei*, *C. guilliermondii* and *C. parapsilosis*. It also has activity against *Aspergillus* species.

Following slow intravenous infusion of micafungin once a day, steady-state concentrations are reached within 4–5 days. Micafungin undergoes minimal hepatic metabolism and has a terminal half-life of around 10–17 hours. It is mainly eliminated in the faeces. The clearance of micafungin in premature infants is 2–6 times faster than in adults.

The efficacy of micafungin has been assessed for the treatment of invasive and oesophageal candidiasis[1-5] (Table). In the trials, *C. albicans* was the most common species isolated from patients, with *C. tropicalis*, *C. parapsilosis* and *C. glabrata* being less common.

Micafungin was compared to liposomal amphotericin B for invasive candidiasis in adults[1] and children[2] (including newborn and premature babies). The median dose of micafungin was 100 mg/day in adults and 2 mg/kg in children, for 15 days. A successful response was defined as mycological eradication and complete or partial clinical improvement. Micafungin was found to be comparable to amphotericin B in both studies.[1,2] Similar results were found in another comparison with caspofungin[3] (Table).

Micafungin (100–150 mg/day) has also been compared to fluconazole in two trials of adults with oesophageal candidiasis. As this is an opportunistic infection, most of the patients had HIV. In both studies, endoscopic cure rates for micafungin were found to be comparable to fluconazole after two weeks of treatment (see Table).[4,5]

Micafungin has also been investigated for the prevention of invasive fungal infections in adults and children undergoing stem cell transplant.[6] Patients received intravenous micafungin (50 mg/day or 1 mg/kg in patients less than 50 kg) or fluconazole (400 mg/day or 8 mg/kg in patients less than 50 kg) within 48 hours of starting the transplant conditioning regimen. (Most patients were neutropenic at baseline.) Treatment continued until the patient's neutrophil count had recovered or they developed a fungal

Some of the views expressed in the following notes on newly approved products should be regarded as tentative, as there may be limited published data and little experience in Australia of their safety or efficacy. However, the Editorial Executive Committee believes that comments made in good faith at an early stage may still be of value. As a result of fuller experience, initial comments may need to be modified. The Committee is prepared to do this. Before new drugs are prescribed, the Committee believes it is important that full information is obtained from the manufacturer's approved product information, a drug information centre or some other appropriate source.

Table **Success rates of micafungin in comparative trials** [1-6]

Indication	Overall treatment success	
Invasive candidiasis ‡	**micafungin**	**amphotericin B**
adults[1]	74.1% (183/247)	69.6% (172/247)
children[2]	72.9% (35/48)	76% (38/50)
	micafungin	**caspofungin**
adults[3]	100 mg: 76.4% (146/191) 150 mg: 71.4% (142/199)	72.3% (136/188)
Oesophageal candidiasis δ	**micafungin**	**fluconazole**
adults[4]	87.7% (228/260)	88% (227/258)
adults[5]	100 mg: 77.4% (48/62) 150 mg: 89.9% (53/59)	86.7% (52/60)
Prophylaxis in patients undergoing stem cell transplant §	**micafungin**	**fluconazole**
adults and children[6]	80% (340/425)	73.5% (336/457)

‡ eradication of *Candida* species and clinical improvement for treatment trials
δ endoscopic cure rates
§ absence of proven or probable fungal infection in the prevention trial

infection (mean duration of 19 days for adults and 23 days for children). The proportion of patients who remained infection free was higher in the micafungin group than in the fluconazole group (see Table).

Microbial resistance and reduced susceptibility to micafungin has been reported and is thought to be associated with mutations in a gene encoding the major subunit of the glucan synthase. Persistence of *Candida* species at the end of micafungin treatment occurred in 9% of adults[1] and 15.5% of children[2] with invasive candidiasis.

In a safety cohort of 3028 patients, adverse reactions possibly caused by micafungin included allergic reactions such as rash (1.9%) and rigors (1.1%), injection-site reactions (2.5%), headache (1.8%), nausea (2.8%), vomiting (2.5%), diarrhoea (2%), fever (2.1%), abdominal pain (0.9%) and pruritus (0.8%). Anaphylactic reactions occurred in two patients. Serious adverse events that led to treatment discontinuation included hepatic, renal and allergic or infusion-related events.

Haematological adverse reactions were observed in up to 10% of patients – leucopenia, neutropenia and anaemia were the most common. Thrombocytopenia was reported less frequently (0.9%). Electrolyte disturbances such as low potassium, magnesium and calcium were also common. Renal effects, including increased serum creatinine and urea, were observed in 1.7% of patients receiving micafungin.

Micafungin was associated with significant liver impairment in healthy volunteers and patients (8.6% in the safety cohort), and hepatic failure has been reported. Monitor liver function and if problems develop, consider stopping treatment. In pre-clinical studies, rats treated with micafungin developed liver tumours after three months. Alternative treatment options may need to be considered for patients with preneoplastic conditions such as liver cirrhosis, viral hepatitis, advanced liver fibrosis and neonatal liver disease, and for those receiving concomitant hepatotoxic or genotoxic drugs.

Some adverse events were more common in children than in adults. Increases in liver enzymes were twice as likely in those under one year. Renal effects were also more common (acute renal failure occurred in 1% of children) as were thrombocytopenia, tachycardia, hypertension and hypotension (1–2% of children).

Micafungin is contraindicated in people who have hypersensitivity to other echinocandin drugs. In animal studies, micafungin was associated with fetal abnormalities and increased abortion rates. It is a category C pregnancy drug and should only be used if the benefit outweighs the risk. Caution is also urged during breastfeeding.

The efficacy of micafungin seems to be comparable to several other antifungal drugs and provides another option for patients with, or at risk of, serious fungal infections. However, allergic and infusion-site reactions are a problem in some patients and hepatic effects may limit treatment.

In clinical practice guidelines, micafungin is one of the options recommended as first-line therapy for candidiasis in adults. However, in neonates the guidelines recommend its use be limited to incidences of fluconazole resistance or toxicity.[7]

T T manufacturer provided additional useful information

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The Transparency score (T) is explained in 'New drugs: T-score for transparency', Aust Prescr 2014;37:27.

* At the time the comment was prepared, information about this drug was available on the website of the Food and Drug Administration in the USA (www.fda.gov).

† At the time the comment was prepared, a scientific discussion about this drug was available on the website of the European Medicines Agency (www.ema.europa.eu).