Micafungin

Section: 6. Anti-infective medicines > 6.3. Antifungal medicines

EMLc | ATC codes: J02AX05

Indication	Systemic or invasive candidosis ICD11 code: 1F23.3
INN	Micafungin
Medicine type	Chemical agent
List type	Complementary
Formulations	**Parenteral > General injections > IV:** 50 mg in vial (as sodium) powder for injection ; 100 mg in vial (as sodium) powder for injection
EML status history	First added in 2021 (TRS 1035)
Sex	All
Age	Also recommended for children
Therapeutic alternatives	anidulafungin (ATC codes: J02AX06) caspofungin (ATC codes: J02AX04)
Patent information	Patents have expired in most jurisdictions Read more about patents.
Wikipedia	Micafungin
DrugBank	Micafungin

Expert Committee recommendation

The Expert Committee noted that there is good evidence to support the use of echinocandin antifungals in the empiric treatment of suspected or proven invasive Candida infections in critically ill patients (especially where the probability of azole resistance is high). Therefore, the Committee recommended echinocandins be added to the EML and EMLc for this indication. The Committee noted that fluconazole (which can be taken orally and is substantially cheaper than echinocandins) is still effective and has a good safety profile for prophylaxis and treatment of invasive and oesophageal Candida infections; therefore it did not recommend listing echinocandins for these indications. The Committee acknowledged the potential role for echinocandins in the second-line treatment of invasive Aspergillus infections but did not recommend listing echinocandins for this indication given the availability of established alternatives. The Committee recommended listing micafungin as the representative medicine, noting that: the patent has recently expired; micafungin is approved for use in neonates and paediatric patients; it is widely available globally; and it has the simplest dosing scheme (caspofungin and anidulafungin require loading doses). The Committee recommended anidulafungin and caspofungin be included with the listing as therapeutic alternatives, and that all three echinocandins be considered equivalent for procurement purposes. The Committee noted that echinocandins are expensive medicines and considerably more expensive than amphotericin B and fluconazole in most settings. Furthermore, antifungal resistance is becoming an increasing problem in many settings (mostly to azoles but also described for echinocandins). The Committee therefore stressed the importance of antimicrobial stewardship activities to support the appropriate use of echinocandins.

Background

Echinocandin antifungals had not previously been considered for inclusion on the EML and EMLc. In 2017, the

Expert Committee recommended the inclusion of itraconazole and voriconazole to the core list of the EML and EMLc for treatment and prophylaxis of various invasive fungal infections. Voriconazole was specifically listed for the treatment of chronic pulmonary aspergillosis and acute invasive aspergillosis (1). The EML and EMLc also include amphotericin B, fluconazole and nystatin for the indication of candidosis.

Public health relevance

Invasive candidiasis Invasive candidiasis refers to bloodstream infections and deep-seated organ infections caused by Candida spp. (Infections concerning only the skin or mucosal surfaces thus do not fall into this category, e.g. oesophageal candidiasis, a common opportunistic infection in HIV patients with low CD4 counts.) An increasing proportion of invasive candidiasis cases is caused by azole-resistant strains of Candida spp. (2). Invasive candidiasis is more common at the extremes of age (premature infants and older people). Several risk factors have been reported, notably intravascular catheters (for bloodstream infections), immunocompromised status (especially neutropenia), diabetes, renal dysfunction, previous antibiotic exposure (especially broad-spectrum antibiotics for prolonged durations), parenteral nutrition and prolonged stay in an intensive care unit (3,4). The global incidence of invasive candidiasis is estimated to range from 934 800 to 2 243 500 cases a year. Up to 40% of patients with secondary or tertiary peritonitis may develop intra-abdominal candidiasis, another subtype of invasive candidiasis (5–8). Diagnosis of intra-abdominal candidiasis is difficult as there are no specific clinical signs and blood cultures are usually negative (9). Considering these limitations, the estimated worldwide burden of these infections ranges from 60 000 to 100 000 cases a year (4) with an average global incidence of 1.15 cases/100 000 inhabitants: 5.0/100 000, 4.6/100 000, 1.5/100 000 and 1.4/100 000 in Mexico, Germany, Nigeria and Spain, respectively (10–13). One of the associated syndromes in patients with haematological malignancy is chronic disseminated candidiasis. This syndrome is a relatively rare infection but is more common if antifungal prophylaxis is not routinely given in patients with leukaemia (14–16). Candidaemia, a specific subtype of invasive candidiasis, is one of the most common hospital-associated bloodstream infections; it has been the fourth to the seventh cause of hospital-associated bloodstream infections worldwide for more than 15 years. The incidence of bloodstream infections related to intravascular devices (IVD) ranges from 0.5/1000 IVD-days to 2.7/1000 IVD-days depending on the catheter type and setting, and Candida spp. are a frequent cause (17). More than 70% of the cases of candidaemia in non-neutropenic patients are associated with intravascular devices (18–21). These infections arise because of the ability of Candida spp. to form biofilms on foreign bodies such as intravascular catheters (22,23). The incidence of candidaemia is lowest in very low-income countries and in high-income countries such as Australia, Canada, New Zealand, and countries in northern Europe, and highest in middle-income countries such as Brazil, India and Pakistan (4). The global burden of candidaemia is estimated to be between 5 and 12/100 000 population, or between 374 000 and 897 410 cases a year; short-term mortality ranges from 46% to 75% (the attributable mortality is probably much lower) (4,24–26). Non-invasive candidiasis The annual incidence of oesophageal candidiasis in the population not infected with HIV is difficult to estimate. A global total of about 1.6 million cases a year of oesophageal candidiasis is considered likely (27). Invasive aspergillosis Aspergillus spp. are the most common filamentous fungal pathogens. These pathogens usually affect patients with underlying immunosuppression (e.g. people with leukaemia, lymphoma, lung cancer, advanced HIV disease, and organ transplant recipients), chronic pulmonary diseases (e.g. chronic obstructive pulmonary disease) or concomitant viral infections in critically-ill, intubated patients (e.g. influenza, severe acute respiratory syndrome coronavirus 2). In leukaemia, lung cancer, HIV and chronic obstructive pulmonary disease, the global minimum annual incidence is 860 000. With other risk groups not accounted for, the total global annual incidence is likely to be > 1 million. Invasive aspergillosis is almost always fatal unless treated (28,29). Chronic pulmonary aspergillosis in non-immunocompromised patients The annual incidence and 5-year period prevalence of chronic pulmonary aspergillosis has been estimated at 372 000 and 1 174 000 (30). A recent prospective study in Uganda of patients 2 to 7 years after completing antituberculosis treatment found an equal number of cases of chronic pulmonary aspergillosis in people with and without HIV infection (31). According to a study from Indonesia, 13% of patients had chronic pulmonary aspergillosis at the time of finishing their antituberculosis therapy (32).

Benefits

Echinocandins are fungicidal against most Candida spp. and show in vitro activity against some filamentous fungi including Aspergillus spp. (33). These medicines act by inhibiting the production of the main component of the cell wall of ascomycete fungi – β 1,3-glucan, a molecule absent in mammalian cells (34–36). Echinocandins are not substrates of fungal efflux pumps, which makes them active against fungal strains with overexpression of these pumps (a key mechanism of azole antifungal resistance) (37,38). The European Medicines Agency has approved micafungin for treatment of invasive candidiasis and prophylaxis against Candida infections in neutropenic patients (< 500 neutrophils/μL for ≥ 10 days) for adults and children. The use of micafungin to treat oesophageal candidiasis is only indicated for adults (39). Caspofungin is approved for treatment of invasive candidiasis and invasive aspergillosis that are not responsive to the usual therapeutic dose and/or for treatment of invasive aspergillosis in patients unable to take amphotericin B and/or itraconazole (40). Anidulafungin is approved for Candida infections (candidaemia, intra-abdominal abscess and peritonitis) and oesophageal candidiasis (41). General considerations In clinical practice, treatment of fungal infections is often empirical since the invasive procedures potentially required to make a microbiological diagnosis are often thought to be have too many risks in severely ill patients. This complicates making a definitive diagnosis and makes it difficult to determine objective microbiological endpoints in clinical studies. For this reason, the initial studies on echinocandins were conducted for oesophageal candidiasis, where treatment efficacy can be relatively easily evaluated (through endoscopy and/or biopsy) and a large number of potentially eligible patients are available (42,43). As a general overview of all the data analysed in the application, the authors stated that “Echinocandins are better than or at least as efficient as different comparators for all the described Candida infections including oesophageal candidiasis, candidaemia, different forms of invasive candidiasis and infections caused by different Candida species. Moreover, some good results were obtained for echinocandins as treatment options in the paediatric population and as prophylaxis and empiric therapy for invasive candidiasis in different immunosuppressed populations. Echinocandins are recommended as salvage therapy for aspergillosis that is refractory to approved therapy (amphotericin B and Aspergillus active azole agents)”. Oesophageal candidiasis In the three randomized trials identified, the cure rate with echinocandins was similar or better than treatments with comparator drugs (amphotericin B or fluconazole) (42,44,45). The studies drew the following conclusions. • Caspofungin appeared to be as effective as and better tolerated than amphotericin B for the treatment of oesophageal candidiasis (42). • At the end of therapy, the rate of endoscopic success for anidulafungin (242/249 patients treated; 97.2%) was statistically non-inferior to that for fluconazole (252/255 patients treated; 98.8%): treatment difference –1.6%; 95% confidence interval (CI) –4.1 to 0.8 (44). • The endoscopic cure rate for 100 mg and 150 mg of micafungin per day (83.5%) was comparable to that of 200 mg of fluconazole per day (86.7%); 95% CI for the difference in endoscopic cure rate –14.0% to 7.7% (45). Candidaemia and common forms of invasive candidiasis Five randomized trials were included in the analysis. Two trials compared micafungin and caspofungin for invasive candidiasis. In one of these trials, dosages of micafungin 100 mg daily and 150 mg daily were non-inferior to a standard dosage of caspofungin for the treatment of candidaemia and other forms of invasive candidiasis (46), and the other trial found that the efficacy of caspofungin and micafungin was similar (47). Three randomized trials compared echinocandins with amphotericin B or fluconazole and reported the following: • Caspofungin was as effective as amphotericin B in patients with candidaemia, with a favourable response in 71.7% and 62.8% of patients, respectively (difference, 10.0 percentage points, 95% CI –4.5 to 24.5) (48). • Treatment success was observed for 181 (89.6%) patients receiving micafungin and 170 (89.5%) patients treated with liposomal amphotericin B. After stratification by neutropenic status at baseline, the difference in proportions was 0.7% (95% CI –5.3 to 6.7). Micafungin was as effective as liposomal amphotericin B as first-line treatment of candidaemia and invasive candidiasis, and caused fewer adverse events (49). • At the end of intravenous therapy, treatment was successful in 75.6% of patients receiving anidulafungin, compared with 60.2% of patients treated with fluconazole (difference 15.4 percentage points, 95% CI 3.9 to 27.0). The results were similar for other efficacy endpoints. Anidulafungin was non-inferior to fluconazole in the treatment of invasive candidiasis (50). The application noted that when fluconazole was used as a comparator, anidulafungin had a better response rate for all Candida spp. except C. parapsilosis. This showed for the first time that some Candida spp. would behave differently. A recent network meta-analysis of 13 randomized trials with 3528 participants with candidaemia and/or invasive candidiasis treated with either an echinocandin (n = 1531), amphotericin B (n = 944) or an azole (n = 1053)

showed that echinocandins were associated with greater treatment success than amphotericin B (odds ratio (OR) 1.41, 95% CI 1.04 to 1.92) and the azoles (OR 1.82, 95% CI 1.35 to 2.51) (51). Less common forms of invasive candidiasis A comparative study showed that the efficacy of caspofungin in uncommon infections (endocarditis, osteomyelitis, peritonitis, and chronic disseminated and septic arthritis caused by Candida spp.) was similar to its observed effectiveness for candidaemia (52). Non-albicans Candida spp. infections Some evidence suggests that echinocandins produce similar outcomes to other classes of antifungal agents (such as liposomal amphotericin B) independent of the Candida species causing the infection (53). A pooled analysis of two randomized trials included one study comparing micafungin (100 mg/day) and liposomal amphotericin B, and a second study comparing different micafungin doses and caspofungin. Clinical cure rates in those receiving micafungin were similar to those randomized to the comparator (73.5% (86/117) versus 62.1% (41/66), $P > 0.05$). Mortality at 28 days was also similar (29.1% (34/117) with micafungin versus 34.8% (23/66) with the comparator, $P > 0.05$). Micafungin resulted in similar outcomes to comparators for candidaemia and invasive candidiasis caused by C. glabrata and C. krusei. The 100 mg/day dose is an acceptable option in this setting. Patient characteristics and catheter management appeared to be more important factors affecting clinical outcomes (53). Prophylaxis for invasive candidiasis in different immunosuppressed populations Two randomized trials compared the usefulness of prophylactic echinocandins against invasive candidiasis in immunosuppressed populations (54,55). In the first trial, the overall efficacy of micafungin was superior to that of fluconazole for antifungal prophylaxis during the neutropenic phase after haematopoietic stem cell transplantation (80.0% efficacy for micafungin versus 73.5% for fluconazole; 95% CI 0.9% to 12%) (54). In the second trial intravenous itraconazole and caspofungin gave similar protection against invasive fungal infection during induction chemotherapy (55). Echinocandins as first-line treatment against invasive aspergillosis Azoles are the drug of choice to treat invasive aspergillosis. This fungal infection is a common complication in haematopoietic stem cell transplantation recipients. In these patients, it is difficult to keep an equilibrium between efficacy and toxicity when using regular antifungal treatments. Three randomized trials examined echinocandin efficacy and safety to treat invasive aspergillosis (56–58). The success rate was low with caspofungin, but better for micafungin when using voriconazole as the comparator. However, based on these trials, echinocandins have not been recommended in treatment guidelines as the primary monotherapy for the treatment of invasive aspergillosis. Echinocandins against aspergillosis refractory to approved therapy (salvage therapy) Invasive aspergillosis is associated with frequent treatment failures. The mortality is worse for refractory infections, especially when the antifungal is switched to a salvage monotherapy. The results of four studies were assessed. • A non-comparative open-label trial using micafungin alone or in combination with another systemic antifungal agent (amphotericin B) was designed to show the safety and efficacy of micafungin in the treatment of acute invasive aspergillosis that had failed to respond to previous therapy. Micafungin as primary or salvage therapy was efficacious and safe in high-risk patients with invasive aspergillosis, although there were few patients in the micafungin-only group (59). • A non-comparative open-label study included 53 adults with documented invasive aspergillosis refractory to standard antifungal therapy or who could not tolerate standard therapy. The participants received caspofungin and another antifungal agent (at the investigator’s discretion). Caspofungin, combined with a triazole or polyene, was an effective alternative as salvage therapy for patients with refractory Aspergillus infections (60). • A prospective multicentre study analysed a series of transplant recipients who received voriconazole + caspofungin ($n = 40$) as primary therapy for invasive aspergillosis (proven or probable). The outcomes were compared to a control group of consecutive transplant recipients treated with lipid formulation of amphotericin B. The authors concluded that a combination of voriconazole and caspofungin could be a preferable treatment for subsets of organ transplant recipients with invasive aspergillosis, for example, patients with renal failure or A. fumigatus infection (61). The study did not analyse the effect of voriconazole alone. • A non-comparative study included 98 haematopoietic stem cell transplant recipients with invasive aspergillosis (refractory in 83) who received micafungin either alone or in combination with other therapies. The study found that micafungin was well tolerated, even at high doses, and concluded that micafungin was a reasonable option for treatment of invasive aspergillosis in such high-risk patients (62). Echinocandins in children Data on the pharmacokinetics and safety of echinocandins in children are few. • An ascending dosage study assessed the pharmacokinetics of anidulafungin in neutropenic paediatric patients (2–11 years and 12–17 years) and concluded that paediatric patients receiving 0.75 mg/kg/day or 1.5 mg/kg/day of anidulafungin have concentration profiles similar to those of adult patients given 50 mg/day or 100 mg/day, respectively (63). • An

open-label study included children with proven or probable invasive aspergillosis, proven invasive candidiasis or proven oesophageal candidiasis. All children received caspofungin 70 mg/m2 on day 1, followed by 50 mg/m2 per day (maximum: 70 mg/day) as primary or salvage monotherapy. Caspofungin was generally well tolerated in patients aged 6 months to 17 years. The efficacy of caspofungin in patients with invasive aspergillosis or invasive candidiasis was consistent with previous adult studies for these indications (64). • A paediatric substudy was conducted of a double-blind, randomized trial to compare micafungin (2 mg/kg) with liposomal amphotericin B (3 mg/kg) as first-line treatment of invasive candidiasis. Treatment success was observed for 35/48 (72.9%) patients receiving micafungin and 38/50 (76.0%) patients receiving liposomal amphotericin B. The difference in proportions adjusted for neutropenic status was –2.4% (95% CI –20.1% to 15.3%). The authors concluded that micafungin seemed as effective and as safe as liposomal amphotericin B for treatment of invasive candidiasis in children (65). The application also lists different guidelines published by European and North American infectious diseases societies and endorsed by different South American and Asian societies. These guidelines include echinocandins as the recommended first-treatment option for Candida spp. infections and as salvage therapy, or echinocandins in combination with other antifungals for Aspergillus spp. infections (66–68).

Harms

The main reported adverse effects of echinocandins are related to infusion reactions (e.g. phlebitis and fever), mild increases in liver enzymes, minor hypokalaemia and unspecific signs (including gastrointestinal discomfort, headache or skin rash) (39–41,69,70). Anidulafungin seems to produce fewer adverse effects than micafungin or caspofungin, although fewer studies have used this medicine. The most common reported adverse effects of anidulafungin were diarrhoea, hypokalaemia and elevated levels of alanine aminotransferase (all ≤ 3% of the patients). Compared with fluconazole, the adverse effects profile seems similar, but with a lower incidence of hepatic adverse effects among patients receiving anidulafungin (50). The most frequent adverse effects reported for caspofungin were infusion-related events because the solution is quite acidic. Reducing the rate of infusion or infusion using a central venous catheter may reduce these events. A comparison of caspofungin and amphotericin B in 224 patients with invasive candidiasis showed that caspofungin was better tolerated than amphotericin B. Nephrotoxicity and hypokalaemia were observed in both groups. However, they were significantly less frequent and milder in the group treated with echinocandin. Abnormalities in liver function markers were also mild and seen in only 8% of the patients treated with caspofungin (48). For micafungin, the most frequent adverse effects reported in clinical trials with 202 patients were infusion-related reactions, hypokalaemia, abdominal discomfort and nausea, and elevation of liver enzymes (55). According to the results of these three clinical studies, liver adverse effects related to echinocandin treatment (including increases in aminotransferases) are mild and less frequent than cases reported with fluconazole and amphotericin B (48–50). Hepatocellular tumours in animal models Hepatocellular tumours were observed in rat models using human therapeutic doses of micafungin. These effects were found after prolonged exposure (> 3 months) (71). The European Medicines Agency imposed a black box warning for micafungin and extensive phase 4 pharmacovigilance requirements (39). A multicentre cohort study was designed to determine the risk of fatal hepatocellular carcinoma among patients treated with micafungin and other parenteral antifungals with up to 12 years of follow-up. Both micafungin and comparator antifungals were associated with hepatocellular carcinoma mortality rates of < 0.2 per 1000 person-years. Given the very low event rates, the authors considered that any potential risk for hepatocellular carcinoma should not affect clinical decisions on treatment with micafungin or other parenteral antifungals investigated in the study (72). Drug–drug interactions Echinocandins are poor substrates for cytochrome P450 enzymes. Thus, co-administration with cytochrome P450 inhibitors or inductors (e.g. carbamazepine and phenytoin) is not clinically significant. Caspofungin may interact with halogenated penicillins (e.g. dicloxacillin) as it potentially induces CYP3A4 enzyme (73–76). Clinically significant interactions with caspofungin were documented with rifampicin, tacrolimus and ciclosporin (77–79). Ciclosporin showed clinically significant interactions with micafungin, but this effect was not seen when coadministered with anidulafungin (80,81).

Cost / cost effectiveness

Several pharmacoeconomic evaluations have been published comparing echinocandins with azoles (fluconazole

and voriconazole), echinocandins with amphotericin B, and two of the three echinocandins with each other (summarized in Table 17 of the full application (82)). Limitations of these evaluations include the fact that few included the concept of life-years gained in their cost estimations and few compared one echinocandin versus other medicines of the same group. In some of the evaluations, caspofungin was cheaper and in others, micafungin was a more cost-effective option. When lipid amphotericin B and fluconazole were compared with echinocandins, echinocandins were more cost-effective, especially in high-income countries, since the cost of health personal and other associated expenditures are higher than in low-income countries. In low- and middle-income countries, deoxycholate amphotericin B and fluconazole are regarded as more cost-effective than the echinocandins. In these countries, the main cost drivers are drug acquisition costs.

WHO guidelines

Not available

Availability

Micafungin is proposed as the representative of the echinocandin class because it is registered in more countries than caspofungin or anidulafungin. It also has the simplest dose regimen and there are data to support its use in neonates. Echinocandins are approved by different medicine agencies, including the US Food and Drugs Administration, European Medicines Agency and Japanese Medicines Agency. For caspofungin and micafungin, different approved generic products are already authorized.

Other considerations

Confirmation of the fungal etiology of infection, identification of the causative agent and ideally its susceptibility to antifungals is necessary for optimal treatment of fungal infections. Specimens for fungal cultures and other relevant studies (wet mount, histopathology, serology, antigen detection, polymerase chain reaction testing and imaging) should be obtained for this purpose whenever possible. Echinocandin minimum inhibitory concentrations are low for most Candida spp., including intrinsically azole-resistant species and strains with secondary resistance (37,83–86). Antifungal susceptibility testing should be performed whenever possible for any strain isolated from a normally sterile site. Echinocandin susceptibility testing can be carried out using standardized and commercially available microdilution and agar diffusion methods. It should be noted that antifungal susceptibility testing is more difficult to perform than antibiotic susceptibility testing. Therefore such testing may be unavailable in many settings, especially in low- and middle-income countries. The EML Antibiotic Working Group discussed the application during a virtual meeting on 14 April 2021. The Working Group agreed that echinocandins are efficacious medicines with fungicidal activity against most Candida spp. and some activity against Aspergillus spp. The Working Group also acknowledged that echinocandins generally have a good safety profile and that resistance to this class of antifungals remains low. The Working Group therefore supports the inclusion of echinocandins on the EML and EMLc, although for more limited indications than requested in the application. Indications for which the Working Group supports the listing: • Empiric treatment of suspected fluconazole - resistant candidaemia or suspected candidaemia/invasive candidiasis in critically ill patients treated in intensive care settings, especially patients with neutropenia. Indications for which the Working Group does not support the listing: • Invasive aspergillosis. The Working Group decided that given the weak evidence available, it does not support listing echinocandins at this time for the treatment of aspergillosis. For aspergillosis, it was noted that echinocandins are not the treatment of choice but rather salvage therapies for refractory cases and these indications are usually not addressed in the EML and EMLc, which focuses on empiric therapy. • Prophylaxis for invasive candidiasis, as it was concluded that fluconazole remains effective in most cases. • Oesophageal candidiasis, as it was concluded that fluconazole remains effective in most cases. The Working Group supports the request of listing micafungin as a representative of the echinocandins class in the EML and EMLc for the reasons provided in the application (availability), noting that micafungin is not licensed for the treatment of aspergillosis. Caspofungin and anidulafungin could be listed as therapeutically equivalent alternatives so that countries have more options to choose from based on price and availability.

1. The selection and use of essential medicines. Report of the WHO Expert Committee, 2017 (including the 20th WHO Model List of Essential Medicines and the 6th WHO Model List of Essential Medicines for Children). Geneva: World Health Organization; 2017 (WHO Technical Report Series, No. 1006; https://apps.who.int/iris/handle/10665/259481, accessed 28 August 2021).
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