A.10	Echinocandins for Fungal Infections
Does the application adequately address the issue of the public health need for the medicine?	☒ Yes ☐ No ☐ Not applicable Comments: The application provides a summary of the unmet public health need for antifungal treatment. The data is more limited from the LMIC setting and several references are now from over 10 years ago. However, this reflects the limitation of the available literature, with limited formal evaluation of the global burden of disease.
Briefly summarize the role of the proposed medicine(s) relative to other therapeutic agents currently included in the Model List, or available in the market.	The EML currently lists for parenteral antifungal therapy Amphotericin B, flucytosine, fluconazole and voriconazole. The only drugs with an indication to treat candidosis is Amphotericin B, first listed in 1977 and fluconazole, listed in 1999. Amphotericin B is recognised to have significant toxicity, including renal and hepatic concerns. Significant resistance to fluconazole in multiple *Candida* species is now a major global concern.
Have all important studies and all relevant evidence been included in the application?	☒ Yes ☐ No ☐ Not applicable If no, please provide brief comments on any relevant studies or evidence that have not been included: The application provides a detailed and extensive summary of the many studies that have been conducted over the last 20 years. There is no Cochrane directly focussed on the parenteral treatment of Candidosis, or very specifically focussed on the efficacy of echinocandins in invasive fungal infections (IFI). In patients with haematological disease and febrile neutropenia a recent Systematic Review of 6 RCTs compared empiric antifungal therapy with echinocandins and non-echinocandins (mainly caspofungin and liposomal amphotericin). Mortality and adverse events were lower in the echinocandin treated patients (RR 0.70 CI 0.49-0.99; RR0.48 CI 0.33-0.71) (Yamashita 2020). A further SR and Network Meta-analysis of 17 RCT involving 4583 patients in all cause FN also noted that echinocandins appeared to be the most effective agents for the empiric treatment of FN patients based on mortality and treatment response (Chen 2017).

Does the application provide adequate evidence of efficacy/effectiveness of the medicine for the proposed indication?	☒ Yes ☐ No ☐ Not applicable Briefly summarize the reported benefits (e.g. hard clinical versus surrogate outcomes) and comment, where possible on the actual magnitude and clinical relevance of benefit associated with use of the medicine(s). See above. There is a significant evidence base to show that the echinocandins have clinical efficacy against *Candida* spp, with some activity against *Aspergillu*s spp, where they are not usually regarded as first line therapy, but as salvage therapy for refractory cases. Is there evidence of efficacy in diverse settings (e.g. low-resource settings) and/or populations (e.g. children, the elderly, pregnant patients)? There is a more limited evidence base for echinocandins in the LMIC setting, although they have been extensively used in patients with HIV infection. There are several trials of echinocandins in children and for micafungin in neonates.
Does the application provide adequate evidence of the safety and adverse effects associated with the medicine?	☒ Yes ☐ No ☐ Not applicable Comments: The echinocandins are generally well tolerated with a very good safety profile, with nausea, rash, mild liver function abnormalities noted, but major organ toxicity is very rare.
Are there any adverse effects of concern, or that may require special monitoring?	☐ Yes ☒ No ☐ Not applicable Comments:
Briefly summarize your assessment of the overall benefit to risk ratio of the medicine (e.g. favourable, uncertain, etc.)	Overall the echinocandins have a good clinical and safety profile since caspofungin was first licenced by the FDA 20 years ago. There is a clear favourable benefit to risk ratio.
Briefly summarize your assessment of the overall quality of the evidence for the medicine(s) (e.g. high, moderate, low etc.)	The evidence for the efficacy of the echinocandins for the treatment of invasive candida infection is high, with SR evidence of improved mortality outcomes. There is only moderate level evidence for their utility in invasive aspergillus infection.

Are there any special requirements for the safe, effective and appropriate use of the medicine(s)**?** (e.g. laboratory diagnostic and/or monitoring tests, specialized training for health providers, etc)	☐ Yes ☒ No ☐ Not applicable Comments:
Are you aware of any issues regarding the registration of the medicine by national regulatory authorities? (e.g. accelerated approval, lack of regulatory approval, off-label indication)	☐ Yes ☒ No ☐ Not applicable Comments: Multiple generic manufacturer's.
Is the proposed medicine recommended for use in a current WHO Guideline approved by the Guidelines Review Committee? (refer to: https://www.who.int/publications/who-guidelines)	☐ Yes ☒ No ☐ Not applicable Comments:
Briefly summarize your assessment of any issues regarding access, cost and affordability of the medicine in different settings.	Caspofungin is relatively widely available in HIC and MIC settings, Micafungin and Anidulafungin are also available in multiple countries. In the LMIC setting, echinocandin's are significantly more expensive than the deoxycholate amphotericin B and fluconazole.
Any additional comments	
Based on your assessment of the application, and any additional evidence / relevant information identified during the review process, briefly summarize your proposed recommendation to the Expert Committee, including the supporting rationale for your conclusions, and any doubts/concerns in relation to the listing proposal.	There is reasonable evidence for the use of the echinocandins in the empiric treatment of suspected or proven *Candida* invasive infections (especially where there is a high probability of azole resistance) in critically ill patients, particularly febrile neutropenic adults and children. The recommendation is that echinocandins should be added to the EML and EMLc for this indication. Micafungin should be listed as the representative drug, with caspofungin and anidulafungin listed as having therapeutic equivalence (square box). There is less clear evidence for the listing of echinocandins for the indication of prophylaxis of invasive/oesophageal candida infections, where fluconazole (which can also be taken orally) still has efficacy and a good safety profile. This indication is not recommended. There is less clear evidence of benefit for the treatment of *Aspergillus* infections. As noted above the evidence is focussed on the role in salvage therapy in refractory cases, which is not the usual focus of the EML. This indication is not recommended.
References (if required)	