

A.10	Echinocandins – fungal infections
Does the application adequately address the issue of the public health need for the medicine?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Not applicable Comments: The application provides information the burden from a number of potential indications for echinocandins, namely candidaemia, abdominal sepsis, refractory/resistant candida infections, candida oesphagitis, neutropaenic sepsis , invasive aspergillosis, chronic aspergillosis.
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.	<p>Echinocandins are not currently listed on the EML. They are used to treat fungal infection as alternative options to azoles (particularly fluconazole and voriconazole) and amphotericin formulations.</p> <p>There are three echinocandins proposed for inclusion (caspofungin (CSF), anidulofungin(ANF), and micofungin(MCA)) in both EML and EML/c. The case is presented that they offer superior treatment options for some infection due to candida and aspergillus species</p>
Have all important studies and all relevant evidence been included in the application?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Not applicable If no, please provide brief comments on any relevant studies or evidence that have not been included: The application references a wide range of studies
Does the application provide adequate evidence of efficacy/effectiveness of the medicine for the proposed indication?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> 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). Is there evidence of efficacy in diverse settings (e.g. low-resource settings) and/or populations (e.g. children, the elderly, pregnant patients)? Data on efficacy is presented in tables 7 to 9. Table 7 summarises 5 RCTS are presented for invasive candidiasis. Studies tend to use surrogate outcomes defined by treatment response. Some evidence that CSF greater efficacy and less toxicity than amphotericin B. No evidence of difference between CSF/MCA. Table 8 reports one study of CSF in a range of patients settings for rarer presentations of candida infection without comparator

	<p>Table 9 3 meta-analyses of studies looking at non-candida infections. Efficacy between CSF/MCF and AMB similar</p> <p>Table 10 paediatric data including one RCT which found similar efficacy for MCA and liposomal amphotericin</p> <p>Table 11 prophylaxis one high quality RCT suggesting MCA better than FLC</p> <p>Table 12 treatment of aspergillosis. Two non-comparative studies of CSP and one RCT comparing MCA to voriconazole suggesting similar efficacy and better toxicity profile of CSP</p> <p>Table 13 treatment of refractory aspergillosis</p> <p>There is evidence for the use of agents in children, for capsosungin and micafungin.</p>
Does the application provide adequate evidence of the safety and adverse effects associated with the medicine?	<p><input checked="" type="checkbox"/> Yes</p> <p><input type="checkbox"/> No</p> <p><input type="checkbox"/> Not applicable</p> <p>Comments:</p> <p>There is a detailed summary of adverse events. There are challenges in interpretation as AEs are compared against different drugs (mostly amphotericin) and there are not good comparative head-to-head data on the different agents.</p> <p>Table 16 (p64) provides a helpful overview of toxicity from a number of references presented</p>
Are there any adverse effects of concern, or that may require special monitoring?	<p><input type="checkbox"/> Yes</p> <p><input checked="" type="checkbox"/> No</p> <p><input type="checkbox"/> Not applicable</p> <p>Comments:</p>
Briefly summarize your assessment of the overall benefit to risk ratio of the medicine (e.g. favourable, uncertain, etc.)	<p>There appears to be evidence of favourable benefit/risk ratio for echinocandins in treatment of invasive candidiasis in neutropaenic and non-neutropaenic patients, including in deep-seated infections. Evidence for a role in refractory aspergillosis. More uncertain role in prophylaxis, invasive aspergillosis.</p>
Briefly summarize your assessment of the overall quality of the evidence for the medicine(s) (e.g. high, moderate, low etc.)	<p>Tables 56-61 provided an assessment of quality of evidence across range of recommendations.</p>

2021 Expert Committee on Selection and Use of Essential Medicines
Application review

<p>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)</p>	<p><input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not applicable Comments:</p>
<p>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)</p>	<p><input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not applicable Comments: PP72/73 outline the approvals for each of the 3 echinocandins. FDA has the broadest approval for caspofungin, including in children.</p>
<p>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)</p>	<p><input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> Not applicable Comments: Echinocandins are recommended in some international guidelines including IDSA,</p>
<p>Briefly summarize your assessment of any issues regarding access, cost and affordability of the medicine in different settings.</p>	<p>From the information provided, it is difficult to assess the relative costs and affordability of agents. It would be helpful to know when the patents for the listed agents expire, whether there is licensing to generic manufacturers and what prices are in low-income countries where registered for sale. This may have some bearing on</p>
<p>Any additional comments</p>	

2021 Expert Committee on Selection and Use of Essential Medicines
Application review

<p>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.</p>	<p>Based on the evidence provided, echinocandins should be included on the EML. There are some challenges in listing as a class as different agents may be preferred for different indications (e.g. candidaemia, peritonitis, neutropaenic sepsis, oesophageal candidiasis). At this time, echinocandins should be recommended for treatment of invasive candidiasis.</p> <p>The choice of agent representative of the class is challenging. The proposal recommends micafungin, and the argument in its favour appears to be simplicity of dosing and approval by EMA for children. Anidulofungin and caspofungin require loading doses and all agents require some dose adjustment for weight (particularly caspofungin). Consideration of differential access to each option needs to be taken into account (data provided pp 74-6 illustrate registrations rather than access) and may favour caspofungin</p>
<p>References (if required)</p>	