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Pharmacotherapeutic report liposomal amphotericin B (Ambisome®) for use in the treatment of severe systemic fungal infections within the framework of an application for inclusion in the NZa policy regulation for expensive medicines in hospitals (BDG)

Medicine and composition: liposomal amphotericin B (50 mg), powder for infusion fluid (lyophilisate).

Registered indications:
- the treatment of severe systemic mycoses, caused by *Candida albicans* of *Aspergillus* spp in patients who are contraindicated for the use of conventional amphotericin B (amphotericin B deoxycholate [**C-AMB**] due to severe loss of renal function.
- empirical treatment of suspected fungal infections in patients with neutropenia.
- liposomal amphotericin B (**L-AMB**) has also been successfully used for the treatment of visceral leishmaniasis. Immunocompromised patients (such as patients infected with HIV), frequently suffered a relapse, just as they do after other forms of treatment for visceral leishmaniasis.
- National and/or local guidelines should be observed for the correct use of antimycotic products.

Indications for which inclusion in the BDG is being requested:
- secondary care use (after voriconazol) for the treatment of severe systemic fungal infections which were (probably) caused by *Aspergillus* spp or for treatment in primary care when the use of voriconazol is less suitable,
- the empirical treatment of a possible severe systemic fungal infections in patients with neutropenia and persistent fever,
- the treatment of patients with a severe systemic fungal infections caused by zygomycetes.

Dose: the initial dose is 1 mg/kg/day. Where necessary, increase to 3 mg/kg/day. For infections due to *Aspergillus* spp, where necessary, gradually increase to 5 mg/kg/day. A dose of 5/mg/kg/day is recommended for patients with febrile neutropenia who have not responded to a minimum of 96 hours treatment with antibiotics (empiric treatment).

Mode of action: amphotericin B is a macrocyclic broad-spectrum, polyene antimycotic that is active against fungal infections. These products usually have a fungicidal effect that is created due to their being bound to the ergosterol that is necessary for the synthesis of the fungal cell membrane. Binding causes damage to the cell membrane and a loss of intracellular ingredients, which eventually leads to cell death.

<u>Summary of therapeutic value:</u>
Favourable effects: - when used for the treatment of infections probably caused by *Aspergillus* spp., voriconazol is more effective than C-AMB. Based on a direct comparison, L-AMB is equally effective as C-AMB. In particular when it is not possible to exclude a (multiple) infection with zygomycetes, L-AMB is first choice for patients previously treated with voriconazol.
- C-AMB and L-AMB have a comparable effect in the treatment of a possibly severe invasive fungal infection (empiric treatment). Caspofungin and voriconazol have the same effect as L-AMB.

Unfavourable effects: In many patients the use of C-AMB leads to infusion-related side effects. Furthermore, C-AMB is often extremely nephrotoxic. The renal toxicity is dose-related. L-AMB leads to fewer side effects and less renal toxicity than C-AMB. Voriconazol caused alterations in the range of vision, which were usually transient, in about 30% of the patients. Furthermore, the use of voriconazol led to infusion-related side effects. Voriconazol often causes an alteration and/or a reduction, sometimes significant, in the liver function. With regard to the severity and frequency of the side effects, the safety

profile of QL-LAMP is comparable with that of voriconazol. This is because the hepatotoxic effects of voriconazol is offset by the nephrotoxicity caused by QL-LAMP. Caspofungin causes infusion-related side effects. The side effects profile of caspofungin is slightly more favourable than that of L-AMB. Caspofungin is also less nephrotoxic.

Experience: Ample experience has been obtained with L-AMB.

Applicability: The applicability of L-AMB is limited due to the possibly reduced renal function and the hypokalaemia that often follows. Voriconazol cannot always be used in combination with medicines that are metabolised by CYP450 enzymes in the liver (in particular CYP3A4). Liver and renal function disorders also limit the use of this product. Being an azole, voriconazol is associated with QT-prolongation.

Ease of use: L-AMB is intended for intravenous administration.

Final conclusion: when used to combat severe systemic fungal infections caused by *Aspergillus* spp (aspergillosis), L-AMB is equally effective as C-AMB, but leads to fewer side effects. As a result, L-AMB can often be given in higher doses than C-AMB. When it is not possible to exclude a (multiple) infection with zygomycetes, L-AMB has an added value for patients with an aspergillosis that was previously treated with voriconazol. There is also an added value if patients cannot be receive treatment with voriconazol in primary care. For the treatment of patients with neutropenia and persistent fever, possibly resulting from a severe systemic fungal infection (empiric treatment), the therapeutic value of L-AMB is comparable with that of caspofungin and voriconazol. When it is not possible to exclude an infection with zygomycetes, L-AMB is first choice. L-AMB is first-choice treatment for infections caused by zygomycetes.

*The original text of the summary of this **CFH-report** was in Dutch. Although great care was taken in translating the text from Dutch to English, the translation may nevertheless have resulted in discrepancies. Rights may only be derived on the basis of the Dutch version of the summary of the CFH-report.*
Furthermore, CVZ points out that only the summary of this report was translated. A proper understanding of all relevant considerations and facts would require familiarity with the Dutch version of this report, including all appendices.