# Flucytosine

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

EMLc | ATC codes: J02AX01

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|---|---|
| **Indication** | Cryptococcosis ICD11 code: 1F27.Z |
| **INN** | Flucytosine |
| **Medicine type** | Chemical agent |
| **List type** | Core |
| **Formulations** | **Parenteral > General injections > IV:** 2.5 g per 250 mL infusion<br>**Oral > Solid:** 250 mg capsule |
| **EML status history** | First added in 1977 (TRS 615)<br>Changed in 1979 (TRS 641)<br>Changed in 1982 (TRS 685)<br>Changed in 2007 (TRS 950)<br>Changed in 2013 (TRS 985) |
| **Sex** | All |
| **Age** | Also recommended for children |
| **Therapeutic alternatives** | The recommendation is for this specific medicine |
| **Patent information** | Patents have expired in most jurisdictions<br>Read more about patents. |
| **Wikipedia** | Flucytosine |
| **DrugBank** | Flucytosine |

## Summary of evidence and Expert Committee recommendations

The Department of HIV/AIDS, WHO, submitted applications to move amphotericin B and flucytosine to the core list of the EML and the EMLc. Cryptococcal meningitis accounts for 20–25% of AIDS-related mortality and is the most common cause of adult meningitis in sub-Saharan Africa, constituting a major public health burden. The mortality from this infection remains high at 35–65%. Poor or delayed access to effective drug treatments is an important contributing factor to mortality. WHO rapid advice guidelines on Diagnosis, prevention and management of cryptococcal disease in HIV-infected adults, adolescents and children were published in December 2011 (1). Amphotericin-based regimens were recommended as preferred in three of the five regimens. A two-week regimen of amphotericin B plus flucytosine was recommended as the preferred option. Where amphotericin is unavailable, or cannot be monitored safely, the treatment guidelines recommend flucytosine in conjunction with high-dose fluconazole. However, the guidelines with flucytosine could not be followed in many parts of Africa because flucytosine was not available. A cost–effectiveness analysis that also analysed mortality from pooled clinical trial data showed that regimens containing amphotericin were consistently superior (2). The addition of flucytosine to amphotericin B during induction therapy, compared with amphotericin B alone, was found to be associated with increased rates of cerebrospinal fluid (CSF) sterilization, a reduced risk of relapse, and a nonsignificant reduction in mortality at 2 weeks and a significant reduction at 10 weeks (2). The 2011 WHO rapid advice guidelines also recommended appropriate strategies to ensure the safe administration of amphotericin, including intravenous hydration coupled with electrolyte monitoring. In a review of seven trials, using the recommended dose of 100

mg/kg per day of flucytosine for 14 days with either amphotericin B or fluconazole, the incidence of grade IV neutropenia was 8 out of 183 (4.4%). A dose adjustment for renal function is needed for flucytosine. Amphotericin B is produced by multiple generic manufacturers; generic flucytosine is not available in many countries although it has been off-patent for many years. The combination of flucytosine + fluconazole can be managed in resource-limited settings and an effective oral option is important. The evidence provided to the Expert Committee included a published cost-utility analysis cited in the WHO guidelines (116). The Expert Committee noted that there were several problems with the analysis that led to difficulty in interpreting the results. The estimates of survival from different treatment regimens were extrapolated from 10 weeks to 1–3 years on the basis of several different cohorts that may or may not provide valid data for deriving incremental survival benefit. Quality-adjusted life years (QALYs) were calculated on the basis of Karnofsky performance scores from patients treated with antiretroviral treatment (a completely different intervention), and these scores were then used to calculate incremental changes in estimated life years. This is not a valid approach to calculating QALYs, which should be calculated on the basis of an implied trade-off between survival and quality of life. As it was difficult to rely on the results of the analysis as presented, the Expert Committee decided that its decision should be weighted by other factors. Given the obvious public health need, the potential to promote the availability of effective combinations in countries with heavy disease burdens, and the evidence of safety in the context where the products will be used, the Expert Committee decided to move these products to the core list. The Committee considered that transferring these medicines to the core list could improve availability. The Committee also strongly recommended that WHO should monitor the change in availability over the next five years. References: 1. Rapid advice: diagnosis, prevention and management of cryptococcal disease in HIV-infected adults, adolescents and children. Geneva: World Health Organization; 2011. 2. Rajasingham R, Rolfes MA, Birkenkamp KE, Meya DB, Boulware DR. Cryptococcal meningitis treatment strategies in resource-limited settings: a cost-effectiveness analysis. PLoS Med. 2012;9(9):e1001316. http://dx.doi.org/10.1371/journal.pmed.1001316 PMID:23055838

