Ethionamide is currently included on the complementary list of the EML and EMLc for use in the treatment of multidrug-resistant tuberculosis.

Expert Committee recommendation

The Expert Committee noted that tuberculosis meningitis is responsible for considerable morbidity and mortality, and that a shorter, intensified ethionamide-containing treatment regimen in children and adolescents has shown favourable outcomes in comparison with the alternative WHO-recommended 12-month regimen of isoniazid, rifampicin, pyrazinamide and ethambutol. The Committee therefore recommended the inclusion of ethionamide on the core list of the EML and EMLc for the new indication of drug-susceptible tuberculosis meningitis in children and adolescents, consistent with the recommendations in current WHO guidelines for management of drug-susceptible tuberculosis meningitis in children and adolescents.

Background

Tuberculous meningitis is the most lethal form of tuberculosis. Globally in 2019, there were an estimated 164 000 cases and 78 200 deaths due to tuberculous meningitis (1). Mortality and severe permanent disabilities remain high in both children and adults, particularly in people living with HIV (2,3).

Public health relevance

The application referenced a systematic review and meta-analysis of seven cohort studies comparing the effectiveness of shorter regimens including at a minimum isoniazid, rifampicin and pyrazinamide, versus the WHO-recommended 12-month regimen of isoniazid, rifampicin, ethambutol and pyrazinamide in children and adolescents with drug-susceptible tuberculosis meningitis (4).
This meta-analysis informed a 2022 WHO guideline recommendation in favour of the shorter regimen (conditional recommendation; very low-certainty evidence). Details of the findings of the systematic review were not provided in the application but are summarized below. Three of the included studies (724 patients) evaluated a 6-month intensive regimen of isoniazid, rifampicin, pyrazinamide and ethionamide. This regimen was associated with a lower pooled proportion of death (5.5%, 95% confidence interval (CI) 2.1% to 13.4%) compared with the 12-month regimen (23.9%, 95% CI 17.5% to 31.7%). The pooled proportions of treatment success were 94.6% (95% CI 73.9% to 99.1%) for the 6-month intensive regimen and 75.4% (95% CI 68.7% to 81.1%) for the 12-month regimen. For survivors who completed treatment and who had neurological sequelae the pooled proportions were 66.0% (95% CI 55.3% to 75.3%) for the 6-month regimen and 36.3% (95% CI 30.1% to 43.0%) for the 12-month regimen, although there was substantial heterogeneity for both regimens. For survivors who completed treatment and who did not have neurological sequelae, the pooled proportions were 29.9% (95% CI 20.4% to 41.4%) and 47.9% (95% CI 42.1% to 53.7%) for the 6-month and 12-month regimens, respectively.

**Cost / cost effectiveness**

No information was provided in the application. The 2023 Global Drug Facility catalogue reports the price of ethionamide 250 mg tablets as US$ 9.16 for 100 tablets, and of ethionamide 125 mg dispersible tablets as US$ 13.30–14.48 for 100 tablets.

**WHO guidelines**

Current WHO guidelines for the management of tuberculosis in children and adolescents include a conditional recommendation (very low-certainty evidence) that in children and adolescents with bacteriologically confirmed or clinically diagnosed tuberculosis meningitis (without suspicion or evidence of multidrug- or rifampicin-resistant tuberculosis), a 6-month intensive regimen of isoniazid, rifampicin, pyrazinamide and ethionamide may be used as an alternative to the 12-month regimen of isoniazid, rifampicin, ethambutol and pyrazinamide (6).

**Availability**

Ethionamide tablets and dispersible tablets are available through the Stop TB Partnership’s Global Drug Facility.

**Other considerations**

In adults, WHO guidelines recommend that drug-susceptible tuberculosis meningitis be treated with the same regimen used for pulmonary tuberculosis, that is, a 6-month regimen composed of 2 months of isoniazid, rifampicin, pyrazinamide and ethambutol, followed by 4 months of isoniazid and rifampicin, noting that some expert groups suggest longer therapy (7).