Ethambutol

REJECTED

The Expert Committee, after evaluation, declines to list the medicine proposed in the application.
The Model List of Essential Medicines reports reasons that Committee Members have identified for denying listing.

Section: 6. Anti-infective medicines > 6.2. Antibacterials > 6.2.5. Antituberculosis medicines

EMLc | ATC codes: J04AK02

Indication	Other specified tuberculosis ICD11 code: 1B1Y
INN	Ethambutol
Medicine type	Chemical agent
List type	Core
Formulations	**Parenteral > General injections > IV:** 1000 mg per 10 mL ; 2000 mg per 20 mL
EML status history	Application rejected in 2021 (TRS 1035)
Sex	All
Age	Also recommended for children
Therapeutic alternatives	The recommendation is for this specific medicine
Patent information	Patents have expired in most jurisdictions Read more about patents.
Wikipedia	Ethambutol
DrugBank	Ethambutol

Expert Committee recommendation

The Expert Committee noted that tuberculosis is a major cause of ill health and one of the top 10 causes of death worldwide. About a quarter of the world's population is infected with M. tuberculosis, with the life-time risk of developing tuberculosis of about 5–10% among those infected. Ethambutol, isoniazid, and rifampicin are already included in EML as oral formulations. The Committee recognized that intravenous formulations may be useful for a subgroup of severely ill patients and those who have disorders affecting oral drug absorption. The Committee considered that intravenous isoniazid and rifampicin may be recommended in specific circumstances (e.g. tuberculous meningitis). However, the role of ethambutol in the treatment of central nervous system tuberculosis disease was more limited and other agents (e.g. fluoroquinolones and aminoglycosides) are often used instead. The current applications were resubmissions following recommendations made in 2019 not to include these formulations on the EML. The Committee considered that the applications did not provide a clear estimate of the numbers of patients who might need intravenous therapy globally and included very little evidence on the comparative efficacy of intravenous formulations compared with oral formulations. The Committee was of the opinion that a large, simple, pragmatic trial is feasible in this setting and could provide information relevant for decision-making. Moreover, the Committee considered that intravenous formulations may carry a small increased risk (e.g. of infection, thrombosis) because of the need for venous access. The cost of intravenous formulations also appears to be higher than the cost of oral formulations, and market availability is very limited. The Committee noted that no additional evidence was submitted that would give it reason to reach a different conclusion to the recommendation made in 2019. Therefore, the Expert Committee again recommended that intravenous formulations of ethambutol, isoniazid, and rifampicin not be included on the EML and EMLc for the treatment of severe forms of tuberculosis.

Background

Three separate applications proposed inclusion of intravenous formulations of ethambutol, isoniazid and rifampicin to the EML and EMLc for the treatment of tuberculosis in patients with severe forms of the disease associated with poor outcomes, patients

with acute or chronic gastrointestinal disease or malabsorption disorders, patients with severe comorbidities, and patients unable or unwilling to take oral dosage forms. The current applications are resubmissions of applications submitted for consideration by the Expert Committee in 2019. In 2019, inclusion of the proposed formulations was not supported by the WHO Global Tuberculosis Programme, who in response to the applications emphasized: • WHO recommends oral treatment regimens, ideally administered in fixed-dose combinations (where such formulations exist) for the treatment of drug-sensitive tuberculosis. • WHO's updated treatment guidelines for multidrug-resistant and rifampicin-resistant tuberculosis, recommend that injectable agents no longer be included among the priority medicines when designing longer regimens for multidrug-resistant tuberculosis. • In view of these WHO policy recommendations, in most tuberculosis patients, intravenous administration for first- or second-line medicines is not indicated. • For most indications listed in the applications for intravenous formulations, patients can be treated with oral formulations, if necessary using alternative forms of oral administration. • For adult patients with drug-sensitive tuberculosis, a four-drug regimen is recommended; therefore with only three of the four medicines available as intravenous formulations, patients would still be required to take pyrazinamide orally. The 2019 Expert Committee did not recommend their inclusion on the Model Lists. The Committee noted that WHO guidelines recommend use of oral, preferably fixed-dose combination therapy for tuberculosis, but acknowledged that parenteral administration of tuberculosis medicines may be useful in a small number of critically unwell patients unable to tolerate oral therapy, or patients with tuberculous meningitis. The Committee considered that the inclusion of parenteral formulations of these medicines could result in inappropriate use of parenteral therapy in patients otherwise able to take oral therapy. The Committee also noted that the global market availability of these products was limited, and the comparative cost was unknown (1).

Public health relevance

The public health relevance of medicines for the treatment of tuberculosis is well established. Globally in 2019, an estimated 10 million people fell ill with tuberculosis, and there were 1.2 million deaths among HIV-negative people and 208 000 deaths among HIV-positive people (2). The applications identified the severe forms of tuberculosis for which intravenous therapy would be indicated as miliary tuberculosis, caseous pneumonia, tuberculous meningitis, tuberculosis sepsis and tuberculosis pericarditis. In addition, it was proposed that intravenous treatment would also be suitable for patients with gastrointestinal malabsorption conditions, patients with severe comorbidities (HIV, diabetes) and patients unable or unwilling to take oral therapy. However, no information was provided on the burden of disease of these cases as a proportion of the total tuberculosis cases that would be eligible for intravenous treatment. Extrapulmonary tuberculosis is reported to account for about 14% of tuberculosis cases worldwide, and particularly affects children and people living with HIV (3). Tuberculous meningitis, in particular, has been reported to account for about 1% of all tuberculosis cases worldwide and its incidence is directly related to the prevalence of pulmonary tuberculosis (4).

Benefits

The clinical benefits and place in tuberculosis treatment of ethambutol, isoniazid and rifampicin are well established and have been evaluated previously by the Expert Committee. Compared with the 2019 applications, the current applications did not include any comparative clinical evidence for the benefits of the intravenous formulations of ethambutol, isoniazid and rifampicin versus oral formulations in treating severe forms of tuberculosis or in the other population groups for which listing was proposed. As in 2019, the applications presented few pharmacokinetic data describing higher achievable peak plasma concentrations with intravenous administration compared with oral administration.

Harms

The safety profiles of ethambutol, isoniazid and rifampicin are well established and have been evaluated previously by the Expert Committee. The applications described common adverse events associated with ethambutol, isoniazid and rifampicin. Any differences in adverse events with oral versus intravenous administration were not specified.

Additional evidence

A small randomized trial evaluating the effectiveness of intravenous isoniazid and ethambutol in the intensive phase of treatment of patients with tuberculous meningoencephalitis and HIV co-infection was identified during the review process (5). Patients were randomized to receive intravenous ethambutol and isoniazid plus oral rifampicin and pyrazinamide (n = 23) or the same medicines administered orally (n = 31) for the intensive phase of therapy (2 months), followed by oral therapy for the continuation phase. Patients in the intravenous treatment group had a significant improvement in clinical symptoms and X-ray signs compared with patients in the oral treatment group. Sputum Mycobacterium tuberculosis positivity in the second month of treatment was 25.0% and 76.1% in the intravenous and oral treatment groups, respectively. At 6 months, mortality was

significantly greater in the oral treatment group compared with the intravenous treatment group (70.9% versus 39.1%, P = 0.023).

Cost / cost effectiveness

No comparative cost–effectiveness data were available. The applications report that the intravenous formulations are more expensive than the corresponding oral formulations, but that oral and intravenous formulations should not be considered alternatives to each other in patients with severe forms of the disease.

WHO guidelines

For patients with drug-susceptible pulmonary tuberculosis, the 2017 WHO guidelines recommend a 6-month rifampicin-based oral regimen (2HRZE/4HR: 2 months isoniazid, rifampicin, pyrazinamide and ethambutol followed by 4 months isoniazid and rifampicin) (6). The 2016 WHO target regimen profiles for tuberculosis treatment (7) state that oral formulations are optimal, but that intravenous formulations should also be available. It further states that intravenous formulations should be reserved for sever forms of disease such as central nervous system tuberculosis or tuberculosis sepsis.

Availability

The proposed intravenous formulations have very limited regulatory approval and global availability.

Other considerations

Comments on the application were provided by the WHO Global Tuberculosis Programme. As was the case in 2019, the technical department did not support the inclusion of the proposed intravenous formulations of ethambutol, isoniazid and rifampicin. It was highlighted that WHO recommends oral treatment regimens for both patients with drug-susceptible and drug-resistant tuberculosis as the preferred options. In addition, most patients with severe forms of tuberculosis, patients with severe comorbidities and patients who are unable to take oral medicines can be treated with oral formulations, if necessary, using alternative forms of administration. It was also highlighted that for adult patients with drug-susceptible tuberculosis, a four-drug regimen including isoniazid, ethambutol, rifampicin and pyrazinamide is recommended; therefore, patients would still need to take pyrazinamide orally.

1. The selection and use of essential medicines. Report of the WHO Expert Committee, 2019 (including the 21st WHO Model List of Essential Medicines and the 7th WHO Model List of Essential Medicines for Children). Geneva: World Health Organization; 2019 (WHO Technical Report Series, No. 1021; (https://apps.who.int/iris/handle/10665/330668, accessed 19 August 2021).
2. Global tuberculosis report 2020. Geneva, World Health Organization; 2020 (https://apps.who.int/iris/handle/10665/336069, accessed 19 August 2021).
3. Foppiano Palacios C, Saleeb PG. Challenges in the diagnosis of tuberculous meningitis. J Clin Tuberc Other Mycobact Dis. 2020;20:100164.
4. Thwaites GE, van Toorn R, Schoeman J. Tuberculous meningitis: more questions, still too few answers. Lancet Neurol. 2013; 12(10):999–1010.
5. Butov D, Feshchenko Y, Kuzhko M, Gumenuik M, Yurko K, Grygorova A, et al. Effectiveness of intravenous isoniazid and ethambutol administration in patients with tuberculosis meningoencephalitis and HIV infection. Tuberc Respir Dis (Seoul). 2020;83(1): 96–103.
6. Guidelines for treatment of drug-susceptible tuberculosis and patient care, 2017 update. Geneva: World Health Organization; 2017 (https://apps.who.int/iris/handle/10665/255052, accessed 6 February 2019).
7. Target regimen profiles for TB treatment: candidates: rifampicin-susceptible, rifampicin-resistant and pan-TB treatment regimens. Geneva, World Health Organization; 2016 (https://apps.who.int/iris/handle/10665/250044, accessed 19 August 2021).