P-aminosalicylic acid

Essential medicine status ✓

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

EMLc | ATC codes: J04AA01

Indication	Multi-drug resistant tuberculous Mycobacterium ICD11 code: ML32.00
Medicine type	Chemical agent
List type	Complementary Medicines for the treatment of multidrug-resistant tuberculosis (MDR-TB) should be used in specialized centres adhering to WHO standards for TB contol.
Formulations	Oral > Solid: 500 mg tablet ; 4 g granules in sachet
EML status history	First added in 1999 (TRS 895) Changed in 2007 (TRS 950) Changed in 2019 (TRS 1021)
Sex	All
Age	Also recommended for children
Therapeutic equivalence	The recommendation is for this specific medicine
Patent information	Patents have expired in most jurisdictions Read more about patents.
Wikipedia	P-aminosalicylic acid
DrugBank	P-aminosalicylic acid (Aminosalicylic Acid)

Expert Committee recommendation

The Expert Committee did not recommend the addition of injectable formulations of ethambutol, isoniazid, PAS and rifampicin to the EML and EMLc for treatment of drug-susceptible TB in combination with other firstline medicines. The Committee noted that WHO guidelines recommend use of oral, preferably fixed-dose combination therapy for TB, but acknowledged that parenteral administration of TB medicines may be useful in a small number of critically unwell patients unable to tolerate oral therapy or patients with TB meningitis. The Committee considered that the inclusion of these parenteral TB formulations on the EML 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 unknown.

Background

Four separate applications requested addition of injectable formulations of ethambutol, isoniazid, p-aminosalicylic acid (PAS) and rifampicin to the EML and EMLc for treatment of drug-susceptible tuberculosis in combination with other first-line medicines. Ethambutol, isoniazid, PAS and rifampicin are all currently included on the EML and EMLc in oral dose forms.

Public health relevance

Worldwide, tuberculosis is one of the top 10 causes of death, and the leading cause from a single infectious agent. In 2017, TB caused an estimated 1.3 million deaths among HIV-negative people, and there were an additional 300 000 deaths from the disease among HIV-positive people. There were an estimated 10.0 million new cases of TB, equivalent to 133 cases per 100 000 population (1). The IV formulations are proposed in the applications for use in cases of severe forms of disease, such as central nervous system (CNS) TB or TB sepsis, patients with gastrointestinal diseases and reduced oral absorption rates, and other patient groups unwilling or unable to take oral dose forms. There is evidence that there is a decrease in the functional absorptive area of the intestine in TB patients, resulting in reduced serum concentrations of orally administered antituberculosis drugs. Patients with

malabsorption syndromes can require higher doses to achieve minimum therapeutic levels (2, 3). Malabsorption of anti-mycobacterial drugs has been reported HIVcoinfected patients (4, 5). A retrospective cohort study in Brazil found that among TB patients admitted to intensive care units (ICU), over 90% have acute respiratory failure (ARF) and require mechanical ventilation. The in-hospital mortality rate for ICU-admitted patients was around 65% (6). CNS TB has been reported to account for 5–10% of extrapulmonary TB cases and approximately 1% of all TB cases (7). It is associated with high morbidity and mortality (8). No information was provided in the applications regarding the proportion of total TB cases that would require IV treatment.

Benefits

The clinical benefits and place in therapy of these medicines (per se) are well established and have been evaluated previously by the Expert Committee. Limited pharmacokinetic data were presented in the applications indicating higher achievable concentrations with IV versus oral formulations, which is to be expected from IV administration where 100% bioavailability is achieved.

Harms

The adverse events (AE) associated with the medicines, rather than of the proposed IV formulations, were described in the applications. The safety profiles of these medicines are well established and have been evaluated previously by the Expert Committee. It is reasonable to assume that the known safety profiles would be applicable to the IV formulations.

Additional evidence

An RCT investigating the efficacy and safety of IV chemotherapy during the intensive treatment phase in patients newly diagnosed with pulmonary TB was identified during the review process (9). 92 patients were randomized to receive oral treatment with isoniazid, rifampicin, pyrazinamide and ethambutol or IV isoniazid, IV rifampicin, IV ethambutol and oral pyrazinamide. Alleviation of chest symptoms (cough, dyspnoea, chest pain) and intoxication symptoms (weakness, loss of appetite, fatigue, night sweats, increased body temperature) was more rapid in the IV therapy group. No serious adverse events associated with IV therapy were observed.

Cost / cost effectiveness

Due to the limited availability of the proposed IV formulations on world markets, no information on the comparative cost and cost-effectiveness of these products are available. The applications suggest that the IV formulations will be more expensive than the currently available oral formulations.

WHO guidelines

WHO guidelines recommend ethambutol, isoniazid, rifampicin and PAS in treatment regimens for drug-susceptible TB and MDR-TB/RR-TB (10, 11). The guidelines recommend the use of oral, preferably fixed-dose combination therapy for TB treatment. In the WHO Target regimen profiles for TB treatment, it is recommended that IV formulations be reserved for cases of severe forms of disease such as CNS TB or TB sepsis (12).

Availability

The proposed formulations have limited market approval and global availability: IV ethambutol: Germany, Kazakhstan, Switzerland, Tajikistan, Ukraine and Uzbekistan. IV isoniazid: Italy, Kazakhstan, Ukraine, United Kingdom, United States and Uzbekistan. IV PAS: Belarus, Germany and Ukraine. IV rifampicin: United States.

Other considerations

Comments on the applications were received from the WHO Global TB Programme. The technical unit advised that it did not support inclusion of the proposed IV formulations of tuberculosis (TB) medicines emphasizing the following: – WHO recommends oral treatment regimens, ideally administered in fixed-dose combinations (where such formulations exist) for the treatment of drug-sensitive TB. – WHO has recently updated treatment guidelines for MDR-TB and RR-TB, recommending that injectable agents are no longer among the priority medicines when designing longer MDR-TB regimens. – In view of these WHO policy

recommendations, in the large majority of TB patients, IV administration for first- or second-line medicines is not indicated. – For the majority of indications listed in the applications for IV formulations, patients can be treated with oral formulations, if necessary, using alternative forms of oral administration. – For adult patients with drug-sensitive TB, 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.

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