Application for the inclusion of ethambutol for intravenous use (addition – new formulation/strength of existing medicine) in the WHO Model List of Essential Medicines and Model List of Essential Medicines for Children, section 6.2.4 as a first-line drug for the treatment of tuberculosis in severely ill patients and those who have absorption disorders as a lifesaving possibility to receive proper anti-tuberculosis treatment

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1. Summary statement of the proposal for inclusion, change or deletion

Tuberculosis (TB) is a communicable disease that is a major cause of ill health, one of the top 10 causes of death worldwide and the leading cause of death from a single infectious agent (ranking above HIV/AIDS). TB is caused by the bacillus Mycobacterium tuberculosis, which is spread when people who are sick with TB expel bacteria into the air; for example, by coughing. The disease typically affects the lungs (pulmonary TB) but can also affect other sites (extrapulmonary TB).

Every year, 10 million people fall ill with tuberculosis (TB). Despite being a preventable and curable disease, 1.5 million people die from TB each year – making it the world's top infectious killer [1].

TB is the leading cause of death of people with HIV and also a major contributor to antimicrobial resistance, which means the urgent need in additional efforts to study the main reasons of treatment failure and additional efforts to save those 1.5 million lives per year.

Among all TB deaths, 77,2% of patients die during intensive phase of treatment and 36.4% of patients die in the first 10 days of the treatment, according to recent studies. [8] That means, severe TB patients are in the blind zone of the standard TB care and require additional treatment efforts, for example hospitalization and using anti-TB preparations with immediate action, such as intravenous drugs instead of tablets.

Ethambutol is one of the most effective chemotherapeutical components that is present in main treatment regimens of drug-susceptible tuberculosis recommended by WHO.

Ethambutol is an anti-tuberculosis agent that inhibits the transfer of mycolic acids into the cell wall of the tubercle bacillus. It may also inhibit the synthesis of spermidine in mycobacteria. The action is usually bactericidal, and the drug can penetrate human cell membranes to exert its lethal effect. [2]

The EML and EMLc already contain preparations of oral ethambutol. This application proposes IV ethambutol for the core list of WHO Model List of Essential Medicines and Model List of Essential Medicines for Children, as a lifesaving medicine for:
1. Patients with severe forms of tuberculosis with poor outcomes, requiring intensive treatment (Miliary TB [37,38], caseous pneumonia [39], TB meningitis [40], TB sepsis [41-42], TB pericarditis [45]).

2. Patients with acute or chronical gastrointestinal diseases, or patients with

reduced absorption rates of oral forms (malabsorption in PLWH [19-23]).

3. Patients with severe comorbidities: HIV/TB, diabetes/TB [46], etc.

4. Patients that are unable (unconscious patients in ICU or in coma [47]) or unwilling to take drugs in periods of depression or due to acute manifestations of altered mental condition. [17]

Target regimen profiles for TB treatment: rifampicin-susceptible, rifampicin resistant and pan-TB treatment regimens, published in 2016 by WHO state that IV formulations should be reserved for cases of severe forms of disease, such as CNS TB or TB sepsis for both susceptible and resistant forms of tuberculosis.

Currently, intravenous ethambutol is not available on most of the markets. The absence of IV ethambutol in both EML and EMLc prevents national and international TB programs from purchasing needed quantity of IV forms.

2. Name of the focal point in WHO supporting the application

Dr Ernesto Jaramillo, MDR-TB Policy & Innovations department, World Health Organization Geneva, Switzerland

Bernadette Cappello, Secretariat, Essential Medicines List, World Health Organization Geneva, Switzerland

3. Name of the organizations consulted and supporting the application

International Union Against Tuberculosis and Lung Disease (The Union),

National institute of phthisiology and pulmonology named after F.G. Yanovsky NAMS of Ukraine,

CU Communicable Diseases Intensive Care Association “Incure”, Ukraine,

Higher State Educational Establishment "Bukovinian State Medical University", Ukraine,

Novosibirsk TB Research Institute (NTRI), Russian Federation,

Universitas Padjadjaran Department of Pharmacology therapy, Indonesia, Clinical Research Unit and Institute of Biomedicine/Center for Global Health,

Department of Physiology and Pharmacology, School of Medicine, Federal

Universitatea de Medicină şi Farmacie „Grigore T. Popa” Iaşi, Romania. "Marius Nasta" Pneumoftiziology Institute, Romania.

4. International non-proprietary name of the medicine (INN, generic name) of the medicine.

ETHAMBUTOL

ATC code J04AK02

5. Formulation proposed for inclusion.

Formulation: solution for infusion/concentrate for solution for infusion,

Strength(s): 1000 and 2000 mg/vial

Indication: treatment of susceptible tuberculosis in combination with other first-line drugs

Addition – new formulation/strength of existing medicine

The EML and EMLc already contain preparations of oral ethambutol. This application is for the additional inclusion of solution for infusion/concentrate for solution for infusion of Ethambutol 1000 and 2000 mg.

Ethambutol was reported to be four times as active as streptomycin in vivo. It was also found to be active against strains that were resistant to isoniazid and streptomycin. [3]

Due to concerns of toxicity in children, a literature review was carried out by the WHO in 2006. The review concluded that in view of the almost total lack of ocular toxicity in children of all ages receiving ethambutol at doses of from 15– 30 mg/kg documented, it can be recommended that children of all ages can be given ethambutol in daily doses of 20 mg/kg (range 15–25 mg/kg) and three times weekly intermittent doses of 30 mg/kg body weight without undue concern. [4]

Ethambutol has also been shown to be effective in the treatment of drug resistant TB. Two studies showed that for drug resistant TB patients that are susceptible to pyrazinamide, ethambutol, or streptomycin, the addition of these medicines improves prognosis. However, ethambutol should not be included as one of the four main medicines that form the basis of treatment for drug resistant TB. [5]

6. Whether listing is requested as an individual medicine or as representative of a pharmacological class.

Listing is requested as an individual medicine. According to WHO Guidelines, first line drugs for the treatment of susceptible tuberculosis (Isoniazid, Rifampicin, Pyrazinamide, Ethambutol) are widely available in their oral forms, however are not yet presented as IV preparations.

7. Treatment details (requirements for diagnosis, treatment and monitoring).

According to WHO guidelines [6], IV formulations should be reserved for cases of severe forms of disease, such as central nervous system (CNS) TB or TB sepsis. [7]

I.e. IV ethambutol should be considered for the patients with severe forms of the disease (TB meningitis, TB sepsis), patients with acute or chronical gastrointestinal diseases, or patients with reduced absorption rates of oral forms (malabsorption in PLWH [19-223]). Patients that are unable (unconscious patients in ICU or in coma [47]) or unwilling to take drugs in periods of depression or due to acute manifestations of altered mental condition. [17] Patients with severe comorbidities: HIV/TB, diabetes/TB [46], etc.

Necessary conditions for intravenous infusion of anti-tuberculosis preparations:

• Placement of an implanted port or peripherally inserted central catheter (PICC) line (a non-tunneled venous catheter)

• Using intravenous (IV) therapy to infuse injectable drugs for 30 to 60 minutes, 5 days per week

• Direct observation of ingestion of prescribed oral anti-TB drugs

• Monitoring for adverse reactions and reporting these to the supervising physician

•Extensive patient education and support to help ensure adherence

IV therapy may be given via an implanted port (placed surgically under the skin, usually in the chest) or by PICC line (placed in the forearm and threaded into the superior vena cava). Both methods have their advantages and disadvantages, and the choice is usually made by the physician based upon the needs of the patient. [53]

Study results indicate the possibility of simultaneous administration of a mixture of isoniazid and ethambutol when the preparation of the mixture was not more than 16 hours prior to administration and mixtures of ethambutol + levofloxacin and ethambutol + moxifloxacin with the preparation of the mixture no more than 24 hours before administration. [54]

8. Information supporting the public health relevance

Epidemiological information on disease burden

Globally, an estimated 10.0 million (range, 8.9–11.0 million) people fell ill with TB in 2019, a number that has been declining very slowly in recent years. There were an estimated 1.2 million (range, 1.1–1.3 million) TB deaths among HIV-negative people in 2019 (a reduction from 1.7 million in 2000), and an additional 208 000 deaths (range, 177 000–242 000) among HIV-positive people (a reduction from 678 000 in 2000). Men (aged under 15 years) accounted for 56% of the people who developed TB in 2019; women accounted for 32% and children (aged under 15) for 12%. Among all those affected, 8.2% were people living with HIV. [1]

Assessment of current use

According to WHO guidelines for susceptible tuberculosis treatment, both pulmonary and extra-pulmonary forms of drug susceptible TB have to be treated with daily dosing of 6-month rifampicin-based regimen 2HRZE/4HR, with the only difference that adjuvant corticosteroid therapy should be considered in case of TB meningitis.

According to the last WHO Model List of Essential Medicines (2019), only oral forms of first line anti-tuberculosis drugs are included [9].

Target population(s)

Several studies show that there is a decrease in the functional absorptive area of the intestine in TB patients, which would explain the reduced serum concentrations of anti-tuberculosis drugs. Patients with malabsorption syndrome don't get the minimum therapeutic level of anti-tuberculosis drugs, therefore such patients have to be treated or with higher doses of these drugs, what will cause higher level of adverse reactions from gastrointestinal system, or another dosage form should be considered. [10-11, 23-34]

Although most HIV-infected patients with tuberculosis (TB) respond well to rifampin-based anti-mycobacterial drug regimens [18], recent reports suggest that malabsorption of anti-mycobacterial drugs occurs in selected HIV-infected patients, particularly those with advanced HIV infection [19-23]

Up to 70% of admissions to ICU with active tuberculosis have acute respiratory failure (ARF) and require mechanical ventilation. [12] Mortality rate for such patients according to a retrospective cohort study in Brazil is up to 80%. The causes of ARF in most of the cases are miliary lesions in lungs. [13]

Other causes of TB death are Mycobacterium tuberculosis sepsis in immunocompromised patients [41-42], tuberculous pericarditis [45] and tuberculous meningitis [40].

9. Review of benefits: summary of comparative effectiveness in a variety of clinical settings.

Intravenous first line drugs for TB treatment are not available in most of the countries. However, IV forms ensure the quickest and the most complete access of the medicinal substance to the foci of TB infection. Ethambutol peak plasma concentrations range from 3.25 to 5.62 mcg/ml when ethambutol is

given orally, comparing to the peak of 11.6 to 15.4 mg/ml when ethambutol is introduced by intravenous infusion. [35-36]

Intravenous anti-TB drugs are essential for treating different categories of TB patients, including those with severe disseminated TB and gastrointestinal impairments for whom oral anti-TB agents might not be effective. In some cases, this is caused by quick decomposition of the drugs during their relatively slow intake from the gastrointestinal tract and, in others, by the impossibility of increasing the dose. In the case of intravenous administration, the drugs are easily resorbed, which leads to the creation of higher concentrations in the infected tissues. [14]

10. Review of harms and toxicity: summary of evidence on safety.

Several groups active during the early clinical assessment of ethambutol (EMB) commented upon the difficulties encountered in assessing the development of ocular toxicity due to EMB [15]. Even among patients who were not receiving EMB, changes in visual acuity were quite commonly documented, and in several clinical trials where the clinicians were blinded to the allocation of patients, ocular "toxicity" was recorded among the control groups. The possibility of toxicity would be sufficient to prompt careful clinicians to stop the drug; authors of a small study referred to this as a "psychological" hazard. [48]

Early studies of the use of EMB tended to be fairly precise in describing how toxicity was assessed; by contrast, some later studies either make no specific mention of ocular toxicity and its assessment, or carried out formal assessment only if patients presented with complaints of visual disturbances. Nevertheless, there is no doubt that the ocular toxicity of EMB is dose-related and that, although incidence declines as the dose declines, ocular toxicity has been encountered at all EMB doses in clinical use.

Disturbingly, more refined ophthalmological testing – by ophthalmologists – of patients receiving EMB has revealed more frequent abnormalities than is the case following a more superficial clinical evaluation [49, 50] The importance of these abnormalities is uncertain, as is the potential for zinc deficiency to precipitate ocular toxicity in patients receiving EMB. At least one study found a considerably higher incidence of ocular toxicity among patients with low zinc concentrations [50]. In another study [51] it was found no difference in the serum concentrations of copper or zinc after 2 months of treatment with EMB at 25 mg/kg. Children with tuberculosis, particularly those with HIV/AIDS, are very likely to be zinc-deficient . [16]

Unfortunately there is no published information about specific side effects of ethambutol due to iv route of administration, it is assumed that all side effects may be similar to those that occur with prolonged infusions - inflammation and pain at the catheter insertion site, the risk of infection and thrombosis, but all these phenomena should be studied in a special study. However, a small study indicated that long-term infusions with isoniazid and rifampicin did not produce specific route-of-administration side effects. [52] There is a small study describing possibility to decrease side effects related by using iv route of administration of 2nd-line anti-TB drugs in MDR-TB patients, such as pain in the place of injection and phlebitis, by using port-catheter for intensive intravenous chemotherapy. [53]

11. Summary of available data on comparative cost and cost- effectiveness within the pharmacological class or therapeutic group.

There is no shown evidence in pharmacoeconomic convenience of IV ethambutol, considering rare presence of IV ethambutol on most of the world markets, because of the absence in EML and EMLc.

According to available online data on the prices, we suppose that injectable dosage form of ethambutol can be more expensive than the oral form.
In Ukraine iv ethambutol 1000 mg is about $ 2-3 / vial, and iv ethambutol 2000 mg is about $ 3-3.5 / vial.
In Kazakhstan iv ethambutol 1000 mg is about $ 5-6 / vial.
In France iv ethambutol 1000 mg is registered but there is no information about price per vial.
Median price for oral form of ethambutol is $ 0.029-0,0375 / tab 400 mg in GDF stock [45] and can reach $1 / tab 400 mg in the pharmacies. But it shouldn't be considered as an alternative drug, because oral forms cannot provide the same benefits for people affected by severe forms of tuberculosis.
Another point is that the appearance of intravenous ethambutol in the list of EML
and EMLc will stimulate the manufacturers to produce IV ethambutol and the concurrence will decrease the prices for the treatment course.

12. Summary of regulatory status of the medicine

Ethambutol 1000 mg is approved for use in countries under EMA regulation (France) and 1000 mg and 2000 mg in Ukraine, Uzbekistan, Tajikistan, Kazakhstan, Moldova.

13. Availability of pharmacopoeia standards (British Pharmacopoeia, International Pharmacopoeia, United States Pharmacopoeia, European Pharmacopeia).

Ethambutol reference standards are available according to BP, IP, USP, EP.

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