Application for inclusion of intravenous isoniazid in the WHO Model List of Essential Medicines 2019 (Core list)

Submitted by

INCURE CU

To: Expert Committee on the Selection and Use of Essential Medicines
1. Summary statement of the proposal for inclusion, change or deletion

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

Isoniazid, the hydrazide of isonicotinic acid, is highly bactericidal against replicating tubercle bacilli. It is rapidly absorbed and diffuses readily into all fluids and tissues. The plasma half-life, which is genetically determined, varies from less than one hour for fast acetylators to more than three hours for slow acetylators. Isoniazid is largely excreted in the urine within 24 hours, mostly as inactive metabolites. According to WHO guidelines 2017, Isoniazid is normally taken orally but may be administered intramuscularly or intravenously to critically ill people. [1]

The EML and EMLc already contain preparations of oral Isoniazid. This application proposes IV isoniazid for the core list of WHO Model List of Essential Medicines, as a lifesaving medicine for the following categories:

1. Patients with severe forms of tuberculosis with poor outcomes, requiring intensive treatment (Miliary TB [35,36], caseous pneumonia[37], TB meningitis [38], TB sepsis [39-40], TB pericarditis[43]).
2. Patients with acute or chronical gastrointestinal diseases, or patients with reduced absorption rates of oral forms (malabsorption in PLWH [17-21]).
3. Patients with severe comorbidities: HIV/TB, diabetes/TB [45], etc.
4. Patients that are unable (unconscious patients in ICU or in coma) 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 isoniazid is not available on most of the markets. The absence of IV isoniazid 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

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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,
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 University of Ceará, Fortaleza, Ceará, Brazil,
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4. **International non-proprietary name of the medicine (INN, generic name) of the medicine**

ISONIAZID

5. **Formulation proposed for inclusion**

The EML and EMLc already contain preparations of oral Isoniazid. This application is for the additional inclusion of powder for injections/solution for injections Isoniazid 300 mg, 500 mg, 900 mg.

300 mg of Isoniazid is maximum recommended daily dose and it can be used as a fast and well-tolerated remedy for severe cases of tuberculosis. According to different sources (FDA, AHFS monograph, guidelines), isoniazid can be used up to 900 mg daily in intermittent regimen thrice a week. [2-5]

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

Listing is requested for a medicine representing a pharmacological class. 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 I.V. preparations.

7. **Treatment details (requirements for diagnosis, treatment and monitoring).**
According to WHO guidelines [5], IV formulations should be reserved for cases of severe forms of disease, such as central nervous system (CNS) TB or TB sepsis. [6] I.V. isoniazid is also recommended for use by American Thoracic Society. [7] I.e. IV isoniazid should be considered for the patients with severe forms of the disease (TB meningitis, TB sepsis), patients with acute or chronic gastrointestinal diseases, or patients with reduced absorption rates of oral forms (malabsorption in PLWH [18-22]). Patients that are unable (unconscious patients in ICU or in coma [46]) or unwilling to take drugs in periods of depression or due to acute manifestations of altered mental condition. [16] Patients with severe comorbidities: HIV/TB, diabetes/TB [45], 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. [41]

8. Information supporting the public health relevance

Epidemiological information on disease burden

In 2017, TB caused an estimated 1.3 million deaths (range, 1.2–1.4 million) among HIV-negative people and there were an additional 300 000 deaths from TB (range, 266 000–335 000) among HIV-positive people.

Globally, the best estimate is that 10.0 million people (range, 9.0–11.1 million) developed TB disease in 2017: 5.8 million men, 3.2 million women and 1.0 million children. There were cases in all countries and age groups, but overall 90% were adults (aged ≥15 years), 9% were people living with HIV (72% in Africa) and two thirds were in eight countries: India (27%), China (9%), Indonesia (8%), the Philippines (6%), Pakistan (5%), Nigeria (4%), Bangladesh (4%) and South Africa (3%). These and 22 other countries in WHO’s list of 30 high TB burden countries accounted for 87% of the world’s cases. Only 6% of global cases were in the WHO
European Region (3%) and WHO Region of the Americas (3%). The severity of national epidemics varies widely among countries. In 2017, there were fewer than 10 new cases per 100,000 population in most high-income countries, 150–400 in most of the 30 high TB burden countries, and above 500 in a few countries including Mozambique, the Philippines and South Africa. Drug-resistant TB continues to be a public health crisis. The best estimate is that, worldwide in 2017, 558,000 people (range, 483,000–639,000) developed TB that was resistant to rifampicin (RR-TB), the most effective first-line drug, and of these, 82% had multidrug-resistant TB (MDR-TB). Three countries accounted for almost half of the world’s cases of MDR/RR-TB: India (24%), China (13%) and the Russian Federation (10%). Globally, 3.5% of new TB cases and 18% of previously 2GLOBAL TUBERCULOSIS REPORT 2018 treated cases had MDR/RR-TB. The highest proportions (>50% in previously treated cases) are in countries of the former Soviet Union. Among cases of MDR-TB in 2017, 8.5% (95% confidence interval, 6.2–11%) were estimated to have extensively drug-resistant TB (XDR-TB). About 1.7 billion people, 23% of the world’s population, are estimated to have a latent TB infection, and are thus at risk of developing active TB disease during their lifetime. [47]

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. The fact of death from tuberculosis is usually confirmed in Intensive care unit (ICU). [8]

**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 (March 2017), 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], [26-34]
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%. [13] The causes of ARF in most of the cases are miliary lesions in lungs.

Other causes of TB death are Mycobacterium tuberculosis sepsis in immunocompromised patients [39-40], tuberculous pericarditis [43] and tuberculous meningitis [38].

Tuberculous meningitis (TBM) is one of the most devastating manifestations of extra-pulmonary tuberculosis (TBEP) and is associated with severe morbidity and high mortality up to 80% of cases. [14]


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.

Intravenous anti-TB drugs are essential for treating different categories of TB patients, including those with severe disseminated and gastrointestinal TB for whom oral anti-TB agents alone 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 absorbed, which leads to the creation of higher concentrations in the infected tissues. [15]


Isoniazid efficiency/safety profile has been studied during long term period and despite it’s great anti-mycobacterial activity it can cause severe hepatotoxicity. Although drug-induced liver injury (DILI) caused by different drugs is somewhat different, the clinical characteristics of INH-induced liver injury are fairly typical for idiosyncratic DILI and include malaise, fatigue, nausea and vomiting. The duration of therapy before manifestation of jaundice can vary between 1–25 weeks with an average of 12 weeks. Fever affects on average 20% of the patients and eosinophilia is present in up to 15% of the affected individuals. In most cases, liver injury is asymptomatic and is only detected by measuring markers of hepatocyte injury such as alanine aminotransferase (ALT) and aspartate aminotransferase (AST). This is especially true for mild cases of liver injury, which
occur in up to 20% of patients treated with the drug. However, in most patients, liver function returns to normal despite continued treatment with the drug, a phenomenon referred to as ‘adaptation’ by hepatologists. Severe liver injury is seen in up to 1% of the patients. Elevations in ALT and AST can start as early as 1 week and sometimes as late as 9 months after starting treatment with INH. However, in more than half of the patients an ALT increase occurs between 1–6 months. The abrupt increase in ALT that leads to liver failure is idiosyncratic in nature and is not clearly related to the duration of treatment, the dose of the drug, fever or eosinophil count. When liver injury is identified, the first line of treatment is to stop the drug and monitor the patient for recovery. In most cases patients recover. However, rechallenge of patients with more severe liver injury can result in a rapid onset of symptoms (within hours) and is contraindicated. Histological characteristics of severe INH-induced liver injury include hepatocellular injury with multi-lobular necrosis and a mononuclear cell infiltrate, which is generally indistinguishable from viral hepatitis. Steatosis is unusual in INH-induced liver injury. However, during active TB treatment, when INH is given in combination with other agents such as ethambutol, pyrazinamide and rifampicin (RMP), there have been reported cases of steatosis and cholestatic liver injury. Prolonged treatment with INH can also lead to a lupus-like autoimmune reaction with the presence of antinuclear antibodies, which occurs in up to 20% of the patients. [16]

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

There is no shown evidence in pharmacoeconomical convenience of IV isoniazid, considering following facts:

1) Low effectiveness of oral isoniazid on severe forms of tuberculosis.
2) Rare presence of IV isoniazid 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 isoniazid can be more expensive than the oral form. Median Price for oral form of Isoniazid 300 mg is 0.019 - 0.02/tab. [42] 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 isoniazid in the list of EML and EMLc will stimulate the manufacturers to produce i.v. isoniazid and the concurrence will decrease the prices for the treatment course.

12. Summary of regulatory status of the medicine

The US Food and Drug Administration (FDA) approved one IV Isoniazid 100 mg/ml in 2005.
Injectable Isoniazid is available in Italy, country under EMA regulation, Ukraine, Kazakhstan, Uzbekistan.


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

14. References

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