Application for inclusion of isoniazid syrup/oral liquid 100 mg/5 ml in the WHO Model List of Essential Medicines for Children 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 component 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.

The EML and EMLc already contain Isoniazid dispersible tablets and oral liquid 50 mg / 5 mL, however oral liquid 50 mg / 5 ml is not available in many countries in existing concentration. Dispersible tablets cannot provide exact dose of Isoniazid, considering weight of children, because they shouldn’t be divided according to instructions for use.

This application proposes extension to a Isoniazid syrup 100 mg / 5 ml for the core list of WHO EMLc as this formulation is available on a lot of markets: Ukraine, Georgia, Uzbekistan, Moldova, Tajikistan, Azerbaijan, Kazakhstan, Kyrgyzstan, Turkmenistan, Uganda, Namibia, Kenya. [1]

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

None

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

Novosibirsk TB Research Institute (NTRI), Russia,

Universitatea de Medicină și Farmacie „Grigore T. Popa” Iași, Romania

"Marius Nasta" Pneumoftiziology Institute, Romania

Kenyatta University Hospital, Kenya

Makerere University Hospital, Uganda

NATIONAL SCIENTIFIC CENTER OF PHTHISOIPULMONOLOGY, Kazakhstan

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

None
ISONIAZID

5. Formulation proposed for inclusion
Syrup / oral liquid 100 mg / 5 ml

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

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

IPT (or isoniazid prophylaxis) is most often the treatment for primary infection in order to sterilize lesions and prevent the development of active tuberculosis (TB). It is more a treatment than a prophylaxis.

It consists of the daily administration of isoniazid (H) for 6 months:

Children <5 years of age who are household or close contacts of people with TB and who, after an appropriate clinical evaluation, are found not to have active TB should be given 6 months of IPT (10 mg/kg per day, range 7–15 mg/kg, maximum dose 300 mg/day) [5]

The following dosages of isoniazid should be used daily for the treatment of susceptible TB in children:

isoniazid (H) 10 mg/kg (range 7–15 mg/kg); maximum dose 300 mg/day [7,8]

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 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. [9]

Assessment of current use

Six months’ daily monotherapy with isoniazid is the standard treatment for both adults and children living in countries with either high or low TB incidence. Several systematic reviews have demonstrated its preventive efficacy. A systematic review of RCTs involving people living with HIV [3] showed that isoniazid monotherapy reduces the overall risk for TB by 33% (RR 0.67; 95% CI 0.51;0.87), and the preventive efficacy reached 64% for people with a positive TST (RR 0.36; 95% CI 0.22;0.61). Furthermore, the efficacy of the 6-month regimen was not significantly different from that of 12 months’ daily isoniazid monotherapy (RR 0.58; 95% CI 0.3;1.12) [3]. A recent systematic review of RCTs also showed a significantly greater reduction in TB incidence among participants given the 6-month regimen than in those given a placebo (odds ratio, 0.65; 95% CI 0.50;0.83).

Target population(s)

Children and infants living with HIV

- Infants aged < 12 months living with HIV who are in contact with a case of TB and are investigated for TB should receive 6 months of isoniazid preventive treatment (IPT) if the investigation shows no TB disease. (Strong recommendation, moderate-quality evidence. Updated recommendation)
- Children aged ≥ 12 months living with HIV who are considered unlikely to have TB disease on the basis of screening for symptoms and who have no contact with a case of TB should be offered 6 months of IPT as part of a comprehensive package of HIV prevention and care if they live in a setting
with a high prevalence of TB. (Strong recommendation, low-quality evidence. Existing recommendation)

- All children living with HIV who have successfully completed treatment for TB disease may receive isoniazid for an additional 6 months. (Conditional recommendation, low-quality evidence. Existing recommendation)

HIV-negative household contacts

- HIV-negative children aged < 5 years who are household contacts of people with bacteriologically confirmed pulmonary TB and who are found not to have active TB on an appropriate clinical evaluation or according to national guidelines should be given TB preventive treatment. (Strong recommendation, high-quality evidence. Updated recommendation)

- In countries with a high TB incidence, children aged ≥ 5 years, adolescents and adults who are household contacts of people with bacteriologically confirmed pulmonary TB who are found not to have active TB by an appropriate clinical evaluation or according to national guidelines may be given TB preventive treatment. (Conditional recommendation, low-quality evidence. New recommendation) [4]

Treatment of TB in children Isoniazid 10 mg/kg (range 7–15 mg/kg); maximum dose 300 mg/ day [5]

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

Children-friendly IPT is currently available in forms of syrup/oral liquid and dispersible tablets. Dispersible tablets cannot provide exact dose of Isoniazid, considering weight of children, because they shouldn’t be divided according to instructions for use. Isoniazid syrup/oral liquid 100 mg/5 ml is already available in following countries: Ukraine, Georgia, Uzbekistan, Moldova, Tajikistan, Azerbaijan, Kazakhstan, Kyrgyzstan, Turkmenistan, Uganda, Namibia, Kenya.

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

Isoniazid efficiency/safety profile has been studied during long term period and despite it’s great antimycobacterial 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 multilobular 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 7-9. 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. [5]

There are two major adverse reactions to INH: neurologic and hepatic. Both are rare in children. The level of INH at any given dosage in children and adults depends on whether the patient is a fast, intermediate or slow acetylator. This is determined by the N-acetyltransferase 2 genotype which differs between ethnic groups [6].

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

Isoniazid oral liquid 50 mg/5 ml is less convenient than oral liquid 100 mg/5 ml because it requires more volume for the same quantity of active ingredient. This makes storage and transportation more expensive. Variety in available products for IPT will stimulate pharmaceutical companies to lower the prices.

12. Summary of regulatory status of the medicine
Isoniazid syrup/oral liquid 100 mg/5 ml is available in Ukraine, Georgia, Uzbekistan, Moldova, Tajikistan, Azerbaijan, Kazakhstan, Kyrgyzstan, Turkmenistan, Uganda, Namibia, Kenya.


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

14. References


3. WHO Latent TB Infection : Updated and consolidated guidelines for programmatic management 2018


