Application for inclusion of intravenous rifampicin 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**

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

A semisynthetic derivative of rifamycin, a complex macrocyclic antibiotic that inhibits ribonucleic acid synthesis in a broad range of microbial pathogens. It has bactericidal action and a potent sterilizing effect against tubercle bacilli in both cellular and extracellular locations. [1]

The EML and EMLc already contain preparations of oral rifampicin. This application proposes IV rifampicin 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 chronic gastrointestinal diseases, or patients with reduced absorption rates of oral forms (malabsorption in PLWH [18-22]).
3. Patients with severe comorbidities: HIV/TB, diabetes/TB [44], etc.
4. 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]

Currently, intravenous rifampicin is not available on most of the markets. The absence of IV rifampicin in both EML and EMLc leads to low interest in production of this dosage form and prevents the addition of it in tender drug lists of national and international TB programs.

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

Dr Ernesto Jaramillo  
MDR-TB Policy & Innovations department  
World Health Organization  
Geneva, Switzerland  
Email: jaramilloe@who.int

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

**RIFAMPICIN**

5. **Formulation proposed for inclusion**

The EML and EMLc already contain preparations of oral Rifampicin. This application is for the additional inclusion of an intravenous (IV) preparation of Rifampicin 450 or 600 mg, powder for injections.

600 mg of Rifampicin is currently 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, triple dose of rifampicin can be used combined with other TB drugs for 30 days for the treatment of TB meningitis, showing survival benefit with no significant damage to patient’s safety. [2-4]

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 IV 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] IV. rifampicin is also recommended for use by American Thoracic Society. [6] I.e. IV rifampicin 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 [18-33]). Patients that are unable (unconscious patients in ICU or in coma [6]) 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) [2] 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. [46]

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). [7]

**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 [8].

**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. [9-10], [23-33]

Although most HIV-infected patients with tuberculosis (TB) respond well to rifampin-based anti-mycobacterial drug regimens [17], recent reports suggest that malabsorption of anti-mycobacterial drugs occurs in selected HIV-infected patients, particularly those with advanced HIV infection [18-22].

Up to 70% of admissions to ICU with active tuberculosis have acute respiratory failure (ARF) and require mechanical ventilation. [11] Mortality rate for such patients according to a retrospective cohort study in Brazil is up to 80%. [12] 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, 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. [13]

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

Injectable 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.

Rifampicin peak plasma concentrations range reaches 8.9 mcg/ml when Rifampicin is given orally, comparing to the peak of 22.9 mg/ml when Rifampicin is introduced by intravenous infusion. [34]

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. [14]

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

HUMAN EXPOSURE: The main target organs are the liver and the gastrointestinal system. Risks of concern are toxic hepatitis with elevation of bile and bilirubin concentrations, anaemia, leukopenia, thrombocytopenia and bleeding. Summary of clinical effects: Some clinical manifestations of overdosage are extension of adverse effects. During therapy, rifampicin is usually well tolerated, however, adverse side-effects are common in intermittent rifampicin intake. These include febrile reaction, eosinophilia, leukopenia, thrombocytopenia, purpura, hemolysis and shock, hepatotoxicity and nephrotoxicity. Gastrointestinal adverse reactions may be severe leading to pseudomembranous colitis. Neurotoxic effects include confusion, ataxia, blurring of vision, dizziness and peripheral neuritis. A common toxic effect is red skin with orange discoloration of body fluids. Fatalities from adverse reactions have been reported. Rifampicin has shown no significant effects on the human fetus. It diffuses into milk and other body fluids. Contraindications: Rifampicin is contraindicated in known cases of hypersensitivity to the drug. It may be contraindicated in pregnancy (because of teratogenicity noted in animal studies and since the effects of drugs on fetus has not been established) except in the presence of a disease such as severe tuberculosis. It is contraindicated in
alcoholics with severely impaired liver function and with jaundice. Routes of entry: Oral: This is the common route of entry. Eye: Use for ocular chlamydial infection treatment. Parenteral: Rifampicin may be given intravenously. [15]

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

There is no shown evidence in pharmaco economical convenience of i.v. rifampicin, considering following facts:

1) Low effectiveness of oral rifamicin on severe forms of tuberculosis.

2) Rare presence of i.v. rifampicin 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 rifampicin can be more expensive than the oral form. Median Price for oral form of rifampicin is 0,06-0,19 usd/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 rifampicin in the list of EML and EMLc will stimulate the manufacturers to produce IV rifampicin and the concurrence will decrease the prices for the treatment course.

12. **Summary of regulatory status of the medicine**

I.V. Rifampicin is available in the United States, country under FDA regulation.

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

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

14. **References**

1. WHO Model Prescribing Information: Drugs Used in Mycobacterial Diseases (1991; 44 pages)
3. E. Aarnoutse, R & S. Kibiki, G & Reither, Klaus & H. Semvua, H & Haraka, Fredrick & Mtabho, Charles & Mpagama, Stellah & van den Boogaard, J & M. Sumari-de Boer, I & Magis-Escurra, Cecile & Wattenberg, M & Logger,


7. The causes of death among patients with tuberculosis; Ljiljana Simonovska, Mirjana Trajcevska, Vladimir Mitreski, Iva Simonovska; European Respiratory Journal Sep 2015, 46 (suppl 59) PA2713; DOI: 10.1183/13993003.congress-2015.PA2713


24. Todoriko L.D., Pidverbetska O.V. Clinical features of the drug susceptible, multi drug resistant and HIV-associated pulmonary tuberculosis depending on the degree of colon dysbiosis / Science and Education a New Dimension.


