Application for inclusion of intravenous Para-aminosalicylic acid (PAS) 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**

Para-aminosalicylic acid (INN aminosalicylic acid; PAS) is a bacteriostatic chemotherapeutic agent used in the therapy of all forms of tuberculosis, both pulmonary and extrapulmonary, caused by sensitive strains of the mycobacteria resistant to other antituberculotics or if the patient is intolerant towards other drugs. Since its clinical introduction in the late 1940s aminosalicylic acid (PAS) has been a mainstay in the treatment of TB into the 1960s. Along with isoniazid and streptomycin, it was a 'first-line' agent for tuberculosis. However, it was plagued by poor gastro-intestinal tolerance and rare but severe allergic reactions. [1]

The EML and EMLc already contain preparations of oral PAS. This application proposes IV PAS 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 sepsis [38-39], TB pericarditis [42], TB meningitis [12]).
2. Patients with acute or chronical 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 [43], etc.
4. Patients that are unable (unconscious patients in ICU or in coma [44]) or unwilling to take drugs in periods of depression or due to acute manifestations of altered mental condition. [16]

Currently, intravenous PAS is not available on most of the markets. The absence of IV PAS 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**

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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
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

Novosibirsk TB Research Institute (NTRI), Russian Federation,

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

Centers for Diseases Control and Prevention, US

Universitas Padjadjaran Department of Pharmacology therapy, Indonesia.

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

Para-aminosalicylic acid

5. **Formulation proposed for inclusion**

The EML and EMLc already contain preparations of oral PAS. This application is for the additional inclusion of an intravenous (IV) preparation of Powder for injections 3 g, 9 g and 12 g

PAS can be used as a fast and well-tolerated remedy for severe cases of tuberculosis. A 12 g daily dose of gastro-resistant PAS should be the preferred dose in hospital settings, where it remains the best regimen to cover the around-the-clock suppression of mycobacteria based on the minimal inhibitory concentration for PAS. [2-4]

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).**

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.e. IV PAS 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 [17-21]). Patients that are unable (unconscious patients in ICU or in coma [44]) or unwilling to take drugs in periods of depression or due to acute manifestations of altered mental condition. [15] Patients with severe comorbidities: HIV/TB, diabetes/TB [43], 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.

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. [45]

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). [6]

**Assessment of current use**

According to WHO guidelines for MDR-TB treatment, both pulmonary and extra-pulmonary forms of drug resistant TB may be treated with regimens containing PAS as a group C drug.

According to the last WHO Model List of Essential Medicines (March 2017), only oral forms of PAS is included [7].

**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. [8-19]

Although most HIV-infected patients with tuberculosis (TB) respond well to rifampin-based anti-mycobacterial drug regimens [16], recent reports suggest that malabsorption of anti-mycobacterial drugs occurs in selected HIV-infected patients, particularly those with advanced HIV infection [17-21]

Up to 70% of admissions to ICU with active tuberculosis have acute respiratory failure (ARF) and require mechanical ventilation. [10] Mortality rate for such patients according to a retrospective cohort study in Brazil is up to 80%. [11] 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. [42]
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. [12]


Intravenous second line drugs for TB treatment are not available in most of the countries. However, i.v. forms ensure the quickest and the most complete access of the medicinal substance to the foci of TB infection.

Using intravenous infusion the initial plasma levels of aminosalicylic acid of 400 μg/ml or higher could be attained [33-34].

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. [13]


In one retrospective study of 7492 patients on rapidly absorbed aminosalicylic acid preparations, drug-induced hepatitis occurred in 38 patients (0.5%); in these 38 the first symptom usually appeared within three months of the start of therapy with a rash as the most common event followed by fever and much less frequently by GI disturbances of anorexia, nausea or diarrhea. Only one patient was diagnosed on routine biochemistry.

Premonitory symptoms in 90% of these 38 patients preceded jaundice by a few days to several weeks with the mean time of onset 33 days with a range of 7-90 days. Half of the adverse reactions occurred during the third, fourth or fifth weeks. When aminosalicylic acid-induced hepatitis was diagnosed, hepatomegaly was invariably present with lymphadenopathy in 46%, leucocytosis in 79%, and eosinophilia in 55%. Prompt recognition with discontinuation led to the recovery of all 38 patients. If recognized in the premonitory stage, the reaction is reported to "settle" in 24 hours and no jaundice ensues. From other reported studies failure to recognize the reaction can result in a mortality of up to 21%. The patient must be monitored carefully during the first three months of therapy and treatment must be discontinued immediately at the first sign of a rash, fever or other premonitory signs of intolerance.

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 i.v. PAS, considering following facts:

1) Low effectiveness of oral PAS on severe forms of tuberculosis.
2) Rare presence of i.v. PAS 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 intravenous dosage form of PAS can be more expensive than the oral form. Median Price for oral form of PAS 4 g mg is 1.32 – 1.33 per unit. [41]

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 PAS in the list of EML and EMLc will stimulate the manufacturers to produce IV. PAS and the concurrence will decrease the prices for the treatment course.

12. Summary of regulatory status of the medicine

Intravenous PAS (powder for solution for infusions) is available in countries under EMA regulation (Germany) and in Belarus, Ukraine.


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

13. References

2. WHO treatment guidelines for drug-resistant tuberculosis 2016
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