Essential Medicines List (EML) 2021

Application for the inclusion of pyrazinamide 500mg tablet in the WHO Model List of Essential Medicines, as a drug for the treatment of tuberculosis

General items

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

This application concerns the updating of the forthcoming WHO Model List of Essential Medicines (EML) to add a 500mg formulation of pyrazinamide, complementing the 400mg formulation that is currently listed. This application proposes an amendment to the core list in section 6.2.5 Antituberculosis medicines as per the latest edition of the core EML (21st edition)[i].

This application is not proposing to add any new medicines to the EML but only to include an additional formulation of an already listed medicine. Pyrazinamide has been an antituberculosis medicines on the core list of the EML for more than two decades, having been listed since 1995. Regimens including pyrazinamide are recommended by WHO guidelines for treatment of both drug-susceptible (DS) and drug-resistant (DR) tuberculosis (TB).[ii,iii,iv] The main reason for the addition of a 500mg pyrazinamide tablet is to reduce pill-burden, to the benefit of adherence to treatment.

2. Relevant WHO technical department and focal point (if applicable).

The WHO Global TB Programme, Geneva, Switzerland has collaborated in the preparation of this application and the focal points are Dr Fuad Mirzayev and Dr Kerri Viney.

3. Name of organization(s) submitting the application.

The application is made by Dr Jennifer Furin of Harvard Medical School, Boston USA and Dr Brian Kaiser of the Global Drug Facility, Stop TB Partnership in Geneva, Switzerland in collaboration with the TB Procurement and Market-Shaping Action Team (TPMAT).

4. International Nonproprietary Name (INN) and Anatomical Therapeutic Chemical (ATC) code of the medicine.

INN	ATC
Pyrazinamide	J04AK01

5. Dose forms(s) and strength(s) proposed for inclusion; including adult and age-appropriate paediatric dose forms/strengths (if appropriate).

The proposed formulation is a 500mg tablet of pyrazinamide.

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

The application is for the inclusion of the 500mg tablet formulation drug as an individual medicine.

Treatment details, public health relevance and evidence appraisal and synthesis

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

Pyrazinamide is a mainstay of therapy for the treatment of DS-TB and for many forms of DR-TB. For DS-TB it is recommended as part of a four-drug regimen consisting of isoniazid, rifampicin, pyrazinamide, and ethambutol and is given at a dose of 30-35mg/kg/day for the first 2 months of treatment (intensive phase).[v] The WHO guideline recommends that treatment of DS-TB use fixed-dose combination (FDC) products whenever possible.[vi] Pyrazinamide single formulations are reserved for when FDCs cannot be used, for example in people living with HIV on a protease inhibitor where there is a drug-drug interaction with the rifampicin component of the FDC.

For DR-TB, it is recommended as part of a standard, short-course regimen consisting of high-dose isoniazid, ethambutol, bedaquiline, levofloxacin, clofazimine, pyrazinamide, and ethionamide, and it is given at a dose of

30-35mg/kg/day for 9 to 12 months.[vii] Pyrazinamide is also a group C drug in the longer, all-oral regimen for DR-TB (18-20-month regimen) for those who do not qualify for the standard shorter-regimen.[viii] Pyrazinamide is also a key component of the regimen for isoniazid resistant, rifampicin susceptible TB, in which it is used throughout the 6 months (6(H)REZLfx).[ix]

Persons with TB are usually diagnosed by finding evidence of M. tuberculosis in a clinical specimen (usually sputum), which can be found either on smear microscopy, nucleic acid amplification tests (such as Xpert MTB/RIF or Truenat) or on mycobacterial culture. Sometimes the diagnosis is made clinically. Treatment is usually given with strong adherence support, often via direct observation. One of the main barriers to treatment success is the high pill burden and long duration of treatment which can lead to missed doses and poor adherence or early discontinuation of treatment. Patients receiving treatment for DS or DR-TB are usually assessed monthly for clinical progress, weight gain, bacteriologic clearance (via monthly sputum smear or culture) and via other forms of laboratory tests—especially liver function testing given that pyrazinamide can cause a transaminitis.

8. Information supporting the public health relevance.

Epidemiological information on disease burden

Tuberculosis 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).[x] 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). About a quarter of the world's population is infected with M. tuberculosis with the lifetime risk of developing TB disease about 5–10% among those infected.[xi]

Globally, an estimated 10.0 million people fell ill with TB in 2019, a number that has been declining very slowly in recent years.[xii] There were an estimated 1.2 million TB deaths among HIV-negative people in 2019, and an additional 208,000 deaths among HIV-positive people.[xiii] Men (aged ≥15 years) accounted for 56% of the people who developed TB in 2019; women accounted for 32% and children (aged <15 years) for 12%.[xiv] Among all those affected, 8.2% were people living with HIV.[xv] Drug-resistant TB continues to be a public health threat. Worldwide in 2019, close to half a million people developed rifampicin-resistant TB (RR-TB), of which 78% had multidrug-resistant TB (MDR-TB).[xvi]

Globally, the TB incidence rate is falling, but not fast enough to reach the 2020 milestone of the WHO End TB Strategy of 20% reduction between 2015 and 2020. The cumulative reduction from 2015 to 2019 was 9%.[xvii] Similarly, the annual number of TB deaths is falling but not fast enough to reach milestone of a 35% reduction between 2015 and 2020. The cumulative reduction between 2015 and 2019 was only 14%.[xviii]

TB is curable and preventable. About 85% of people who develop DS-TB disease can be successfully treated with a 6-month drug regimen; and this figure is 57% for those with multi-drug resistant TB.[xix] Treatment has the additional benefit of curtailing onward transmission of infection. Preventive treatment is also available for people with TB infection. Prevention of new infections of *Mycobacterium tuberculosis* and their progression to TB disease is critical to reduce the burden of ill health and death caused by TB, and to achieve the End TB Strategy targets set for 2030 and 2035.

Estimate of total patient exposure to date

Pyrazinamide was first synthesized in 1936 and was first used in the treatment of TB in the 1950s.[xx] It was primarily used as a second-line drug until the 1970s when additional information on dosing and duration made

it a main stay in first-line treatment.[xxi] It remains a core second-line medicine in the treatment of DR-TB. Effectively, every person treated for TB since the 1970s should have received pyrazinamide at some disease point.

Target population(s)

More than 7 million people take pyrazinamide for TB each year.[xxii] The target populations are people of all ages diagnosed with DS-TB, isoniazid resistant, rifampicin susceptible TB, or for DR-TB for patients who qualify for the 9-11 month, WHO-recommended regimen.

Assessment of current use

In 2019, 7.1 million people were started on treatment for DS or DR-TB with regimens that contain pyrazinamide.[xxiii]

Likely impact of treatment on the disease

Pyrazinamide is a core therapeutic agent for all forms of TB, and its use is necessary to achieve non-relapsing cure for people with TB.[xxiv,xxv] Not only is the drug necessary for individual health, but it is an essential agent for the treatment of TB from a public health point of view, contributing to reduction of morbidity and mortality as well as a reduction of ongoing transmission. The WHO recommends a dose of 30-35mg/kg/day.[xxvi] The current formulation of pyrazinamide on the EML is a 400mg tablet. In an email communication with the WHO Secretariat it was noted that in 1995 the Model List initially listed 500mg tablet. However, in the following update (1997) the 500-mg tablet was replaced by a 400-mg tablet. The rationale for the change of the formulation is not reported in the 1997 Technical Report Series. This tablet is not convenient for many people with TB at the recommended WHO dosing, as it requires to use several pills (four or five in most cases) to reach the target daily dose. This higher pill burden could lead to adherence challenges, poor treatment outcomes, and the development of pyrazinamide resistance. The 500mg tablet allows reducing the pill burden, optimising the daily dose.

9. Review of benefits: summary of evidence of comparative effectiveness.

There is a strong need to include the 500mg tablet formulation of pyrazinamide. As noted, the WHO recommends a dose of 30-35mg/kg/day. A sample dosing table based on weight bands is shown below, with a comparison of the number of 400mg tablets versus 500mg tablets. Of note, with the 400mg formulation, the pill burden is higher for those over the weight of 30kg. It is well documented in the scholarly literature that a higher pill burden is associated with lower rates of treatment adherence, which could lead to poor treatment outcomes, increased morbidity and mortality, the development of drug resistance, and further ongoing transmission of TB.[xxvii]

Weight Band	WHO-recommended dose	Number of 400mg tablets	Number of 500mg tablets
30-35kg	1000-1200mg/day	3	2
36-45kg	1500-1600mg/day	4	3
46-55 kg	1500-1600mg/day	4	3
56-70kg	1500-1600mg/day	4	3
>70kg	2000mg/day	5	4

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

Pyrazinamide has been used in the treatment of TB for more than 50 years and its safety and efficacy have been well established. The pharmacokinetics and pharmacodynamics, (e.g., absorption, exposure, clearance

and safety) have been well established and confirmed in recent studies including in people living with HIV and other comorbidities.[xxviii,xxix,xxx,xxxi,xxxii] These were studied across different formulations including the 400mg tablet and 500mg tablet.

11. Summary of available data on comparative cost and cost-effectiveness of the medicine.

The reason for the inclusion of the pyrazinamide 500mg tablet is to decrease the pill burden for patients and to allow for more accurate dosing of this medication given the WHO recommended dosing of 30-35mg/kg/day. Pyrazinamide 500mg tablets are available globally at a cost of 12.91-14.00 USD for a pack of 672 tablets and are used in several countries as the preferred formulation to facilitate daily dose scheme.[xxxiii] The 500mg tablet price is either lower or comparable to the cost of the 400mg tablet of pyrazinamide. In facts, since there will be fewer pills used, even if the price is the same, the costs for the 500mg formulation will be lower than the 400mg tablet.

Regulatory information

12. Summary of regulatory status and market availability of the medicine.

There are three suppliers of pyrazinamide 500mg tablets that are currently prequalified by the WHO's Prequalification of Medicines Programme. These include: Micro Labs (TB 172) which was prequalified 29 June 2009[xxxiv], Macloeds (TB243) which was prequalified 4 December 2012[xxxv] and Antibiotice (TB267 (a)) which was prequalified 28 February 2013[xxxvi]. Additional quality-assured suppliers are approved by the United States Food and Drug Administration.[xxxvii]

According to unpublished data from the Global Drug Facility, the largest procurer of quality-assured TB medicines and diagnostics for the public sector globally, the procurement of pyrazinamide 400mg and 500mg tablets was relatively equal between 2014 through 2017. In 2018, however, the procurement of the 500mg tablet was more than 80% of all single formulations of pyrazinamide and was more than 60% in 2019 and 2020 (partial data).

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

Pyrazinamide is listed in multiple pharmacopoeia including the United States Pharmacopeia and European Pharmacopoeia.

References

14. Comprehensive reference list and in-text citations.

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