Pyrazinamide

Essential medicine status

Section: 6. Anti-infective medicines > 6.2. Antibacterials > 6.2.5. Antituberculosis medicines

EMLc | ATC codes: J04AK01

Indication	Tuberculosis ICD11 code: 1B4Z
INN	Pyrazinamide
Medicine type	Chemical agent
List type	Core
Additional notes	WHO recommends and endorses the use of fixed-dose combinations and the development of appropriate new fixed-dose combinations, including modified dosage forms, non-refrigerated products and paediatric dosage forms of assured pharmaceutical quality.
Formulations	Oral > Liquid: 30 mg per mL (EMLc) Oral > Solid: 400 mg ; 150 mg tablet (dispersible) ; 500 mg
EML status history	First added in 1982 (TRS 685) Changed in 1997 (TRS 882) Changed in 2007 (TRS 946) Changed in 2007 (TRS 950) Changed in 2021 (TRS 1035)
Sex	All
Age	Also recommended for children
Therapeutic alternatives	The recommendation is for this specific medicine
Patent information	Patents have expired in most jurisdictions Read more about patents.
Wikipedia	Pyrazinamide
DrugBank	Pyrazinamide

Expert Committee recommendation

1. Application to include a new strength formulation (500 mg tablet) of pyrazinamide on the EML and EMLc for the treatment of tuberculosis. The Expert Committee noted that tuberculosis is a major cause of ill health and one of the top 10 causes of death worldwide. About a quarter of the world's population is infected with Mycobacterium tuberculosis, with the life-time risk of developing tuberculosis of about 5–10% among those infected. The Expert Committee noted pyrazinamide 400 mg tablet is already listed in the EML and the addition of 500 mg formulation would help reduce the pill burden for patients and may increase adherence to treatment. It also noted that pyrazinamide 500 mg is already listed in many national essential medicine lists. Therefore, the Expert Committee recommended the inclusion of the pyrazinamide 500 mg tablet formulation in the core list of the EML and EMLc for the treatment of tuberculosis. ---------- 2. Application for the deletion of various antituberculosis medicine formulations from the EML and EMLc. The Expert Committee recommended the deletion of the following formulations from the EML and/or EMLc as requested in the application, noting that they are not the most appropriate formulations for the treatment of tuberculosis, which is in line with recommendations in the current WHO tuberculosis treatment guidelines. • Amikacin: powder for injection: 100 mg, 500 mg and 1 mg (as sulfate) in vial • Amoxicillin + clavulanic acid: oral liquid 125 mg + 31.25 mg/5 mL • Isoniazid tablet (scored): 50 mg • Isoniazid + pyrazinamide + rifampicin tablet: 75 mg + 400 mg + 150 mg • Linezolid: injection for intravenous administration: 2 mg/mL in 300 mL bag; tablet 400 mg • p-aminosalicylic acid tablet: 500 mg • Pyrazinamide tablet (scored): 150 mg The Committee recommended the inclusion of amikacin injection solution 250 mg/mL, noting that injection solutions are preferred over powder for injection formulations as they do not require reconstitution for administration. To better meet the dosing needs of paediatric patients, the Committee also recommended the addition of a 100 mg/2 mL strength of

amikacin injection solution. The Committee recommended that formulation strengths rather than strengths ranges for ethambutol and isoniazid tablets be specified, as requested, to facilitate rational selection and provide better clarity for countries in making national selection decisions. The Committee recognized that dispersible tablet formulations are the preferred child-friendly formulations and provide flexible dosing options. However, because of concerns about limited uptake and availability of dispersible-tablet formulations of ethambutol, ethionamide, isoniazid and pyrazinamide in some countries, the Committee did not recommend the deletion of the oral liquid formulations of ethambutol, isoniazid and pyrazinamide, nor the 125 mg tablet formulation of ethionamide at this time. To allow countries time to transition to the adoption of the preferred, listed dispersible-tablet formulations, the Committee advised that these formulations will be deleted from the Model Lists without further consideration in 2023, unless an application is received to support their retention.

Background

1. Application to include a new strength formulation (500 mg tablet) of pyrazinamide on the EML and EMLc for the treatment of tuberculosis. Pyrazinamide 500 mg tablets were added to the EML in 1982 for the treatment of tuberculosis. In 1995, the 500 mg strength tablet was replaced by a 400 mg strength tablet, which remains listed currently. The current EML also includes 150 mg strength tablet formulations. Pyrazinamide is also included in the EML as part as single-pill combinations with ethambutol, isoniazid and rifampicin. The strength of pyrazinamide in these combination formulations is 400 mg. ---------- 2. Application for the deletion of various antituberculosis medicine formulations from the EML and EMLc. The WHO Global Tuberculosis department, and the Stop TB Partnership's Global Drug Facility carried out a comprehensive review of the 2019 Model Lists to examine the availability and appropriateness of the tuberculosis medicines and formulations listed, in the context of the latest available WHO recommendations on tuberculosis and procurement patterns. Formulations for deletion • Ethambutol: oral liquid 25 mg/mL (EMLc) • Isoniazid: oral liquid 50 mg/5 mL (EMLc); tablet (scored) 50 mg (EML and EMLc) • Pyrazinamide: oral liquid 30 mg/mL (EMLc); tablet (scored) 150 mg (EML and EMLc) • Isoniazid + pyrazinamide + rifampicin: tablet 75 mg + 400 mg + 150 mg (EML) • Amikacin: powder for injection 100 mg, 500 mg, 1 g in vial (EML and EMLc) • Amoxicillin + clavulanic acid: oral liquid 125 mg + 31.25 mg/5 mL (EMLc) • Ethionamide: tablet 125 mg (EML and EMLc) • Linezolid: injection for intravenous administration: 2 mg/mL in 300 mL bag; tablet 400 mg (EML and EMLc) • p-aminosalicylic acid: tablet 500 mg (EML and EMLc) Formulations for addition • Amikacin: injection 250 mg (as sulfate)/mL in 2 mL vial Removal of strength ranges • Ethambutol: tablet 100 mg to 400 mg (EML) • Isoniazid: tablet 100 mg to 300 mg (EML and EMLc)

Public health relevance

1. Application to include a new strength formulation (500 mg tablet) of pyrazinamide on the EML and EMLc for the treatment of tuberculosis. Globally, an estimated 10 million people fell ill with tuberculosis in 2019, a number that has been declining slowly in recent years. An estimated 1.2 million deaths caused by tuberculosis occurred among HIV-negative people in 2019 and an additional 208 000 deaths among HIV-positive people. Men (aged ≥ 15 years) accounted for 56% of the people who developed tuberculosis in 2019, women accounted for 32% and children (aged < 15 years) for 12%. Of all those affected by tuberculosis, 8.2% were people living with HIV. Drug-resistant tuberculosis continues to be a public health threat. In 2019, about half a million people developed rifampicin-resistant tuberculosis, of whom 78% had multidrug-resistant tuberculosis (1). About 85% of people who develop drug-susceptible tuberculosis and 57% who develop multidrug-resistant tuberculosis can be successfully treated with a 6-month drug regimen (1).

Benefits

1. Application to include a new strength formulation (500 mg tablet) of pyrazinamide on the EML and EMLc for the treatment of tuberculosis. The application highlighted that the proposed 500 mg strength formulation may lead to better adherence to treatment as a result of a reduced pill burden. WHO recommends a dose of 30–35 mg/kg a day for pyrazinamide. Recommended weight-band dosing for pyrazinamide with 400 mg and 500 mg strength tablets is available in TRS 1035, highlighting the lower pill burden for patients weighing more than 30 kg with the 500 mg strength formulation. A higher pill burden has been associated with lower rates of treatment adherence, which could lead to poor treatment outcomes, increased morbidity and mortality, the development of drug resistance and ongoing transmission of tuberculosis (2). ---------- 2. Application for the deletion of various antituberculosis medicine formulations from the EML and EMLc. In 2019, the Expert Committee recommended the addition of several new formulations for tuberculosis medicines for use in children be added to the core list of the EMLc, including ethambutol

and isoniazid 100 mg dispersible tablet formulations. The Committee acknowledged that quality-assured dispersible tablet formulations are preferred to oral liquid formulations and recommended that the oral liquid formulations of isoniazid and ethambutol be considered for removal from the Model Lists in 2021 (1). Thus, ethambutol, isoniazid and pyrazinamide oral liquid formulations are proposed for deletion. Ethambutol, isoniazid and pyrazinamide dispersible tablet formulations have been available from the Global Drug Facility since January 2018, March 2019 and March 2018, respectively. All are available from at least one WHO-prequalified supplier. The single-pill combination of isoniazid + pyrazinamide + rifampicin is proposed for deletion from the EML as no quality-assured supplier of this formulation has been identified. Ethambutol-containing single-pill combinations with isoniazid, pyrazinamide and rifampicin are listed and remain a suitable option with a lower pill burden for treatment of adults with drug-susceptible tuberculosis (2). Amikacin is included in the recommendations for longer regimens to treat multidrug-resistant tuberculosis, classified in Group C (to be used to complete the regimen when medicines from Groups A and B cannot be used). Amikacin is not included in recommendations for shorter regimens for treatment of drug-resistant tuberculosis (3). Amikacin powder for injection formulations 100 mg, 500 mg and 1 g are proposed for deletion, because of the unavailability of quality-assured formulations (1 g), the low efficiency in dose delivery (100 mg), and the fact that these formulations (all) require reconstitution before administration and are less preferred to liquid injection formulations. The application proposed to replace the current formulations of amikacin with a 250 mg/mL in 2 mL vial liquid injection formulation, noting that this formulation is already included on the Model Lists as an Access group antibiotic, and is available from the Global Drug Facility. Linezolid 400 mg tablet is proposed for deletion because of unavailability of quality-assured formulations. Linezolid intravenous injection 2 mg/mL is proposed for deletion because of WHO's recommendations for use of all-oral regimens to treat drug-resistant tuberculosis (3). The oral formulations of linezolid currently listed are suitable for treatment for both adults and children. Ethionamide 125 mg tablet is proposed for deletion given the availability of a preferred dispersible tablet formulation of the same strength, which is included on the Model Lists. The dispersible tablet formulation is available from the Global Drug Facility, and is available from WHO prequalified suppliers. Amoxicillin + clavulanic oral liquid (125 mg + 31.25 mg/5 mL) is proposed for deletion to consolidate the market for this medicine around the 250 mg + 62.5 mg/5mL strength formulation. This higher strength formulation is included in WHO's recommended dosing schemes (4) and enables appropriate dosing of children across age groups and it uses smaller volumes for administration than the formulation proposed for deletion. The application also proposes changes to the listing for isoniazid and ethambutol tablets, to replace strength ranges with specific strength formulations. In the case of ethambutol, 100 mg and 400 mg strength formulations deliver appropriate dosing for adults and children with tuberculosis. No quality-assured formulation within the strength range of 100 mg to 400 mg that could deliver added value to patient dosing is currently available on the market. In the case of isoniazid, 100 mg and 300 mg strength formulations are suitable to achieve appropriate dosing for adults and children. A 200 mg strength tablet formulation is available and approved in Germany; however, this formulation does not deliver added value in terms of facilitating dosing for adults or children.

Harms

1. Application to include a new strength formulation (500 mg tablet) of pyrazinamide on the EML and EMLc for the treatment of tuberculosis. Pyrazinamide has been used in the treatment of tuberculosis for more than 50 years and its safety profile is well known. The pharmacokinetics and pharmacodynamics of pyrazinamide have been confirmed in many studies involving different formulations including the 400 mg and 500 mg tablets (3–7).

Cost / cost effectiveness

1. Application to include a new strength formulation (500 mg tablet) of pyrazinamide on the EML and EMLc for the treatment of tuberculosis. Pyrazinamide 500 mg tablets are available from the Stop TB Partnership Global Drug Facility at a price of US$ 13.40–14.00 per pack. In contrast, the price for the 400 mg tablets is US$ 14.00 per pack. In both cases the pack size is 672 tablets. ----------

WHO guidelines

1. Application to include a new strength formulation (500 mg tablet) of pyrazinamide on the EML and EMLc for the treatment of tuberculosis. Regimens including pyrazinamide are recommended by WHO guidelines for treatment of both drug-susceptible and drug-resistant tuberculosis (8–10). ---------- 2. Application for the deletion of various antituberculosis medicine formulations from the EML and EMLc. The proposed changes are in alignment with recommendations in current WHO guidelines for the treatment of

drug-susceptible and drug-resistant tuberculosis.

Availability

1. Application to include a new strength formulation (500 mg tablet) of pyrazinamide on the EML and EMLc for the treatment of tuberculosis. There are three suppliers of pyrazinamide 500 mg tablets that are currently prequalified by the WHO Prequalification of Medicines Programme: Micro Labs, Macleods Pharmaceuticals Ltd and Antibiotice SA. Additional quality-assured suppliers are approved by the US Food and Drug Administration. According to unpublished data from the Global Drug Facility, the procurement of pyrazinamide 400 mg and 500 mg tablets was about equal between 2014 and 2017. In 2018, however, procurement of the 500 mg tablet was more than 80% of all single formulations of pyrazinamide and was more than 60% in 2019 and 2020, indicating that this formulation is already being procured and used, despite not being on the EML.

1. Application to include a new strength formulation (500 mg tablet) of pyrazinamide on the EML and EMLc for the treatment of tuberculosis.

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10. WHO operational handbook on tuberculosis. Module 4: treatment – drug-resistant tuberculosis treatment. Geneva: World Health Organization; 2020 (https://apps.who.int/iris/handle/10665/332398, accessed 13 August 2021).

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2. Application for the deletion of various antituberculosis medicine formulations from the EML and EMLc.

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