Isoniazid + rifapentine

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

EMLc | ATC codes: J04AC51

Indication	Latent tuberculosis ICD11 code: 1B14
INN	Isoniazid + rifapentine
Medicine type	Chemical agent
List type	Core
Formulations	**Oral > Solid:** 300 mg + 300 mg tablet (scored)
EML status history	First added 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	Isoniazid + rifapentine
DrugBank	Isoniazid, Rifapentine

Expert Committee recommendation

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 M. tuberculosis, with the life-time risk of developing active disease of about 5–10% among those infected. The Committee considered that tuberculosis preventive treatment reduces the risk of progression from tuberculosis infection to tuberculosis disease by about 60% but can be as high as 90% among certain high-risk groups. Systematic tuberculosis preventive treatment is currently recommended by WHO for target populations at high risk. Furthermore, with the commitments from governments and donors, the availability of shorter regimens is expected to facilitate uptake of tuberculosis preventive treatment. The Committee noted that WHO recommends tuberculosis preventive treatment regimens including rifapentine in combination with isoniazid as a weekly dose for 3 months (3HP) or a daily regimen for 1 month (1HP). The Committee noted that both rifapentine and isoniazid as single agents have been included as antituberculosis medicines on the core list of the EML for several years and that the effectiveness and potential harms of the two medicines are expected to be similar for the single-pill formulations and the fixed-dose combination. Therefore, the availability of rifapentine and isoniazid in a fixed-dose combination tablet would reduce the pill burden substantially and improve adherence to treatment. This fixed-dose combination should be primarily used in the 3HP regimen for individuals older than 14 years, but it may also be used for younger children able to swallow the dosage form. Individuals on shorter regimens were shown to be 1.5–3 times more likely to complete treatment, which is beneficial as it is important to maximize its effectiveness in preventing active tuberculosis. The Committee noted that countries have access to different formulations (in terms of registration, affordability and supply) and adding options may increase availability and the pool of suppliers. The Expert Committee therefore recommended adding the fixed-dose combination of isoniazid and rifapentine to the core list

of the EML and EMLc for tuberculosis preventive treatment for use in line with dosing recommendations in WHO guidelines.

Background

Single ingredient formulations of rifapentine and isoniazid are currently included on the EML.

Public health relevance

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 TB 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 (1). About a quarter of the world's population is infected with Mycobacterium tuberculosis, with the life-time risk of developing tuberculosis disease of about 5–10% among those infected (2). Tuberculosis preventive treatment is available for people with tuberculosis infection. Prevention of new infections of M. tuberculosis and their progression to tuberculosis disease is critical to reduce the burden of ill health and death caused by tuberculosis, and to achieve the End TB Strategy targets set for 2030 and 2035. Current health interventions for tuberculosis prevention, in addition to tuberculosis preventive treatment, include the prevention of transmission of M. tuberculosis through infection prevention and control, and vaccination of children with the bacille Calmette–Guérin (BCG) vaccine. Tuberculosis preventive treatment reduces the risk of progression from tuberculosis infection to tuberculosis disease by about 60% but this reduction can be as high as 90% among certain high-risk groups, such as people living with HIV (3,4). Systematic tuberculosis preventive treatment is currently recommended by WHO for: household contacts of bacteriologically confirmed pulmonary tuberculosis patients, people living with HIV, people with silicosis, people receiving dialysis or antitumour necrosis factor treatment and people preparing for haematological or organ transplantation. Depending on the country context, people with risk factors other than those mentioned above (such as prisoners, non-household close contacts and people with diabetes) can also be considered for systematic screening and tuberculosis preventive treatment. At the first UN high-level meeting on tuberculosis in 2018, Member States committed to providing tuberculosis preventive treatment to at least 30 million people in the 5-year period 2018–2022, including 6 million people living with HIV, 4 million children aged under 5 years who are household contacts of people with bacteriologically confirmed tuberculosis, and 20 million household contacts in older age groups.

Benefits

Evidence for the benefits of rifapentine and isoniazid as tuberculosis preventive treatment was reviewed in 2015 (5). The effectiveness of the single-pill combination formulation is expected to be similar to the combination use of the individual medicines as separate formulations. In general, providing tuberculosis preventive treatment to high-risk individuals prevents morbidity and mortality at the individual level and reduces the tuberculosis burden by limiting its transmission from individuals who would otherwise develop tuberculosis. Recent epidemiological data from the WHO South–East Asia region indicate that tuberculosis disease prevention at scale is an essential intervention if the End TB Strategy targets are to be met. Optimal implementation of tuberculosis preventive treatment alone in certain high-risk groups, such as household contacts or people living with HIV, has the potential to reduce the annual tuberculosis incidence rate by 8.3% (95% credible interval (CrI) 6.5 to 10.8) relative to 2015, in the absence of any additional interventions (6,7).

Harms

Evidence for the harms of rifapentine and isoniazid as tuberculosis preventive treatment was reviewed in 2015 (5). The harms associated with the single-pill combination formulation are expected to be similar to combination use of the individual medicines as separate formulations.

Cost / cost effectiveness

The median cost per person treated for drug-susceptible tuberculosis in 2019 was US$ 860 and about US$ 5660 for treatment of multidrug-resistant tuberculosis (1). Recent modelling work in the WHO South-East Asia region showed that the number of individuals at high risk of tuberculosis disease who need preventive treatment to avert one tuberculosis case is 64 (95% CrI 55 to 74) which is considered an attractive public health proposition (7). Tuberculosis preventive treatment can result in useful savings for the individual and the health system by avoiding the need for tuberculosis treatment, given the longer isoniazid monotherapy regimens needed for tuberculosis disease treatment. Further reductions in the cost of rifapentine will make this tuberculosis preventive treatment even more cost-effective. The standard regimen of 6 months isoniazid monotherapy has been the most widely used tuberculosis preventive treatment option, costing US$ 4–6 for a patient course. However, the uptake and completion of tuberculosis preventive treatment with this longer regimen has been limited (10). Furthermore, WHO considers the 3-month regimen of weekly rifapentine + isoniazid and 1-month regimen of daily rifapentine + isoniazid as equivalent options for tuberculosis preventive treatment among high-risk individuals across all epidemic settings. Individuals on shorter regimens were shown to be 1.5–3 times more likely to complete treatment, which is important to maximize its effectiveness in preventing active tuberculosis (11–14). In published literature, the cost–effectiveness of the two rifapentine-containing regimens has primarily been studied in high-income, low-burden settings using the price of Sanofi-branded rifapentine (Priftin). In high-burden, low-resource settings, researchers have found the 3-month regimen of weekly rifapentine + isoniazid with directly observed therapy prevents the greatest number of tuberculosis cases compared with other regimens for latent tuberculosis infection, but at a cost of US$ 9402 per disability-adjusted life year (DALY) averted (15). If the price of rifapentine were reduced to US$ 8, the researchers estimated the incremental cost–effectiveness ratio would decrease to US$ 535 per DALY averted. Hence, although currently more costly compared to the isoniazid-only regimen, tuberculosis preventive treatment containing rifapentine is expected to be more cost-effective option for programmes. Rifapentine although off patent, is currently only available from Sanofi, the innovator. There are no other quality-assured sources. In high-income countries, Sanofi sells the drug as a 150 mg tablet at US$ 1 per tablet or US$ 73 for a full patient course of the 3-month regimen inclusive of isoniazid. Through the Global Drug Facility, the company sells the drug for US$ 0.625 per tablet or US$ 46 per treatment course. This cost is significantly higher than the US$ 4–6 for the 6-month isoniazid regimen. Sanofi has entered into an agreement with the Global Fund to Fight AIDS, Tuberculosis and Malaria and UNITAID to reduce the price of rifapentine to US$ 15 per adult patient course for a select set of countries with a high burden of tuberculosis. The generic supplier, Macleods Pharmaceuticals, sells the single-pill combination of rifapentine 300 mg + isoniazid 300 mg, and has also entered into an agreement with the Global Fund and Unitaid to price the product at US$ 15 per patient course through a special agreement.

WHO guidelines

Regimens including rifapentine and isoniazid for tuberculosis preventive treatment are recommended by WHO for tuberculosis preventive treatment in the 2020 WHO consolidated guidelines on tuberculosis (8,9). The following options are recommended regardless of HIV status: • 6 or 9 months of daily isoniazid, or • a 3-month regimen of weekly rifapentine plus isoniazid, or • a 3-month regimen of daily isoniazid plus rifampicin, or • a 1-month regimen of daily rifapentine plus isoniazid, or • a 4-month regimen of daily rifampicin. The proposed single-pill formulation is primarily targeted for use in the 3-month weekly dosing regimen in individuals older than 14 years, in whom the recommended weekly dose is 1200 mg rifapentine + 900 mg isoniazid. The single-pill combination formulation would reduce the weekly pill burden for patients from nine tablets a week (3 x isoniazid 300 mg plus 6 x rifapentine 150 mg) to three tablets a week (9).

Availability

MacLeods Pharmaceuticals has filed the proposed formulation with multiple national drug regulatory authorities, including countries with a high burden of tuberculosis such as India and South Africa. The formulation has been submitted for assessment by the WHO Prequalification Programme. It is currently endorsed for procurement by The Global Fund’s Expert Review Panel meaning the product can be procured using Global Fund funds while the

product undergoes prequalification review. The formulation is available to eligible countries through the Global Drug Facility. A box of 36 tablets (a single treatment for an adult patient) is US$ 15. A second supplier is also at an advanced stage of development of a single-pill combination tablet of rifapentine 300 mg plus isoniazid 300 mg. The supplier has successfully completed stability and pilot bioequivalence studies on the prototype product. Once 6 months of stability information is available, the product will be submitted to WHO Prequalification Programme and the Global Fund's Expert Review Panel. The Expert Review Panel makes recommendations to the Global Fund to allow procurement while a product is undergoing quality assurance review by WHO. Rifapentine + isoniazid single-pill combination is a priority product for review by the Expert Review Panel, meaning the recommendation could be made in as little as 6 weeks from the time of dossier submission. Thus, availability of this product on the market would be expected in late 2021. As there is currently only one supplier of a non-ideal formulation of rifapentine, a Rifapentine Consortium composed of some of the main technical and funding partners that support WHO's drive to scale-up tuberculosis preventive treatment globally was established in 2019 to allocate the very limited available supply against the increasing programmatic demand. Having additional suppliers of a more suitable formulation should help restore the normal market dynamics for rifapentine and the Rifapentine Consortium will no longer be required.

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