Rifapentine

Essential medicine status

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

EMLc | ATC codes: J04AB05

Indication	Latent tuberculosis ICD11 code: 1B14
INN	Rifapentine
Medicine type	Chemical agent
List type	Core (EML) (EMLc)
Formulations	Oral > Solid > tablet: 150 mg ; 300 mg
EML status history	First added in 2015 (TRS 994) 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	Rifapentine
DrugBank	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 people infected. The Committee considered that 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. 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 rifapentine 150 mg has been on the core list of the EML for tuberculosis since 2015, as part of the preferred shorter tuberculosis preventive treatment regimens of rifapentine in combination with isoniazid as a weekly dose for 3 months (3HP) or a daily regimen for 1 month (1HP). The 300 mg formulation of rifapentine would reduce the pill burden by half, thus significantly improving the likelihood of treatment adherence. In addition, individuals on shorter regimens have been shown to be 1.5–3 times more likely to complete the treatment course, which is a significant determinant of the regimen's effectiveness in preventing active tuberculosis. The Committee considered that the overall benefit to risk ratio of the rifapentine 300 mg formulation greatly favours its use for the shorter tuberculosis preventive treatment regimens. Availability of rifapentine 300 mg on the market is expected in late 2021. Additional suppliers of this formulation will increase supply security and competition, leading to lower prices and affordability. The Expert Committee therefore recommended the inclusion of the rifapentine 300 mg scored tablet formulation for the indication of tuberculosis preventive treatment on the core list of the EML and EMLc.

Background

Rifapentine (150 mg tablet) was added to the core list of the EML and EMLc in 2015 for treatment, in combination with isoniazid, of latent tuberculosis infection (now known as tuberculosis preventive treatment) (1). The 2015 application presented a network

meta-analysis of treatments for latent tuberculosis infection for preventing the development of active disease in individuals identified at high risk of progression (2). Fifty-three randomized controlled trials evaluated treatment for latent tuberculosis infection and recorded at least one of the two prespecified endpoints (prevention of active tuberculosis and/or hepatotoxicity of grade III or above). The results of clinical trials demonstrated the effectiveness of the 12-week regimen of rifapentine and isoniazid (3HP), administered once weekly for the treatment of latent tuberculosis infection in adults compared with the 6- or 9-month isoniazid regimen, considered as standard for this indication. Randomized controlled trials explored the effectiveness of rifapentine in combination with isoniazid for children aged 2 years and older (3), people with HIV-infection (4) and people without HIV infection (3). The rifapentine plus isoniazid combination was non-inferior in terms of efficacy, and had significantly better treatment adherence and completion of the 12-week regimen compared with isoniazid alone. Universal treatment of all individuals with latent tuberculosis infection is not recommended because of uncertainties about the balance between benefit and harm. A positive benefit–harm trade-off is evident in individuals with latent tuberculosis infection who are at risk for progression to active tuberculosis disease, that is: people living with HIV; adult and child contacts of pulmonary tuberculosis cases; patients starting treatment with an antitumour necrosis factor; patients receiving dialysis; patients preparing for organ or haematological transplantation; and patients with silicosis (5,6). In terms of harms, the 12-week rifapentine plus isoniazid regimen was shown to be well tolerated when used for the treatment of latent tuberculosis infection, including in children and in adults with and without HIV infection (2,3). The 12-week combination regimen was associated with less hepatotoxicity and more possible hypersensitivity reactions than the standard 6- or 9-month isoniazid therapy. In total, five deaths attributable to toxicity were reported, mostly from a single trial. All deaths were due to severe hepatitis in isoniazid treatment groups, and at least four occurred in patients who were on isoniazid for 12 months or longer (2). In the TBTC-S26 main study, the overall incidence of serious adverse events was low; serious adverse events were reported in 2.7% of patients in the isoniazid arm and 1.5% of patients in the rifapentine plus isoniazid arm (3). In the paediatric substudy of TBTC-S26, serious adverse events were reported in six children (1.2%), all of whom were in the isoniazid arm. In the HIV substudy of TBTC-S26, serious adverse events were reported in 10.8% of patients receiving isoniazid and 3.9% of patients receiving rifapentine plus isoniazid.

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 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 (7). 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 (8). 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 (9,10). 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 upon 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 was reviewed in 2015 (see Background section). The effectiveness of the 300 mg

formulation is not expected to differ from the 150 mg formulation, as long as the tablet is a quality-assured product with proven bioavailability. 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 (11,12).

Harms

Evidence for the harms of rifapentine was reviewed in 2015 (see Background section). The harms associated with the 300 mg formulation are not expected to differ from the 150 mg formulation as long as the tablet is a quality-assured product with proven bioavailability. Nitrosamine impurities in rifapentine have recently stopped its production and distribution (13,14). The WHO Prequalification Unit reported on 30 October 2020 that it was in contact with Sanofi about the presence of 1-cyclopentyl-4-nitrosopiperazine in the Priftin brand of rifapentine, a medicine that had prequalified based on approval of the US Food and Drug Administration. As per its notification of 29 October 2020, the US Food and Drug Administration will not object to the temporary distribution of rifapentine containing 1-cyclopentyl-4-nitrosopiperazine below 20 parts per million. The WHO Prequalification Unit recognizes the decision of the US Food and Drug Administration for this product.

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 (7). 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 (12). Tuberculosis preventive treatment can result in important savings for the individual and the health system by avoiding the need for tuberculosis treatment, given the longer isoniazid monotherapy regimens needed for treatment of tuberculosis disease. Further reductions in the cost of rifapentine will make this tuberculosis preventive treatment even more advantageous. 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 (17). Furthermore, WHO considers the 3-month regimen of weekly rifapentine + isoniazid and the 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 (18–21). 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 (22). 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 tuberculosis 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. Additional suppliers of a more suitable formulation will increase supply security and competition, leading to lower prices without the geographic limitations.

WHO guidelines

Regimens including rifapentine for tuberculosis preventive treatment are recommended by WHO in the 2020 WHO consolidated guidelines on tuberculosis (15,16). 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 recommended dose of rifapentine in rifapentine-containing tuberculosis preventive treatment regimens is: • 1200 mg per week for patients aged > 14 years (for the 3-month regimen of rifapentine plus isoniazid) • 600 mg per day for patients aged ≥ 13 years (for the 1-month regimen of daily rifapentine plus isoniazid). The 300 mg strength formulation would reduce the pill burden for patients.

Availability

Two suppliers are developing a rifapentine 300 mg formulation. One 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 for review by the WHO Prequalification Programme and the Global Fund's Expert Review Panel. A second supplier of the 300 mg formulation is on a similar timeline. As soon as the WHO Prequalification Programme has accepted the product dossiers for review, the products can be reviewed by 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 300 mg is a priority product for review by the Expert Review Panel, meaning the recommendation could be made in only 6 weeks from the time of dossier submission. Thus, availability of this product on the market would be expected in late 2021. These new products should help alleviate some of the backlog of demand for rifapentine-based short-course tuberculosis preventative treatment. 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. The function of the Consortium is 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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