Essential Medicines List (EML) 2021

Application for the inclusion of a rifapentine 300mg in the WHO Model List of Essential Medicines, for the treatment of tuberculosis infection

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 include a formulation of 300mg rifapentine. This application proposes an amendment to the core list in section 6.2.5 Antituberculosis medicines as per the latest edition of the main EML (21st list) (1).

This application is not proposing to add a new medicine to the EML but only to include a different dose of an existing one. Rifapentine has featured as an antituberculosis medicine on the core list of the EML since 2015 at a dose of 150 mg, the formulation that is available on the market. Regimens including rifapentine are recommended by WHO for TB preventive treatment (TPT; previously referred to as treatment of latent TB infection or LTBI) (2,3). The availability of rifapentine at a 300mg dosage would reduce pill-burden by half, significantly improving the likelihood of adherence to treatment.

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

The application is made by the WHO Global TB Programme, Geneva, Switzerland and the focal points are Dr Avinash Kanchar and Dr Dennis Falzon.

3. Name of organization(s) consulted and/or supporting the application.

The Global Drug Facility of the Stop TB Partnership in Geneva, Switzerland has collaborated in the preparation of this application (Dr Brian Kaiser).

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

INN	ATC
Rifapentine	J04AB05

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 scored tablet of 300mg rifapentine. Manufacture of this product is expected to start in 2021.

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

The application is for the inclusion of 300mg rifapentine as an individual medicine.

Treatment details, public health relevance and evidence appraisal and synthesis

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

The requirements for the identification of people eligible for TPT, the indication and contraindication for its use, and the monitoring associated with the proposed medicine are identical to those of 150mg rifapentine. Rifapentine is used in combination with isoniazid as a weekly dosage for 3 months (3HP) or a daily regimen for one month (1HP). The formulation for which this application is being made is primarily targeted for use either in the 3HP or 1HP regimens, as shown in the table below from the WHO operational guidance on TPT (3).

For the 3HP regimen, the 300mg rifapentine tablet would reduce the pill-burden of the weekly dose from at least 9 tablets to 6.

For the 1HP regimen, the 300mg rifapentine tablet would reduce daily pill-burden from at least 5 tablets to only 3 tablets. The added appeal of the 300mg rifapentine tablet would be to supplement the new FDC of 300mg rifapentine and 300mg isoniazid which would reduce the daily dose to only two tablets. The FDC of 300mg rifapentine and 300mg isoniazid is the subject of another application being submitted to EML by the WHO Global TB Programme and partners for the 2021 update.

Three months of rifapentine plus isoniazid weekly (12 doses) (3HP)	Age >14 years					
	Medicine, formulation	30–35 kg	36–45 kg	46–55 kg	56–70 kg	>70 kg
	Isoniazid, 300 mg	3	3	3	3	3
	Rifapentine, 150 mg	6	6	6	6	6
One month of rifapentine plus isoniazid daily (28 doses) (1HP)	Age ≥13 years (regardless of weight band) Isoniazid, 300 mg/day Rifapentine, 600 mg/day					

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) (4). 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 (5), with the lifetime risk of developing TB disease about 5–10% among those infected.

Globally, an estimated 10.0 million people fell ill with TB in 2019, a number that has been declining very slowly in recent years. 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. 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%. Among all those affected, 8.2% were people living with HIV.

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%. 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%.

TB is curable and preventable. About 85% of people who develop TB disease can be successfully treated with a 6-month drug regimen; treatment has the additional benefit of curtailing onward transmission of infection. Preventive treatment is also available for people with TB infection (TPT). Prevention of new infections of M. 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. Current health interventions for TB prevention, in addition to TPT, include the prevention of transmission of M. tuberculosis through infection prevention and control, and vaccination of children with the bacille Calmette Guérin (BCG) vaccine.

Estimate of total patient exposure to date

Target population(s)

TPT reduces the risk of progression from TB infection to TB disease by about 60% but can be as high as 90% among certain high-risk groups (such as PLHIV) (6,7). Systematic TPT is currently recommended by WHO for household contacts of bacteriologically confirmed pulmonary TB patients, PLHIV, those with silicosis, those receiving dialysis or anti-tumour necrosis factor treatment, or individuals 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, people with diabetes) can also be considered for systematic screening and TPT. At the first United Nations (UN) high-level meeting on TB in 2018, Member States committed to providing TPT 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 TB, and 20 million household contacts in older age groups.

Assessment of current use

The number of people provided with TPT has increased in recent years, from 1.0 million in 2015 to 2.2 million in 2018 and 4.1 million in 2019. The combined total of 6.3 million in 2018–2019 is 21% of the 5-year (2018–2022) target of 30 million. Most of those provided with TB preventive treatment were people living with HIV: 1.8 million in 2018 and 3.5 million in 2019. The combined total of 5.3 million suggests that the sub-target of providing treatment to 6 million people living with HIV in the period 2018–2022 will be achieved in 2020. Numbers of household contacts provided with TPT have been much smaller at 423,607 in 2018 and 538,396 in 2019. Of these, 81% were children under 5 years (349,796 in 2018 and 433,156 in 2019, equivalent to 27% and 33% of the 1.3 million estimated to be eligible) and 19% were people in older age groups (73,811 in 2018 and 105,240 in 2019). The numbers of household contacts provided with TPT in 2018 and 2019 fall far short of those required to achieve the targets for 2018–2022 set at the UN high-level meeting on TB. The combined 2018–2019 totals for children under 5 years and people in older age groups represent 20% and 0.9% of the 5-year targets (4 million and 20 million), respectively.

Likely impact of treatment on the disease

TPT is a potent public health intervention to reduce the TB disease burden. Providing TPT to high-risk individuals has dual benefits. It prevents morbidity and mortality at the individual level and reduces the TB burden by curtailing its transmission from individuals who would otherwise develop TB. Recent epidemiological data from WHO South East Asia region, indicate that TB disease prevention at scale is an essential intervention if the SDG targets are to be met. Optimal implementation of TPT alone in certain high-risk groups such as household contacts or people living with HIV has the potential to reduce the annual TB incidence rates by 8.3% (95% credible interval [CrI 6.5–10.8] relative to 2015, in the absence of any additional interventions (8,9).

Systematic TPT is currently recommended by WHO among target populations mentioned above, further along with the commitments from Governments and donors and availability of shorter TPT regimens such as 4R, 3HP and 1HP is expected to facilitate uptake of TPT. Due to its shorter duration, improved clinical profile, and programmatic benefits, the new, once weekly regimen of rifapentine and isoniazid (3HP) is expected to not only replace six months of isoniazid (6H) as the preferred TPT regimen, but also drive overall scale–up of TB prevention programs.

In summary, the current slow pace of the scale-up of TPT in the world is withholding countries from achieving the targets struck by their governments and stopping many people from benefiting from a treatment that can help them avoid unnecessary disease and death. The application for the inclusion of the 300mg rifapentine tablet will help achieve this end by reducing the pill-burden and increasing the chances for a price reduction to a more affordable range in the countries with the highest burden of TB.

9. Review of benefits: summary of evidence of comparative effectiveness.
10. Review of harms and toxicity: summary of evidence of safety.

The potential benefits and harms of rifapentine has been extensively reviewed and summarised at the time of the original application of the medicine to EML. Rifapentine was approved by EML for inclusion under the core list of TB medicines in 2015 and the associated evidence is available at:
https://list.essentialmeds.org/files/trs/NYoeKtlFYadb2HI1fdNfOyiluryY0W3EHufAfotP.pdf.

The effectiveness and potential harms associated with the 300mg formulation is not expected to differ from the 150mg preparation, so long as the tablet is a quality-assured product with proven bioavailability.

Nitrosamine impurities in rifapentine have recently halted its production and distribution (10,11). The WHO Prequalification Unit reported on 30 October 2020 that it was in contact with Sanofi regarding the presence of 1-cyclopentyl-4-nitrosopiperazine (CPNP) in Priftin (rifapentine), a medicine that it had prequalified based on US FDA approval. As per US FDAs notification dated 29 October 2020, US FDA will not object to the temporary distribution of rifapentine containing CPNP below 20 ppm. PQ recognises the US FDA decision for this product.

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

The median cost per person treated for drug-susceptible TB in 2019 was US$ 860 (12). Recent modelling work in WHO South East Asia region showed that numbers of individuals at high risk of TB disease that need preventive treatment to avert one TB case is 64 (95% CrI 55–74) which is considered a highly attractive public health proposition (13). TPT can make important savings to the individual and the services by avoiding TB treatment when compared with longer isoniazid monotherapy regimens; further reductions in the cost of rifapentine will make this even more advantageous.

The standard regimen of 6-months isoniazid monotherapy has been the most widely used TPT option, costing between $4-6 USD for a patient course. However, the uptake and TPT completion with this longer regimen has been limited (14). Further WHO recommended 3HP and 1HP as equivalent options for TPT 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 maximise its effectiveness in preventing active TB (15-18). In published literature, the cost-effectiveness of 3HP and 1HP has primarily been studied in high income, low burden settings using a high price of Sanofi's branded rifapentine (Priftin). In high burden, low resource settings, researchers have found 3HP with directly observed therapy (DOT) prevents the greatest number of TB cases compared to other LTBI regimens, but at a cost of $9,402 per DALY averted (19). If the price of RPT was reduced to $8 USD, the researchers estimated the incremental cost-effectiveness ratio would decrease to US$535 per DALY averted. Hence, although currently more costly compared to INH only regimen the rifapentine containing TPT 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. Sanofi sells the drug as a 150mg tablet at a price of $1 per tab or $73 for a full patient course of the 3HP regimen inclusive of isoniazid in high-income countries and for $0.625 per tablet or $46 per treatment course through GDF. This is significantly higher than the $4-6 for the 6H regimen. Sanofi has entered into an agreement with the Global Fund to Fight AIDS, TB and Malaria and UNITAID to reduce the price of rifapentine to US$15 per adult patient course for a select set of high-burden TB countries (GDF Product Catalogue https://unitaid.org/news-blog/landmark-deal-secures-significant-discount-on-price-of-medicine-to-prevent-tb/#en). Additional suppliers of a more suitable formulation will increase supply security and competition, leading to lower prices without the geographic restrictions.

Regulatory information

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

There are two suppliers developing a rifapentine 300mg formulation. One supplier has successfully completed stability and pilot bioequivalence studies on the prototype product and by February 2021 will have completed exhibit batches. Once six months of stability information is available, the product will be submitted to WHO Prequalification and the Global Fund's Expert Review Panel. A second supplier of the 300mg formulation is on a similar timeline.

As soon as the WHO Prequalification Programme (WHO/PQ) has accepted the product dossiers for review, the products can be reviewed by the Global Fund's Expert Review Panel (ERP). The ERP makes recommendations to the Global Fund to allow procurement while a product is undergoing quality assurance review by WHO/PQ. Rifapentine 300mg is a priority product for ERP review, meaning the recommendation can be made in as little as 6 weeks from the time of dossier submission.(20) Thus, market availability of this product would be expected around the middle of Quarter 4, 2021.

This should help alleviate some of the backlog of programmatic demand for rifapentine-based short-course TB preventative treatment. As there is only one supplier of a non-ideal formulation of rifapentine currently, a Rifapentine Consortium composed of some of the major technical and funding partners that support WHO's drive to scale-up TPT globally was established in 2019 to allocate the very limited available supply against the increasing programmatic demand. Having an additional supplier of a more suitable formulation should help restore the normal market dynamics for rifapentine and the Rifapentine Consortium will no longer be required.

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

The United States Pharmacopeia Convention (USP) under the USAID-funded Promoting the Quality of Medicines (PQM) programme has issued a product information report to support development of rifapentine. https://www.usp-pqm.org/sites/default/files/pqms/article/rifapentine-pir-jul2018.pdf. Otherwise, rifapentine is not listed in any pharmacopeia to date.

References

14. Comprehensive reference list and in-text citations.

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