Essential Medicines List (EML) 2021

Application for the inclusion of a fixed-dose combination of rifapentine (300mg) and isoniazid (300mg) in the WHO Model List of Essential Medicines, for the treatment of tuberculosis infection (adults only)

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 fixed dose combination of rifapentine (300mg) and isoniazid (300mg). 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)[i]. This application does not concern the EML for children (EMLc).

This application is not proposing to add any new medicines to the EML but only to include a fixed-dose combination of two existing medicines. Both rifapentine and isoniazid have featured as antituberculosis medicines on the core list of the EML for several years (2015 and 1977 respectively). Regimens including the two medicines are recommended by WHO for TB preventive treatment (TPT; previously referred to as treatment of latent TB infection or LTBI)[ii,iii]. The availability of rifapentine and isoniazid as a single, fixed-dose combination tablet would reduce pill-burden significantly to the benefit 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
Isoniazid	J04AC01, J04AC51 (combinations)

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 and 300mg isoniazid for adults.
This formulation is manufactured by Macleods Pharmaceuticals Limited, Atlanta Arcade, Marol Church Road, Andheri (East), Mumbai – 400059, India (https://www.macleodspharma.com/).

Manufacture of same product by a second supplier 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 the combination drug 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, indication and contraindication, and the monitoring associated with the proposed FDC are common to those for single dose rifapentine plus isoniazid regimens. The combination of rifapentine and isoniazid is recommended to be taken as a weekly dosage for 3 months (3HP) or a daily dosage for one month (1HP). The FDC for which this application is being made is primarily

targeted for the 3HP regimen in individuals over 14 years of age, as shown in the table below from the WHO operational guidance.[iii] The release and large-scale use of the FDC had already been envisaged by the latest WHO guidelines in 2020, to enhance administration.[ii] This would reduce the weekly dose for 3HP from 9 or 11 tablets to only three. Use of the FDC for 1HP regimens would require supplemental dosing with 2 tablets of rifapentine 150mg per day and would still reduce daily pill-burden from 5 or 7 tablets to only 3 tablets.

Regimen	Dose by age and weight band					
Three months of rifapentine plus high dose isoniazid weekly (12 doses) (3HP)	**Age 2–14 years**[d]					
	Medicine, formulation	10–15 kg	16–23 kg	24–30 kg	31–34 kg	> 34 kg
	Isoniazid 100 mg[b]	3	5	6	7	7
	Rifapentine 150 mg	2	3	4	5	5
	Isoniazid + rifapentine FDC (150 mg/150 mg)[c]	2	3	4	5	5
	Age > 14 years[d]					
	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
	Isoniazid + rifapentine FDC (300 mg/300 mg)[c]	3	3	3	3	3
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).[iv] 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[v], 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. 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).

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. 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 are treatment of people with TB infection (TB preventive treatment-TPT), 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).[vi,vii] 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.[viii,ix]

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 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 300/300 HP FDC will go a long way towards this end as it will facilitate even further the administration of the 3HP regimen, 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.

The summary of evidence of comparative effectiveness of rifapentine and isoniazid have been extensively reviewed in the past at the point of the original applications of the two medicines to EML.

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

The potential benefits and harms of rifapentine and isoniazid have been extensively reviewed in the past at the point of the original applications of the two medicines to EML. Rifapentine was approved by EML for inclusion under the core list of TB medicines in 2015 and the associated evidence is available here: https://list.essentialmeds.org/files/trs/NYoeKtlFYadb2HI1fdNfOyiluryY0W3EHufAfotP.pdf.
Isoniazid was approved by the EML in 1977: https://list.essentialmeds.org/files/trs/sC1L9Ib4I8o8cDqlyfhnKyoa8MGm7XUFDffFVNUc.pdf.

The effectiveness and potential harms associated with these two medicines are expected to be similar between the loose dose formulations and the FDC.

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 and about US$ 5659 for treatment of MDR-TB.[x] A 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 highly attractive public health proposition.[xi]By averting costly treatment of drug sensitive and drug resistant TB, TPT can be a very cost-effective intervention for TB control with the longer Isoniazid containing regimen and if the current high cost of shorter rifapentine containing regimen.

The standard regimen of 6-month Isoniazid only has been 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.[xii] Further WHO recommended use of 3HP and 1HP as equivalent option 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 the treatment course, which is a significant determinant of the effectiveness of the regimen in preventing active TB.[xiii][xiv],[xv][1][xvi] 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.[xvii] If the price of RPT was reduced to $8 USD, the researchers estimated the incremental cost-effectiveness ratio (ICER) 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, due to low demand. There are no other quality-assured sources. Sanofi sells the drug as a 150mg tablet at a price of $1 per tab or $72 for a full patient course of the 3HP regimen. This results in a total price of $73 per patient course for 3HP for both RPT and INH, which is significantly higher than the $4-6 for the standard regimen 6-month INH only regimen. Sanofi has entered into an agreement to a reduced price of rifapentine to $15 USD per patient course with the Global fund, Unitaid (GDF Product Catalogue https://unitaid.org/news-blog/landmark-deal-secures-significant-discount-on-price-of-medicine-to-prevent-tb/#en). The generic supplier Macleods Pharmaceutical limited has now commercialized a fixed dose combination of RPT and INH with 300mg of each drug and similarly entered into an agreement to price the product at $15 USD per patient course through a special agreement with the Global Fund and Unitaid (to be announced).

Government institutions in and international organizations procuring for eligible Low-Income Countries and Middle-Income Countriesprices, including (i) Governments of Eligible Countries (ii) United Nations-related organizations, non-governmental organizations and not-for-profit organizations; and (iii) development and/or public health financing mechanisms, or a procurement agent appointed by any of these entities. The Ceiling Price does not apply to product sales in the private sector.

This product is included on the GDF medicines catalogue (http://www.stoptb.org/assets/documents/gdf/drugsupply/GDFMedicinesCatalog.pdf.) A second generic manufacturer, A second supplier is also at advanced stage of development of the FDC 300/300mg Isoniazid and rifapentine and likely to be commercialized in 4Q 2021. As uptake of TPT increases in line with the UN HLM commitments, the cost per patient course of rifapentine is expected to continue decreasing trajectory.

Regulatory information

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

The manufacturer of proposed FDC, MacLeods Pharma has filed with multiple National Drug Regulatory Authorities including high TB burden countries like India and South Africa. The formulation is currently endorsed for procurement by The Global Fund's Expert Review Panel (https://www.theglobalfund.org/media/4757/psm_productstb_list_en.pdf) meaning the product can be procured using Global Fund funds while the product undergoes review by the WHO Prequalification Programme (https://extranet.who.int/pqweb/medicines/dossier-status). The product is also eligible for PEPFAR procurement following a review by GHSC -QA.

The drug is available on the Global Drug Facility catalogue[xviii]. A box of 36 tablets (a single treatment for an adult patient) is US$15, making it comparable to the cost of the original manufacturer under temporary concessionary

[1] Sandgren A, Vonk Noordegraaf-Schouten M, van Kessel F, Stuurman A, Oordt-Speets A, van der Werf MJ. Initiation and completion rates for latent tuberculosis infection treatment: a systematic review. *BMC Infect Dis*. 2016;16(1):204.

pricing for 100 eligible countries (a pricing arrangement that is renewable every year). The product is made available as a patient pack of 36 scored FDC tablets presented as three alu-alu strips of 12 tablets each for a course of 3HP

A second supplier is also at an advance stage of development of the rifapentine/Isoniazid (300mg+300mg) FDC formulation. The 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. 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+Isoniazid FDC 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.xix 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. Otherwise, rifapentine is not listed in any Pharmacopeia to date. https://www.usp-pqm.org/sites/default/files/pqms/article/rifapentine-pir-jul2018.pdf

Isoniazid is included in at least three renown pharmacopeias (see below)

Drug	***Standard***	***Reference*** *(*accessed 3 December 2020*)*
Isoniazid	United States Pharmacopeia	https://store.usp.org/OA_HTML/usp3_ibeCSrdSrchResults.jsp (isoniazid 200mg)
	European Pharmacopeia	https://crs.edqm.eu/db/4DCGI/View=I0500000
	The International Pharmacopeia	https://apps.who.int/phint/en/p/docf/

References

14. Comprehensive reference list and in-text citations.

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[ii] *WHO consolidated guidelines on tuberculosis: Module 1: Prevention - tuberculosis preventive treatment. Geneva, World Health Organization. 2020. Available from: https://www.who.int/publications/i/item/who-consolidated-guidelines-on-tuberculosis-module-1-prevention-tuberculosis-preventive-treatment*

[iii] *WHO operational handbook on tuberculosis: Module 1: Prevention - tuberculosis preventive treatment. Geneva, World Health Organization. 2020. Available from: https://www.who.int/publications/i/item/who-operational-handbook-on-tuberculosis-module-1-prevention-tuberculosis-preventive-treatment*

[iv] *Global tuberculosis report 2020. Geneva, World Health Organization; 2020. https://www.who.int/tb/publications/global_report/en/*

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