F.13	Rifapentine + isoniazid
Does the application adequately address the issue of the public health need for the medicine?	☒ Yes ☐ No ☐ Not applicable Comments: 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 lifetime risk of developing TB disease about 5–10% among those infected. TB is curable and preventable. Prevention of TB infection 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. 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. Systematic TPT is currently recommended by WHO among target populations at high-risk. Both rifapentine and isoniazid have featured as anti-tuberculosis 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). 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, 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.
Briefly summarize the role of the proposed medicine(s) relative to other therapeutic agents currently included in the Model List, or available in the market.	Both rifapentine and isoniazid have featured as anti-tuberculosis 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). 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, primarily targeted for the 3HP regimen in individuals over 14 years of age.
Have all important studies and all relevant evidence been included in the application?	☒ Yes ☐ No ☐ Not applicable If no, please provide brief comments on any relevant studies or evidence that have not been included:

Does the application provide adequate evidence of efficacy/effectiveness of the medicine for the proposed indication?	☒ Yes ☐ No ☐ Not applicable Briefly summarize the reported benefits (e.g. hard clinical versus surrogate outcomes) and comment, where possible on the actual magnitude and clinical relevance of benefit associated with use of the medicine(s). 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. 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. The results of RCTs demonstrated the effectiveness of the 12-week regimen of rifapentine and isoniazid (3RPT/INH), administered once weekly for the treatment of LTBI in adults, compared with the 6- or 9-month INH standard regimen (6INH, 9INH). RCTs explored the effectiveness of RPT/INH in children aged 2 years or more, HIV-infected and non-HIV-infected patients. Non-inferiority in terms of efficacy, and significantly better treatment adherence and completion of the 3RPT/INH regimen compared with INH were observed, although higher treatment completion rates could have been biased in favour of 3RPT/INH. Is there evidence of efficacy in diverse settings (e.g. low-resource settings) and/or populations (e.g. children, the elderly, pregnant patients)? Yes.
Does the application provide adequate evidence of the safety and adverse effects associated with the medicine?	☒ Yes ☐ No ☐ Not applicable Comments: 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. The results of a network meta-analysis of published data and the TBTC-S26 study show that 3RPT/INH is well tolerated when used for the treatment of LTBI, including by children (2–17 years old) and by HIV-infected and HIV-non-infected adults. The 3RPT/INH regimen is associated with less hepatotoxicity and more possible hypersensitivity reactions than the standard 6INH or 9INH therapy. A total of five toxicity-attributable deaths were reported, mostly from a single trial. All were due to severe hepatitis in INH treatment groups, and at least four occurred in patients who were on INH for 12 months or longer. In the TBTC-S26 main study, the overall incidence of serious adverse events (SAEs) was low; SAEs were reported in 2.7% of patients in the INH arm and 1.5% of patients in the RPT/INH arm (87). In the paediatric sub-study of TBTC-S26, SAEs were reported in six children (1.2%), all of whom were in the INH arm. In the HIV sub-study of TBTC-S26, SAEs were reported in 10.8% of INH patients and 3.9% of RPT/INH patients.

Are there any adverse effects of concern, or that may require special monitoring?	☐ Yes ☒ No ☐ Not applicable Comments: Drug-specific adverse reactions can occur with both RPT and INH. The results of a network meta-analysis of published data and the TBTC-S26 study show that 3RPT/INH is well tolerated when used for the treatment of LTBI, including by children (2–17 years old) and by HIV-infected and HIV-non-infected adults. The 3RPT/INH regimen is associated with less hepatotoxicity and more possible hypersensitivity reactions than the standard 6INH or 9INH therapy. A total of five toxicity-attributable deaths were reported, mostly from a single trial. All were due to severe hepatitis in INH treatment groups, and at least four occurred in patients who were on INH for 12 months or longer. WHO does not have specific recommendations on standards of clinical monitoring during LTBI treatment because of the lack of evidence on the optimal monitoring strategy. However, the Organization suggests regular routine clinical monitoring of individuals receiving treatment for LBTI through a monthly visit to healthcare providers. Severe hepatitis (hepatotoxicity) related to longer course of INH therapy can result in death, therefore liver function should be monitored for individuals presenting with hepatitis-related symptoms or signs.
Briefly summarize your assessment of the overall benefit to risk ratio of the medicine (e.g. favourable, uncertain, etc.)	Both rifapentine and isoniazid have featured as anti-tuberculosis medicines on the core list of the EML for several years (2015 and 1977 respectively). The effectiveness and potential harms associated with these two medicines are expected to be similar between the loose dose formulations and the fixed-dose combination (FDC). Regimens including the two medicines are recommended by WHO for TB preventive treatment (TPT). The availability of rifapentine and isoniazid as a single, FDC tablet would reduce pill-burden significantly to the benefit of adherence to treatment, primarily targeted for the 3HP regimen in individuals over 14 years of age. The overall benefit to risk ratio of rifapentine and isoniazid is favourable.
Briefly summarize your assessment of the overall quality of the evidence for the medicine(s) (e.g. high, moderate, low etc.)	The overall quality of the evidence for rifapentine and isoniazid is high.
Are there any special requirements for the safe, effective and appropriate use of the medicine(s)**?** (e.g. laboratory diagnostic and/or monitoring tests, specialized training for health providers, etc)	☐ Yes ☒ No ☐ Not applicable Comments: WHO does not have specific recommendations on standards of clinical monitoring during LTBI treatment because of the lack of evidence on the optimal monitoring strategy. However, the Organization suggests regular routine clinical monitoring of individuals receiving treatment for LBTI through a monthly visit to healthcare providers. As severe hepatitis related to INH hepatotoxicity can result in death, therefore liver function should be monitored for individuals presenting with hepatitis-related symptoms or signs during treatment.

Are you aware of any issues regarding the registration of the medicine by national regulatory authorities? (e.g. accelerated approval, lack of regulatory approval, off-label indication)	☐ Yes ☒ No ☐ Not applicable Comments: Isoniazid is included in at least three renown pharmacopeias. 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. 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.
Is the proposed medicine recommended for use in a current WHO Guideline approved by the Guidelines Review Committee? (refer to: https://www.who.int/publications/who-guidelines)	☒ Yes ☐ No ☐ Not applicable Comments: Regimens including rifapentine and isoniazid are recommended by WHO for TB preventive treatment (TPT). Both the two medicines have featured as anti-tuberculosis medicines on the core list of the EML for several years (2015 and 1977 respectively). The release and large-scale use of the FDC had already been envisaged by the latest WHO guidelines in 2020, to enhance administration.
Briefly summarize your assessment of any issues regarding access, cost and affordability of the medicine in different settings.	1. A total price per patient course for 3HP for both RPT and INH is $73 based on the current Sanofi pricing for RPT at $1 per 150mg tab, which is significantly higher than the $4-6 for the standard regimen 6-month INH only regimen. However, 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. 2. The FDC 300/300mg Isoniazid and rifapentine will be widely accessible in most countries because the new, once weekly regimen of rifapentine and isoniazid (3HP) has significant advantages of shorter duration, improved clinical profile, and programmatic benefits. The release and large-scale use of the FDC had already been envisaged by the latest WHO guidelines in 2020 to enhance administration, and is expected to not only replace six months of isoniazid (6H) as the preferred TPT regimen. 3. The FDC will be affordable in LMICs with a high burden of TB in the near future with the cost per patient course expected to continue decreasing trajectory. So far, Sanofi has entered into an agreement to a reduced price of rifapentine to $15 USD per patient course with the Global fund, Unitaid. Besides, this product is included on the GDF medicines catalogue. 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.
Any additional comments	None

Based on your assessment of the application, and any additional evidence / relevant information identified during the review process, briefly summarize your proposed recommendation to the Expert Committee, including the supporting rationale for your conclusions, and any doubts/concerns in relation to the listing proposal.	1. Both rifapentine and isoniazid have featured as anti-tuberculosis medicines on the core list of the EML for several years. 2. Regimens including rifapentine are recommended by WHO for TB preventive treatment. Rifapentine is used in combination with isoniazid as a weekly dosage for 3 months (3HP) or a daily regimen for one month (1HP). The availability of the FDC 300/300mg Isoniazid and rifapentine tablet would reduce pill-burden significantly to the benefit of adherence to treatment. 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 TB. 4. Shorter TPT regimens such as 4R, 3HP and 1HP is expected to replace six months of isoniazid (6H) as the preferred TPT regimen, which will facilitate the accessibility of the FDC 300/300mg Isoniazid and rifapentine. The release and large-scale use of the FDC had already been envisaged by the latest WHO guidelines in 2020 to enhance administration. 3. The FDC will be affordable in LMICs with a high burden of TB in the near future with the cost per patient course expected to continue decreasing trajectory. Conclusion: I highly recommend the addition of the FDC 300/300mg Isoniazid and rifapentine on the core list of the Model List of Essential Medicines for TB preventive treatment in individuals over 14 years of age.
References (if required)	