F.12	Rifapentine 300mg
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, 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.	1. Rifapentine is not a new medicine is proposed to be added to the WHO EML. 2. Rifapentine has featured as an anti-tuberculosis medicine on the core list of the EML since 2015 at a dose of 150 mg, as the preferred shorter TPT regimen. Rifapentine is used in combination with isoniazid as a weekly dosage for 3 months (3HP) or a daily regimen for one month (1HP). 3. The availability of rifapentine at a 300mg dosage would reduce pill-burden by half, significantly improving the likelihood of adherence to treatment. 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.
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 effectiveness associated with the Rifapentine 300mg formulation is not expected to differ from the 150mg preparation, so long as the tablet is a quality-assured product with proven bioavailability. 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 harms associated with the Rifapentine 300mg formulation is not expected to differ from the 150mg preparation, so long as the tablet is a quality-assured product with proven bioavailability. 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: Hepatotoxicity and more possible hypersensitivity reactions were observed during 3RPT/INH regimen treatment. Severe hepatitis (hepatotoxicity) observed during longer course of INH therapy resulted in death. Therefore, no serious concern on shorter course of 3RPT/INH regimen treatment. 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.
Briefly summarize your assessment of the overall benefit to risk ratio of the medicine (e.g. favourable, uncertain, etc.)	Overall, the overall benefit to risk ratio of the Rifapentine 300mg is greatly favourable for TPT regimen.
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 at a 300mg dosage as a shorter TPT regimen 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: No special laboratory tests are required to monitor the potential adverse effects of rifapentine and effectiveness because there is no specific safety issue associated with shorter course of TPT treatment regimens and the effectiveness of rifapentine-based TPT regimen has been well demonstrated.
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: Two suppliers developing a rifapentine 300mg formulation have successfully completed stability and pilot bioequivalence studies on the prototype products by February 2021. Market availability of rifapentine would be expected around the middle of Quarter 4, 2021.

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 are recommended by WHO for TB preventive treatment. Shorter TPT regimens such as 4R, 3HP and 1HP is expected to facilitate uptake of TPT.
Briefly summarize your assessment of any issues regarding access, cost and affordability of the medicine in different settings.	1. 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. Sanofi has entered into an agreement to reduce the price of rifapentine to US$15 per adult patient course for a select set of high-burden TB countries, 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 treatment, which is important to maximize its effectiveness in preventing active TB. 2. Hence, although currently more costly compared to INH only regimen, the rifapentine containing TPT is expected to be more cost-effective option for programs. 3. Additional suppliers of a more suitable formulation will increase supply security and competition, leading to lower prices without the geographic restrictions and affordability.
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. 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). 2. Shorter TPT regimens such as 4R, 3HP and 1HP is expected to facilitate uptake of TPT compared to the 6H regimen. 3. 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. The availability of rifapentine at a 300mg dosage would reduce pill-burden by half, significantly improving the likelihood of adherence to treatment. 5. Additional suppliers of a more suitable formulation will increase supply security and competition, leading to lower prices without the geographic restrictions and affordability. 6. Market availability of rifapentine would be expected around the middle of Quarter 4, 2021. 7. The overall benefit to risk ratio of the Rifapentine 300mg is greatly favourable. Conclusion: I highly recommend the addition of a rifapentine 300mg on the core list of the Model List of Essential Medicines for TB preventive treatment in adults.
References (if required)	