Application to add rifapentine to the Essential List of Medicines

as a medicine for the treatment of latent tuberculosis infection
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### Abbreviations

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<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>AE</td>
<td>Adverse events</td>
</tr>
<tr>
<td>ALT</td>
<td>Alanine aminotranferase</td>
</tr>
<tr>
<td>ART</td>
<td>Antiretroviral therapy</td>
</tr>
<tr>
<td>AST</td>
<td>Aspartate aminotransferase</td>
</tr>
<tr>
<td>CD4</td>
<td>T-lymphocytes expressing the CD4 receptor</td>
</tr>
<tr>
<td>CDC</td>
<td>Centers for Diseases Control</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence interval</td>
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<tr>
<td>CXR</td>
<td>Chest X ray</td>
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<tr>
<td>CYP450</td>
<td>Cytochrome P450</td>
</tr>
<tr>
<td>DOT</td>
<td>Directly Observed Therapy</td>
</tr>
<tr>
<td>DSMB</td>
<td>Data and Safety Monitoring Board</td>
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<tr>
<td>Efavirenz</td>
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<tr>
<td>EML</td>
<td>Essential Medicine List</td>
</tr>
<tr>
<td>FTC</td>
<td>Emtricitabine</td>
</tr>
<tr>
<td>GRADE</td>
<td>Grading of Recommendations Assessment, Development and Evaluation</td>
</tr>
<tr>
<td>HIV</td>
<td>Human Immunodeficiency Virus</td>
</tr>
<tr>
<td>INH</td>
<td>Isoniazid</td>
</tr>
<tr>
<td>LOQ</td>
<td>Limit of quantification</td>
</tr>
<tr>
<td>LTBI</td>
<td>Latent tuberculosis infection</td>
</tr>
<tr>
<td>MedDRA</td>
<td>Medical Dictionary for Regulatory Activities</td>
</tr>
<tr>
<td>Acronym</td>
<td>Definition</td>
</tr>
<tr>
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<tr>
<td>MITT</td>
<td>Modified Intent To Treat</td>
</tr>
<tr>
<td>PK</td>
<td>Pharmacokinetic</td>
</tr>
<tr>
<td>PP</td>
<td>Per Protocol</td>
</tr>
<tr>
<td>QALY</td>
<td>Quality-adjusted life year</td>
</tr>
<tr>
<td>RPT</td>
<td>Rifapentine</td>
</tr>
<tr>
<td>RPT/INH</td>
<td>Rifapentine and Isoniazid combination</td>
</tr>
<tr>
<td>TAG</td>
<td>Treatment Action Group</td>
</tr>
<tr>
<td>TB</td>
<td>Tuberculosis</td>
</tr>
<tr>
<td>TBTC</td>
<td>Tuberculosis Trials Consortium</td>
</tr>
<tr>
<td>TEAE</td>
<td>Treatment-emergent adverse events</td>
</tr>
<tr>
<td>TNF</td>
<td>tumor necrosis factor</td>
</tr>
<tr>
<td>TST</td>
<td>Mantoux tuberculin skin test</td>
</tr>
<tr>
<td>ULN</td>
<td>Upper limit of normality</td>
</tr>
<tr>
<td>USA</td>
<td>United States of America</td>
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<tr>
<td>WHO</td>
<td>World Health Organization</td>
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Executive summary

What is this application for?

This application is for inclusion of rifapentine (RPT) as an individual medicine, to be used in combination with isoniazid (INH), for the treatment of latent tuberculosis (TB) infection (LTBI). The proposed formulation is oral tablets of 150 mg.

Why is WHO submitting this application?

The World Health Assembly passed a resolution in May 2014 approving with full support the new post-2015 Global TB Strategy with its ambitious vision of a world free of TB and targets for 2035 that include a 90% reduction in TB incidence rate (compared with 2015). To accomplish this mandate the World Health Organization (WHO) started developing policy documents, including the guidelines on the management of LTBI, launched in October 2014, that intend to promote a public health approach for the diagnosis and treatment of LTBI. WHO decided to take direct responsibility in the application to add RPT for the prevention of LTBI to the EML under the consideration that a positive decision would be crucial to strengthen the treatment component of the LTBI management strategy.

What is rifapentine approved for?

RPT is approved by the Food and Drug Administration (FDA) since 1998 for the treatment of pulmonary tuberculosis in combination with one or more antituberculosis drugs and it is currently marketed under the brand name Priftin® by Sanofi. The more than 15-year experience with RPT for the treatment of TB provides a large body of evidence for the safety and efficacy of the drug. In November 2014 the FDA approved a supplemental New Drug Application for RPT for the treatment of LTBI in combination with isoniazid in patients 2 years of age and older at high risk of progression to TB disease. The decision was based on the evidence from high quality randomized controlled trials.

Who should receive rifapentine according to this application?

WHO included the RPT/INH combination in its recommendations for the treatment of LTBI based on the GRADE evaluation of the evidence, demonstrating that RPT/INH has similar efficacy, lower risk of hepatotoxicity, and improved treatment completion rates compared to a 6 or 9-month isoniazid regimen, considered as the standard reference for this indication. Although the combination of RPT/INH is not the only recommended treatment option in the guidelines, it is considered superior the other available options (isoniazid or rifampicin or the two in association) when a combination of safety, efficacy, and likelihood of completion criteria are considered.
The WHO policy recommends systematic testing and treatment of LTBI limited to specific at-risk populations, which include people living with HIV, adult and child contacts of pulmonary TB cases, patients initiating anti-tumor necrosis factor (TNF) treatment, patients receiving dialysis, patients preparing for organ or hematologic transplantation and patients with silicosis. Additional at-risk groups may also be considered for systematic testing and treatment of LTBI, including prisoners, health workers, immigrants from high TB burden countries, homeless persons and illicit drug users, based on countries priorities and resources.
1. Rationale for the application

The World Health Assembly passed a resolution in May 2014 approving with full support the new post-2015 Global TB Strategy (lately renamed END-TB Strategy) with its ambitious vision of a world free of TB and targets for 2035 that include a 90% reduction in TB incidence rate (compared with 2015) [1].

Because of this clear mandate from the Member States, WHO started a process of adaptation of the END-TB strategy in all settings, including those with low TB burden [2]. In this setting, the majority of incident TB cases are generated by re-activation of LTBI [3], so that preventive therapy of LTBI in high-risk groups (the reservoir of the disease) is at least as relevant as treatment for the disease in order to reduce mortality and human suffering. At the end of 2013, WHO started developing the first time ever guidelines on the management of LTBI, following the rigorous development process dictated by the WHO Guidelines Review Committee [4]. The guidelines, launched in October 2014, promote a public health approach for the diagnosis and treatment of LTBI. One of the crucial elements of the LTBI management strategy is the recommendation of safe and effective treatment options for the individuals in need. Although the combination of RPT/INH is not the only recommended option, it is considered superior the other available options (isoniazid or rifampicin or the two in association) based on its safety and efficacy profile, the short treatment duration and the weekly dosing. It is considered that the RPT/INH regimen, by ensuring high completion rates, will make LTBI management competitive in terms of cost-effectiveness, and play a crucial role for the success of the overall strategy.

Although newly registered for the proposed indication (treatment of LTBI), experience on safety and efficacy of RPT is available from more than 15 years of use of the drug for the treatment of TB. Moreover, the recommendation on the indication of RPT for the treatment of LTBI is based on high quality randomized controlled trials.

WHO decided to take direct responsibility in the application to add RPT for the treatment of LTBI to the EML under the consideration that a positive decision would be crucial to support the LTBI management strategy and contribute to achieve the targets of the END-TB strategy. WHO envisages that adding RPT to the EML will greatly widen the access to the drug by soliciting and possibly "encouraging" the manufacturer of RPT to submit approval applications to all relevant regulatory authorities world-wide, and by facilitating the process of registration and distribution of the drug at country level.

The LTBI guidelines are, in principle, intended to benefit all WHO Member States regardless of their epidemiology of TB as the intent is to improve the diagnosis and management of LTBI in population groups with the highest likelihood of progression to active disease. The guidelines are primarily targeted at countries (high-income or upper middle-income countries with an estimated TB incidence rate of less than 100 per 100,000 population) that are most likely to benefit from the guidelines due to their current TB epidemiology and resource availability, and it is anticipated that the number of engaged countries will
continuously grow and eventually all countries will benefit from the strategy. All resource-limited countries should already implement existing WHO guidelines on treatment of LTBI among people living with HIV [5] and child contacts below 5 years of age [6] as a priority.

2. Name of the focal point in WHO submitting or supporting the application

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

None

4. International Nonproprietary Name (INN, generic name) of the medicine

Rifapentine (RPT)
Molecular formula: \( \text{C}_{47}\text{H}_{84}\text{N}_4\text{O}_{12} \)

RPT was first discovered in 1965 by the same company that produced rifampicin; it is synthesized in one step from rifampicin [7]. It has a molecular weight of 877.04; the chemical designation is 2,7-(epoxypentadeca[1,II,13]trienimino)naphtho[2,1-b]furan-2,4,12,16,18,20,22-heptamethyl-8-[N-(4-cyclopentyl-1-piperazinyl)formimidoyl]-21-acetate.

After oral administration of a single 600 mg oral dose, RPT is absorbed slowly from the gastrointestinal tract, reaching peak serum concentrations in plasma of about 15 \( \mu \text{g/mL} \) within 4.83± 1.80 [8]. RPT is metabolized mostly by the liver and is excreted predominantly (70%) in feces by biliary excretion and gastrointestinal secretion, while urinary excretion accounts for less than 5% of the administered dose [9]. The drug is metabolized by hydrolysis and de-acetylation to 25-O-desacetylRifapentine, which is microbiologically active, contributing 38% of the drug's overall activity [10]. The metabolite reaches its peak concentration in 11.25±2.73h, and the mean elimination half-life (t1/2) is 13.35±2.67h.

RPT has a longer terminal elimination half-life compared with rifampicin (13.19± 1.38 hours vs. 2 to 3 hours) [11]. The rational for the administration of RPT at doses of 600 mg once or twice weekly in the treatment of TB is further provided by the "in vitro" pharmacodynamics model of TB demonstrating a long post-antibiotic effect of rifampin (taken as a surrogate of RPT), which prevents regrowth during the entire 1-week dosing interval, so that cycles of killing and regrowth are not encountered [12]. Moreover, RPT has a greater ability to penetrate macrophages, achieving a four- to fivefold greater ratio of intracellular accumulation than rifampicin, resulting in marked reduction of the mycobacterial burden that is maintained over a 4-week period after once-weekly exposures of infected macrophages in an experimental model of intracellular infection [13]. All this observations are considered to be relevant to justify the proposed weekly administration schedule of RPT for the treatment of LTBI.

The interest on RPT as a candidate for the treatment of LTBI started with the demonstration of its potency
in latent infection animal models [14-16]. The interest was increased by the evidence that the use of weekly RPT/INH in the continuation phase of TB treatment could effectively prevent relapses [17].

RPT, like other rifamycins, induces the P450 enzymes—specifically, the CYP3A4, CYP2C8, and CYP2C9 isoenzymes [18]. The relative potency of rifamycins as inducers is as follows: rifampicin, 1; RPT, 0.85; and rifabutin, 0.40. Therefore, interaction of RPT and drugs that are metabolized by these enzymes are anticipated to be clinically significant. Any drug known to have interactions with rifampicin should be considered to have similar interactions with RPT, unless proven otherwise.

5. Formulation proposed for inclusion; including adult and pediatric

Rifapentine: oral tablets of 150 mg.

This is the current formulation marketed in the US (Priftin®, supplied as 150 mg round normal convex dark-pink film-coated tablets debossed “Priftin” on top and “150” on the bottom) [19].

For patients who cannot swallow them, the tablets may be crushed and added to a small amount of semi-solid food, all of which should be consumed immediately.

Fixed dose combinations tablet of RPT and INH are currently being developed and expected to be registered and marketed soon, facilitating treatment. There will be a film- coated tablet containing RPT 300 mg/ INH 300 mg and a water-dispersible tablet containing RPT 150 mg/ INH 150 mg

Children

RPT is not recommended in children <2 years of age [20]. In children ≤2 years, the recommended dose of RPT for the treatment of LTBI should be determined based on weight of the patient (see chapter 9).

Pregnant women

RPT has been assigned to pregnancy category C [19]. It should only be given during pregnancy when benefit outweighs risk. There are no controlled studies in human pregnancy. Animal studies using doses similar to or less than the human dose (based on body surface area) have revealed evidence of teratogenicity.

Breast feeding women

There are no data on the excretion of RPT into human milk. Due to the potential for serious adverse
reactions in nursing infants, a decision should be made to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

6. International availability - sources, of possible manufacturers and trade names

RPT was approved by the FDA in June 1998 for the treatment of pulmonary TB in combination with one or more antituberculosis drugs and it is currently marketed under the brand name Priftin® by Sanofi in the United States [19]. RPT is also registered in Chile.

Since December 2011 CDC has recommended the use of 3RPT/INH as an effective alternative regimen for the treatment of LTBI in patients ≥12 years old in the US [21]. In November 2014 the FDA approved a supplemental New Drug Application for RPT for the treatment of LTBI in combination with INH in patients 2 years of age and older at high risk of progression to TB disease [20].

The current manufacturer for RPT active ingredient is: Sanofi-aventis S.p.A., Zona e Punto Franco, Casella Postale 199, Brindisi, Italy.

Priftin® film-coated tablet is currently manufactured by: Sanofi Aventis S.p.A., Località Valcanello, 03012 Anagni, Italy.

7. Whether listing is requested as an individual medicine or as an example of a therapeutic group

The application is for inclusion of RPT as an individual medicine, to be used in combination with INH, for the treatment of latent TB infection.
8. Information supporting the public health relevance

LTBI, defined as a state of persistent immune response to stimulation by *Mycobacterium tuberculosis* antigens without evidence of clinically manifested active TB [22], is a very frequent condition: one-third of the world’s population is estimated to be infected with *M. tuberculosis* [23].

The relevance of this condition is determined by the fact that, although the vast majority of infected persons have no signs or symptoms of TB disease and are not infectious, they are at risk for developing active TB disease and becoming infectious in the future. The lifetime risk of reactivation for a person with documented LTBI is estimated to be 5–10% [24]. As TB transmission rates decrease, the majority of incident TB cases concentrates in vulnerable population groups and are generated through re-activation of LTBI acquired abroad or domestically in a distant past [25]. In several low incidence countries reactivation of LTBI accounts for the majority of the TB cases so that preventive therapy of LTBI in high-risk groups (the reservoir of the disease) is at least as relevant as treatment for the disease in order to reduce mortality and human suffering [3]. It is considered that the targets of the END-TB strategy will never be met unless optimal tools for LTBI management are widely implemented. There is substantial evidence that the treatment of LTBI is effective in preventing the progression to active clinical TB disease in 60-90% of treated individuals [26].

Because of an explicit request from Member States on the need for standardized practices on LTBI management, WHO launched in October 2014 the guidelines for the management of LTBI, that recommend systematic testing and treatment of LTBI in several at-risk populations [4]. Five regimens are recommended by WHO for the treatment of LTBI. Considering the regimens of daily INH for 6 or 9 months as the current standard of care for the treatment of LTBI, below is a comparative analysis of the advantages of the RPT/INH regimen over the current standard of care:

<table>
<thead>
<tr>
<th></th>
<th>INH</th>
<th>RPT/INH</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficacy*</td>
<td>TB Incidence in treated subjects 0.40% (15 / 3745)</td>
<td>TB incidence in treated subjects 0.18% (7 / 3986)</td>
<td>The Odds Ratio of 0.44 (0.18-1.07) shows a trend towards significantly higher efficacy of RPT/INH</td>
</tr>
<tr>
<td>Safety*</td>
<td>Incidence of severe hepatotoxicity in treated subjects 2.75% (103 / 3745)</td>
<td>Incidence of severe hepatotoxicity in treated subjects 0.45% (18 / 3986)</td>
<td>The Odds Ratio of 0.16 (0.10-0.27) shows that safety is significantly better in RPT/INH treated subjects</td>
</tr>
<tr>
<td>Completion rate*</td>
<td>69%</td>
<td>82%</td>
<td>The proportion of individuals completing treatment is significantly higher for RPT/INH</td>
</tr>
<tr>
<td>Duration of treatment</td>
<td>6 to 9 month</td>
<td>12 weeks</td>
<td>The RPT/INH shorter duration of treatment is considered to translate into better adherence</td>
</tr>
<tr>
<td>----------------------</td>
<td>--------------</td>
<td>----------</td>
<td>------------------------------------------------------------------</td>
</tr>
<tr>
<td>Dosing</td>
<td>Daily</td>
<td>Weekly</td>
<td>The simpler weekly dosing is expected to increase acceptability under program and patients’ perspective</td>
</tr>
<tr>
<td>Total number of tablets#</td>
<td>180 or 270</td>
<td>108</td>
<td>The smaller number of pills is expected to increase patients’ acceptability</td>
</tr>
</tbody>
</table>

* Data on efficacy, safety and completion rate are derived from Sterling et al. [27]

# Considering isoniazid tablets of 300 mg

From both program and patient perspective, the RPT (900 mg) plus INH (900 mg) combination given once weekly for 12 weeks is regarded as particularly favorable given its high efficacy, low risk of hepatotoxicity and short duration of treatment. The latter factors are recognized as important determinants of the treatment completion rate and, hence, have the potential to substantially improve the cost-effectiveness profile of the overall LTBI management strategy. From the patient perspective, the shorter duration, lower number of pills, weekly dosing, and the better tolerability are expected to significantly increase the acceptance of the intervention.

Indiscriminate treatment of all individuals with LTBI is not recommended because of uncertainties concerning the balance between benefits and harms for the individual. A positive trade-off of benefits and harms is certainly present in the small proportion of individuals with LTBI belonging to at-risk groups for the progression from LTBI to active TB disease [28]. Such groups include those with recent (acquired since two years or less) and all those with conditions which debilitate immune competency (i.e. HIV infection, treatment induced depression of the immune system) [28]. According to WHO guidelines, the target population for LTBI treatment (and therefore the RPT / INH combination) are people living with HIV, adult and child contacts of pulmonary TB cases, patients initiating anti-tumor necrosis factor (TNF) treatment, patients receiving dialysis, patients preparing for organ or hematologic transplantation and patients with silicosis [4]. Systematic testing and treatment of LTBI should also be considered for prisoners, health workers, immigrants from high TB burden countries, homeless persons and illicit drug users [4]. The LTBI guidelines are, in principle, intended to benefit all WHO Member States regardless of their epidemiology of TB as the intent is to improve the diagnosis and management of LTBI in population groups with the highest likelihood of progression to active disease. However, the guidelines are primarily targeted at high-income or upper middle-income countries with an estimated TB incidence rate of less than 100 per 100,000 population. All resource-limited countries should already implement existing WHO guidelines on treatment of LTBI among people living with HIV [5] and child contacts below 5 years of age [6] as a priority.
9. Treatment details

The current application is done for the core essential medicine list.

Treatment duration and association with other drugs:

WHO recommends RPT for the treatment of LTBI in combination with INH as a once-weekly, 12-week regimen.

Dosage:

In adults (weight 50 kg or more) the dose of RPT for the treatment of LTBI is 900 mg (approximately equivalent to 15 mg/kg) (6 tablets of 150 mg) once weekly for 12 weeks in association with INH 15 mg/kg (900 mg maximum).

In children ≥ 2 years, the recommended dose of RPT should be determined based on weight of the child (approximately equivalent to 25 mg/kg), in association with INH 25 mg/kg (900 mg maximum) [20]. The table below can be used to define the recommended number of RPT tablets in children according to weight.

<table>
<thead>
<tr>
<th>Weight range</th>
<th>RPT dose</th>
<th>Number of tablets*</th>
</tr>
</thead>
<tbody>
<tr>
<td>10-14 kg</td>
<td>300 mg</td>
<td>2</td>
</tr>
<tr>
<td>14.1-25 kg</td>
<td>450 mg</td>
<td>3</td>
</tr>
<tr>
<td>25.1-32 kg</td>
<td>600 mg</td>
<td>4</td>
</tr>
<tr>
<td>32.1-50 kg</td>
<td>750 mg</td>
<td>5</td>
</tr>
<tr>
<td>&gt; 50 kg</td>
<td>900 mg</td>
<td>6</td>
</tr>
</tbody>
</table>

*T Tablets of 150 mg

The higher dosing recommendation in children was initially based on single-dose PK studies in children aged 2 to 11 years demonstrating low RPT dose-normalized AUC compared with historical data in adults who received comparable mg/kg doses, suggesting that children required higher weight-based doses than adults [29]. The weight-based dosing algorithm in children was then based on a regression model derived from observed RPT exposures in a PK pediatric study and simulations that used the relation...
between age and dose-corrected total body exposure in children and adults [30]. The adequacy of this algorithm was eventually confirmed by a nested study comparing the PK of children (2 to 11 years old) and adults (≥18 years old) in the TBTC-S26 registration study (see below for more details) and by a population PK study that characterized the PK of RPT and its active metabolite 25-DRPT in children and adults (Weiner M, et al, submitted for publication).

Need for clinical monitoring:

Individuals who receive treatment for LTBI do not have active disease, and therefore, it is mandatory to minimize risks during treatment. Drug-specific adverse reactions can occur with both RPT (cutaneous reactions, hypersensitivity reactions, gastrointestinal intolerance and hepatotoxicity), and INH (asymptomatic elevation of serum liver enzyme concentrations, peripheral neuropathy and hepatotoxicity). WHO does not have specific recommendations on standards of clinical monitoring during LTBI treatment due to the absence of evidence on the optimal monitoring strategy (Sotgiu G et al, submitted for publication). However, WHO suggests routine regular clinical monitoring of individuals receiving treatment for latent TB through a monthly visit to health-care providers [4]. The prescribing health-care provider should explain the disease process and the rationale of the treatment and emphasize the importance of completing treatment. Those receiving treatment are educated about the risk and nature of potential adverse events and to contact their health-care providers should they develop symptoms, such as anorexia, nausea, vomiting, abdominal discomfort, persistent fatigue or weakness, dark-coloured urine, pale stools or jaundice. Treated individuals must be educated to immediately stop treatment whenever a health-care provider cannot be consulted at the onset of these symptoms. Baseline laboratory testing for measurements of serum aspartate aminotransferase, alanine aminotransferase, and bilirubin is encouraged for individuals with risk cofactors: history of liver disease; regular use of alcohol; chronic liver disease; HIV infection; age more than 35 years; and pregnancy or the immediate postpartum period (i.e., within three months of delivery). For individuals with abnormal baseline test results, routine periodic laboratory testing should be done.

Drug-drug interactions

The potential drug-drug interaction between RPT and INH was evaluated in one of the registration studies (Study INT12099 – data on Sanofi files). Co-administration of RPT and INH (900 mg single doses) to healthy young male and female subjects, in fasted condition, did not result in significant change of exposure of RPT or INH compared to administration alone in fasted condition.

As an inducer of CYP450 enzymes RPT may interact with other drugs metabolized by these enzymes. Women of child-bearing age should be instructed that RPT may cause a significant decrease in plasma concentrations and loss of therapeutic effect of hormonal contraception. Women using oral, transdermal
patch, or other systemic hormonal contraceptives should be advised to change to non-hormonal methods of birth control [19].

Currently, RPT is not recommended in HIV-infected patients receiving antiretroviral therapy (ART) for treatment of LTBI or active TB, unless in the context of a clinical trial [31], due to anticipated drug-drug interactions with several antiretroviral drugs. To investigate the interactions between the RPT/INH regimen with efavirenz (EFV), 12 HIV+ TB free subjects with a CD4 > 350 cells/mm3 and viral load< limit of quantification (LOQ), receiving ATRIPLA© (a fixed dose combination of EFV 600 mg, emtricitabine (FTC) 200 mg and tenofovir disoproxyl fumarate 300mg) as background therapy, were enrolled in an open-label, single sequence, two periods, non-randomized study. PK interactions were evaluated after single and repeated administration of RPT 900 mg once weekly. Steady state exposures of EFV, FTC and tenofovir were comparable with and without RPT co-administration. No clinically significant change in CD4 cell counts or viral loads were noted [32].

The PK of EFV was investigated in a nested investigation of the A5279 phase III clinical trial (N=3000) that explores whether RPT and INH taken together daily for one month can produce the same or better results when compared to 9 months of daily INH for the treatment of LTBI in HIV-infected individuals. In 86 enrolled individuals the apparent oral clearance of EFV with and without RPT/INH was equivalent [33]. A decrease in the percentage of participants with EFV concentrations ≥ 1 mg/L during RPT/INH therapy suggested induction of EFV clearance, presumably from RPT. Importantly, the proportion did not cross below the pre-specified threshold of >80%. These drug-drug interaction data suggest that RPT/INH for 4 weeks can be co-administered with EFV-containing ART, and provide the necessary PK evidence for continuing the efficacy assessment of RPT/INH ultra-short therapy for the prevention of TB in HIV-infected individuals.

In one open-label, fixed-sequence, three-period study, 21 healthy volunteers were given raltegravir alone (400 mg every 12 h for 4 days) on days 1-4 of Period 1; rifapentine (900 mg once weekly for 3 weeks) on days 1, 8 and 15 of Period 2 and raltegravir (400 mg every 12 h for 4 days) on days 12-15 of Period 2; and RPT (600 mg once daily for 10 scheduled doses) on days 1, 4-8 and 11-14 of Period 3 and raltegravir (400 mg every 12 h for 4 days) on days 11-14 of Period 3. Plasma raltegravir concentrations were measured. The increased raltegravir exposure observed with once-weekly RPT was safe and tolerable, suggesting that once-weekly RPT can be used with raltegravir to treat LTBI in patients who are infected with HIV [34].
10. Summary of comparative effectiveness in a variety of clinical settings

Efficacy in adults

A systematic review and meta-analysis [35], together with a GRADE assessment, was conducted for the preparation of the WHO guidelines on management of LTBI to answer questions: (1) “In individuals identified with LTBI and at high risk of progression to active TB disease, what treatments have demonstrated efficacy and safety in preventing development of active TB disease?" (2) “In individuals identified with LTBI and at high risk of progression to active TB disease, what is the optimum treatment for preventing active TB disease?"

53 studies met the inclusion criteria of the systematic review. All of them were randomized control trials which evaluated LTBI treatment and recorded at least one of the two pre-specified endpoints (preventing active TB, and/or hepatotoxicity of grade III or above).

There was no trial comparing RPT and INH against placebo or no treatment for LTBI treatment, because at the time this regimen was proposed, it was unethical to randomize individuals who are eligible for LTBI treatment to either placebo or no treatment.

The results of the GRADED analysis (efficacy outcome) of randomized controlled trials that compared RPT / INH with other regimens are summarized below:

<table>
<thead>
<tr>
<th>Comparator</th>
<th>Treatment</th>
<th>Comparator-cases / participants</th>
<th>Treatment-cases / participants</th>
<th>OR (95% CI)</th>
<th>Absolute effect</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>INH 9 m</td>
<td>RPT-INH</td>
<td>15 / 3745</td>
<td>7 / 3986</td>
<td>0.44 (0.18-1.07)</td>
<td>2 fewer per 1000 (3-0 fewer)</td>
<td>Low</td>
</tr>
<tr>
<td>INH 6 m</td>
<td>RPT-INH</td>
<td>22 / 327</td>
<td>24 / 328</td>
<td>1.09 (0.60-1.99)</td>
<td>6 more per 1000 (26 fewer-58 more)</td>
<td>Low</td>
</tr>
<tr>
<td>INH 12-72 m</td>
<td>RPT-INH</td>
<td>8 / 164</td>
<td>24 / 328</td>
<td>1.54 (0.68-3.51)</td>
<td>24 more per 1000 (15 fewer-104 more)</td>
<td>Low</td>
</tr>
</tbody>
</table>
The second and third comparisons refer to one study conducted in HIV infected individuals in South Africa which is described in the relevant chapter (see below).

The first trial refers to the pivotal Phase 3 study TBTC-S26 sponsored and conducted by CDC’s TBTC, conducted primarily in the United States of America USA (23 sites) with a small number of study sites in Canada (3 sites), Brazil (1 site), and Spain (1 site) [27]. Patients in USA and Canada (6883 patients) represented approximately 90% of the total population of the study. This was a multicenter, prospective, randomized, open-label trial conducted among high-risk tuberculin skin test (TST) reactors who required treatment of LTBI to prevent TB disease (including household and other close contacts of TB cases, recent (within 2 years) tuberculin converters, persons with fibrotic lesions on chest X-ray (CXR), HIV-infected persons, and young children (>2 years of age). A cluster randomization scheme was used, that is, the first person in the household to enter the study was randomized, and all subsequent participants from the same household could have elected to receive the same regimen as the first person randomized. Of note, all HIV-infected patients were individually randomized.

The primary objective of Study TBTC-S26 was to compare the effectiveness of 3RPT/INH given by directly observed therapy (DOT) to the effectiveness of self-administered 9INH. The primary effectiveness comparison was development of culture-confirmed TB disease in patients ≥18 years of age or the development of culture confirmed or probable (clinical) TB disease in patients <18 years old within 33 months of study enrolment. Culture-confirmed TB disease was defined as a positive culture for \textit{M. tuberculosis} from any body fluid or tissue. Probable (clinical) TB disease was defined as objective evidence of clinical TB disease (cough, fever, night sweats, weight loss, or haemoptysis) based on history and/or physical examination plus radiograph, computed tomography scan, and/or other diagnostic tests, and without concurrent illness that would explain the findings. The primary effectiveness comparison was performed on the modified intent-to-treat (MITT) population. The MITT population included all patients who enrolled in the study and were eligible for the study. For the primary analysis all follow-up time was utilized, even from patients who did not complete treatment or did not complete 33 months of follow-up. A secondary analysis was conducted that included follow-up data up to 24 months following completion of therapy. Because the effectiveness of 3RPT/INH regimen, which was given by DOT (likely resulting in a high compliance rate), would be expected to more closely approximate its efficacy, compared with the 9INH regimen (which was self-administered daily), as a secondary endpoint, efficacy was evaluated comparing development of TB disease using the per protocol (PP) population. The PP population included all enrolled and eligible study patients who completed study drug within the targeted time period or developed TB disease or died while on study therapy (or during follow-up) but competed at least 75% of the expected number of doses prior to the event. Treatment adherence and treatment completions rates were considered as secondary endpoints accounting for effectiveness. Lastly, a description of patterns of antibiotic resistance among \textit{M. tuberculosis} isolates in patients who developed TB disease despite treatment of LTBI was an additional key secondary endpoint.
For the analysis of the primary objective, a non-inferiority study design was chosen [27]. The non-inferiority test statistic was based on the difference of the nonparametric Kaplan-Meier estimators. The asymptotic variance of the test statistic was obtained through Greenwood’s formula and a two-sided 95% confidence interval (CI) was constructed for the difference. If the upper bound of the CI was smaller than the non-inferiority margin $\delta$ (0.75%), then the null hypothesis would be rejected and non-inferiority could be claimed. Because the non-inferiority margin used for the main outcome analysis (0.75%) was high in comparison to the event TB rate actually observed in the 2 treatment arms, a post-hoc analysis was additionally conducted by CDC in which a 50% relative non-inferiority margin (relative to the observed TB disease event rate in the active control [9INH] arm) was used (Sanofi, data on file). Additional sensitivity analyses with different methods of handling deaths, losses to follow-up, and other missing data were also conducted.

In the MITT population at 33 months after enrolment in the TBTC-S26 main study (30 months after 3RPT/INH treatment and 24 months after 9INH treatment), TB disease (culture confirmed) developed in 7 of 3986 patients in the 3RPT/INH treatment arm (cumulative rate, 0.19%) and in 15 of 3745 patients in the 9INH treatment arm (cumulative rate, 0.43%), for a difference of -0.24% with an upper limit of the 95% CI of +0.01%, which is smaller than the non-inferiority margin of +0.75% (Table).

### Table 2. Number of Subjects with Tuberculosis and Event Rates.

<table>
<thead>
<tr>
<th>Population and Study Group</th>
<th>No. of Subjects</th>
<th>Subjects with Tuberculosis</th>
<th>Difference in Cumulative Rate$^\dagger$</th>
<th>Upper Limit of 95% CI for Difference in Cumulative Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Modified intention-to-treat analysis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isoniazid only</td>
<td>1745</td>
<td>15</td>
<td>0.16</td>
<td>0.43</td>
</tr>
<tr>
<td>Combination therapy</td>
<td>1986</td>
<td>7</td>
<td>0.07</td>
<td>0.19</td>
</tr>
<tr>
<td><strong>Per-protocol analysis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isoniazid only</td>
<td>1585</td>
<td>8</td>
<td>0.11</td>
<td>0.32</td>
</tr>
<tr>
<td>Combination therapy</td>
<td>1273</td>
<td>4</td>
<td>0.05</td>
<td>0.13</td>
</tr>
</tbody>
</table>

$^*$ Combination therapy consisted of 3 months of directly observed once-weekly therapy with rifapentine (900 mg) plus isoniazid (900 mg). Isoniazid-only therapy consisted of 9 months of self-administered daily isoniazid (300 mg). Data are shown for a period up to 33 months after study enrollment.

$^\dagger$ The difference is the rate in the combination-therapy group minus the rate in the isoniazid-only group.

The 3RPT/INH regimen was consistently non-inferior to the 9INH regimen from the time of enrolment throughout the entire 33-month follow-up period. The cumulative TB disease event rate increased steadily throughout 33 months of follow-up in the 9INH arm but tended to plateau by 20 months in the 3RPT/INH arm. An increase in TB disease risk late during the follow-up phase was not observed (Figure).
As a secondary endpoint, an analysis of efficacy was conducted among patients who completed treatment. The results of this analysis at 33 months after enrolment were consistent with the primary outcome MITT analysis, with a cumulative TB event rate of 0.32% in the 9INH arm and 0.13% in the 3RPT/INH arm, which met the criteria for non-inferiority [27].

Statistically significantly more patients in the 3RPT/INH arm of the TBTC-S26 main study completed the treatment regimen (82.1%) than in the 9INH arm (69.0%; p<0.0001). Similarly, treatment adherence was higher (84.7% completed 100% or more doses) in the 3RPT/INH arm than in the 9INH arm (74.6%) [27].
Efficacy in HIV infected adults

The second and third comparisons included in the GRADE evaluation are derived from a study conducted on HIV infected individuals [36]. The primary endpoint of this study was TB or death. The trial was designed to assess potential superiority of three investigated regimens (3RPT/INH, rifampicin 600 mg + INH 900 mg twice weekly for 12 weeks [3rifampicin/INH], INH 300 mg daily for up to 6 years [continuous INH], compared with the standard INH therapy (INH 300 mg daily for 6 months [6INH], control group). A total of 1148 HIV-infected patients in Soweto, South Africa (classified as a high burden TB country by WHO) with LTBI and a median CD4 of 484 cells/mm3 were enrolled and followed for a median time of 4 years. The TB event rates per 100 patient-years were similar across treatment groups: 2.0 in the 3RPT/INH group, 2.0 in the 3rifampicin/INH group, and 1.4 in the continuous INH group, as compared with 1.9 in the 6INH group (p>0.05 for all comparisons to the 6INH group, by log-rank test). Adherence was highest in the shorter duration (12 week) weekly or twice weekly regimens compared with the longer daily regimen for 6 months. The proportions of patients who took more than 90% of their assigned doses of study medication in the allotted time were 95.7% in the 3RPT/INH group, 94.8% in the 3rifampicin/INH group, and 83.8% in the 6INH group.

Additional evidence of efficacy of RPT/INH (not included in the systematic review and metanalysis because result are not published yet) in HIV infected persons come from a sub-study of the TBTC-S26 main study [37]. An analysis of the full cohort of 403 HIV-infected patients enrolled in this sub-study was conducted when all HIV-infected patients completed follow-up (up to 33 months after study enrolment). At 33 months after study enrolment, TB disease developed in 6 of 193 patients in the 9INH arm and 2 of 206 patients in the 3RPT/INH arm, resulting in cumulative TB event rates of 3.50% for the 9INH arm and 1.01% for the 3RPT/INH arm. Consistent with the overall TBTC-S26 main study population, the treatment completion rate in the HIV sub-study was higher in the 3RPT/INH arm than in the 9INH arm: 88.8% versus 63.7%, respectively, (p<0.0001). Treatment adherence (i.e., completion of 100% or more doses) was also higher in the 3RPT/INH arm than in the 9INH arm (92.2% versus 77.2%).

Neither of the two above studies had sufficient statistical power for the non-inferiority comparison of effectiveness between the 3RPT/INH and 6 or 9INH treatment groups because of the small numbers of patients, but both provide additional valuable clinical data to indicate the effectiveness of 3RPT/INH treatment in HIV-infected patients. In the Martinson study [36], the incidence of TB disease was higher in all treatment groups compared with that observed in the TBTC-S26 HIV sub-study (reflecting the background TB disease incidence rate), but was generally consistent with the TBTC-S26 HIV sub-study in that there was no difference in the incidence rates of TB disease or death in the 3RPT/INH group compared with group treated with daily INH for 6 months.
Efficacy in children

When the TBTC-S26 main study started, the lack of published data on the efficacy, safety, or PK of RPT in children <12 years old precluded enrolment of young children. TBTC-S26 was subsequently amended to include children ages 2 to 11 years in May 2005. Later, the enrolment of the youngest children (from 2 to 11 years old) was extended beyond the date when the target sample size was reached for the TBTC-S26 main study. The purpose of this was to achieve an adequate sample size for the assessment of tolerability and safety of the study treatments in children. Approximately 67% of the 1058 children ultimately enrolled were included in the TBTC-S26 main study analysis. An analysis of the full cohort of enrolled paediatric patients (ie, those included in the TBTC-S26 main study as well as those included as a result of extending enrolment) was conducted when 98% of the cumulative follow-up expected at the end of study had been collected (as of the data cut-off date of 30 April 2013). At this date, 2294 person-years of follow-up in 908 paediatric patients had been accumulated (98% of the follow-up expected at the end of study) (Sanofi, data on file and submitted for publication).

Three out of 436 children in the 9INH arm and none of the 472 children in the 3RPT/INH arm developed TB disease, for cumulative rates of 0.78% and 0%, respectively.

Consistent with the overall TBTC-S26 main study population, the treatment completion rate in the paediatric sub-study was higher among children in the 3RPT/INH arm than in the 9INH arm: 88.1% versus 81.0%, respectively, (p=0.003). Treatment adherence (i.e., completion of 100% or more doses) was also higher in the 3RPT/INH arm than in the 9INH arm (91.7% versus 85.3%).

While this sub-study was not powered to allow for the non-inferiority comparison of effectiveness between 3RPT/INH and 9INH treatment groups, the available data provide evidence of 3RPT/INH treatment effectiveness in children between the ages of 2 and 17 years that is consistent with the TBTC-S26 main study population and confirm the adequacy of the dosing regimens used in children 2 to 17 years old to protect against the development of TB.

Antibiotic resistance

An increased risk of developing rifamycin resistance had previously been demonstrated while treating patients with HIV associated TB with an intermittent (once weekly) RPT regimen [38]. This effect had never been observed in HIV-uninfected patients [17] and was independent from the use of antiretroviral drugs [38]. It was speculated that the long half-life of RPT and the very short half-life of INH likely leads to exposure to a single drug and to the development of resistance [39]. Hence, while treating LTBI, selection
of resistant mycobacteria may also occur if cases are treated with a preventive therapy regimen while having active TB.

As part of the process for the preparation of the WHO LTBI management guidelines one systematic literature review and meta-analysis, using GRADE assessment, was conducted to answer the question: “Does treatment for LTBI lead to significant development of resistance against the drugs used for LTBI?”.

Six studies were included in the comparison of rifamycin resistance in those treated with a rifamycin containing regimen vs. a regimen not containing rifamycin [27, 36, 40-43]. There were very few cases of rifamycin resistance, a total of 6 (0.1%) cases in 5790 individuals receiving LTBI treatment with a rifamycin containing drug and 5 (0.09%) cases in the 5537 individuals in the control group (RR 1.12, 95% CI 0.41-3.08). The quality of the evidence was rated as very low after downgrading for risk of bias, indirectness and imprecision. The systematic review concluded that preventive treatment with rifamycin containing regimens did not significantly increase rifamycin resistance, although the certainty of this effect was very low.

Among the specific studies, Martinson and colleagues did not detect increased selection of resistant organisms using the 3RPT/INH regimen in HIV infected persons [36]: overall, the prevalence of multidrug-resistant tuberculosis was similar to that estimated in South Africa at the time of the study. However, the sample was very small.

Similarly, no pattern in drug resistance of culture-confirmed TB disease was noted during the TBTC-S26 main study [27]. Of the 22 subjects in whom tuberculosis was diagnosed (15 in the isoniazid, and 7 in the isoniazid and RPT group), 20 cases were confirmed on culture. There were 2 INH-resistant cases (both in the INH-only group) and 1 rifampin-resistant case (in the combination-therapy group). The latter case occurred in a subject with HIV infection (CD4+ count, 271 per cubic millimeter at enrolment) and INH-susceptible M. bovis infection who had treatment interruptions and completed therapy late. In summary, the incidence of drug resistance in this study was low and similar between the 2 treatment arms. During the extended enrolment for the TBTC-S26 HIV sub-study, a case of multi-resistant strain (INH-RIF-streptomycin) was found in one HIV infected patient in the 9INH arm.

Summary on efficacy

The results of clinical trials demonstrate the effectiveness of the once weekly, RPT/INH 12-week regimen for the treatment of LTBI in adults, children ≥2 years, and HIV-infected and HIV-non infected patients. Non-inferiority in terms of efficacy and significantly better treatment adherence and completion of the 3RPT/INH regimen compared with the standard 9INH self-administered one were consistently
demonstrated in various study subpopulations. Multiple sub-analysis indicated that the 3RPT/INH arm was non-inferior to the 9INH arm, thereby suggesting a robust effect.

In the pivotal TBTC-S26 study, treatment in the 3RPT/INH arm was administered as DOT. In addition to shorter treatment duration, DOT likely contributed to the higher treatment completion rate of 3RPT/INH regimen. One study, whose results are expected to be published at the beginning of 2015 (TBTC-S33), will provide evidence on the effectiveness of the RPT/INH under self-administration compared to the DOT one.

Given the small number of patients who developed TB disease in the 5 published trial using rifamycins for the treatment of LTBI, it is unclear whether the very few emerging strains which were resistant to rifampicin or INH were related to the study regimens. It will be important to monitor for RPT resistance in breakthrough TB disease when the combination regimen is used in clinical practice especially in HIV-infected patients due to the favourable conditions for the emergence of resistant strains produced by advanced HIV disease.
11. Summary of comparative evidence on safety

Source of the data

1. The WHO commissioned systematic review and [35], together with a GRADE assessment related to the safety analysis.

2. The evaluation of the safety of 3RPT/INH for the treatment of patients with LTBI is the TBTC-S26 study sponsored and conducted by CDC’s TBTC [27], including 2 TBTC-S26 sub-studies (TBTC-S26 paediatric sub-study and TBTC-S26 HIV sub-study). The safety population consists of a total of 7799 adults (some of whom were HIV-infected) and children. Safety analyses of the paediatric population were performed on a total of 1,032 children (2 to 17 years of age) (TBTC-S26 paediatric sub-study). Approximately half of the children in the safety population were 2 to 11 years of age (522 children) and half were 12 to 17 years old (510 children). The sub-population of subjects with HIV infection consisted of a total of 493 HIV-infected patients (TBTC-S26 HIV sub-study). The safety data from the TBTC-S26 main study and 2 sub-studies are presented separately. There was no pooling of data across studies.

3. Supportive safety information provided by two additional studies that investigated the RPT/INH LTBI regimen in patients at high risk of developing TB disease, conducted in HIV-infected adult patients in South Africa [36] and HIV-non infected adult patients in Brazil [44].

4. Data from the SANOFI pharmacovigilance database, established after Priftin® 150 mg tablets was registered and marketed in the USA in June 1998 for the treatment of active TB.

WHO metanalysis results

A summary of RPT/INH related toxicity (derived from the systematic review and metanalysis published by Stagg and co-workers [35]) is shown in the GRADE table below. RPT-INH (as well as rifampicin alone) ranked with low rates of AEs in the hepatotoxicity analysis.

<table>
<thead>
<tr>
<th>Comparator</th>
<th>Treatment</th>
<th>Comparator-cases / participants</th>
<th>Treatment-cases / participants</th>
<th>OR (95% CI)</th>
<th>Absolute effect</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>INH 6 m</td>
<td>RPT-INH</td>
<td>17 / 327</td>
<td>17 / 328</td>
<td>1.00 (0.50-1.99)</td>
<td>0 fewer per 1000 (25 fewer-46 more)</td>
<td>Low</td>
</tr>
<tr>
<td>INH 9 m</td>
<td>RPT-INH</td>
<td>103 / 3745</td>
<td>18 / 3988</td>
<td>0.16 (0.10-0.27)</td>
<td>23 fewer per 1000 (25-20 fewer)</td>
<td>Moderate</td>
</tr>
<tr>
<td>INH 12-72 m</td>
<td>RPT-INH</td>
<td>35 / 164</td>
<td>17 / 328</td>
<td>0.20 (0.11-0.37)</td>
<td>162 fewer per 1000 (184-122 fewer)</td>
<td>Moderate</td>
</tr>
</tbody>
</table>
Little change in the effect was seen when data were stratified by immunosuppression, HIV status, incidence of TB in the country of study, age, and other factors, including the use of pyridoxine. Serious AEs such as hospitalisation were rare across all studies: this analysis beyond toxic hepatitis, included neuropathies, haematological abnormalities and symptoms such as headaches, dizziness, itch, rash or gastrointestinal symptoms. 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. However, in many studies the cause of deaths was not always clear and there is a possibility of under-ascertainment of toxicity related deaths.

Safety data from the TBTC-S26 study

Safety in adults

In Study TBTC-S26, individuals reported to the clinic every 4 weeks during the Treatment Phase (3 months for the 3RPT/INH arm and 9 months for the 9INH arm) for clinical assessment [27]. Safety was assessed in all patients by evaluation of AEs, clinical evaluation of TB symptoms or toxicities, and safety laboratory testing. AEs were recorded while patients were on study drug therapy and up to 60 days after the last dose of study medication, and deaths were recorded up to 33 months after enrolment. Clinical laboratory testing was done on the first 322 patients in each treatment arm, on HIV-infected persons, and on those with known liver disease (or at risk for same) or when deemed necessary by the Investigator. The sample size of 644 patients for clinical laboratory monitoring was calculated to be sufficient to allow assessment of safety and tolerability by the Data and Safety Monitoring Board (DSMB).

The table summarizes treatment-emergent adverse events (TEAE) reported in ≥0.5% of individuals in TBTC-S26 main study by the Medical Dictionary for Regulatory Activities (MedDRA) system organ class.

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Preferred Term</th>
<th>3RPT/INH (N=4040) N (%)</th>
<th>9INH (N=3759) N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Immune system disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypersensitivity</td>
<td></td>
<td>161 (4)</td>
<td>18 (0.5)</td>
</tr>
<tr>
<td><strong>Hepatobiliary disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatitis</td>
<td></td>
<td>24 (0.6)</td>
<td>113 (3)</td>
</tr>
<tr>
<td><strong>Nervous system disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td></td>
<td>26 (0.6)</td>
<td>17 (0.5)</td>
</tr>
<tr>
<td><strong>Skin and subcutaneous tissue disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin reaction</td>
<td></td>
<td>31 (0.8)</td>
<td>21 (0.6)</td>
</tr>
</tbody>
</table>

*Includes events reported through 60 days after last dose of study drug
By treatment arm, the most frequently reported TEAEs were hepatitis and pregnancy for the 9INH arm and hypersensitivity and pregnancy in the 3RPT/INH arm. Of note, all hypersensitivity events reported in the 3RPT/INH treatment arm and almost all hepatitis events reported in the 9INH treatment arm were considered related to study treatments.

Safety in children
In the TBTC-S26 paediatric sub-study, the most frequently reported TEAEs in the 9INH arm were medication error (2.6%) and otitis media and pregnancy (1.0% each). The most frequently reported events in the 3RPT/INH arm were medication error (1.5%) and hypersensitivity (1.3%). The TEAE profile for 3RPT/INH in the paediatric population was generally similar to that observed in the TBTC-S26 main study. Hypersensitivity was one of the most frequently occurring TEAEs in 3RPT/INH arm in both the populations, but occurred with a higher frequency in the main study compared with the paediatric sub-study (4.0% versus 1.3% respectively). There were no cases of hepatotoxicity in the paediatric sub-study in either treatment group.

Safety in HIV infected individuals
In the TBTC-S26 HIV sub-study, the most frequently reported events in the 9INH arm included hepatitis (7.0%), pharyngitis (4.3%), diarrhoea (3.2%), herpes zoster (2.7%), gastritis (2.7%), anaemia (2.7%), genital herpes (2.2%), and ano-genital warts (2.2%). Each of these TEAEs occurred with a higher frequency in the 9INH arm when compared with the 3RPT/INH arm. The most frequently occurring TEAE in this group was diarrhoea (1.9%). The TEAE incidence rates for the HIV sub-study were generally higher than those observed in the TBTC-S26 main study, which included mostly HIV-non infected patients. The TEAE profile for 3RPT/INH in the HIV population was generally similar in terms of types of TEAEs reported to that observed in the TBTC-S26 main study. A notable exception is that hypersensitivity (MedDRA preferred term) was one of the most frequently reported TEAEs in the TBTC-S26 main study population and only occurred in 1 HIV-infected patient in the 3RPT/INH arm. Also, hepatitis (MedDRA preferred term) was more frequently reported in HIV-infected patients treated with 9INH as compared to HIV-infected patients receiving 3RPT/INH (7.0% versus 1.5%) and compared with the TBTC-S26 main study patients receiving 9INH (7.0% versus 3.0%, respectively).
Adverse events of clinical importance

Hepatotoxicity

Hepatotoxicity was defined as aspartate aminotransferase (AST) ≥3 x upper limit of normal (ULN) in the presence of specific signs or symptoms of hepatitis or AST >5 x ULN regardless of signs/symptoms of hepatitis or an event deemed by the treating clinician investigator as hepatotoxicity. Signs and symptoms associated with hepatotoxicity included jaundice, nausea, vomiting, anorexia, fatigue, weakness, abdominal discomfort/pain over liver, dark urine, pale stools, and itchiness. In the TBTC-S26 main study, hepatitis (hepatotoxicity) was reported as an AE more frequently in patients in the 9INH treatment arm (3.0%) than in the 3RPT/INH treatment arm (0.6%). Most events of hepatotoxicity were reported with a maximum toxicity of Grade 3, including 65% in the 9INH arm and 75% in the 3RPT/INH arm. Fifteen Grade 4 hepatotoxicity events were reported (12 in the 9INH arm and 3 in the 3RPT/INH arm). There were no cases of Grade 5 or death due to hepatotoxicity recorded. The proportion of patients who discontinued due to treatment-related hepatotoxicity was 2.0% in the 9INH arm and 0.3% in the 3RPT/INH arm.

No cases of hepatotoxicity occurred in the paediatric population.

Among the HIV-infected patients in the TBTC-S26 HIV sub-study, the incidence of TEAEs of hepatitis was again higher in the 9INH arm than the 3RPT/INH arm (7.0% versus 1.5%). Eight of the 11 HIV-infected patients in the 9INH arm and 2 of the 3 HIV-infected patients in the 3RPT/INH arm with hepatotoxicity, discontinued treatment due to this event. All cases of hepatotoxicity were considered by the Investigator to be related to treatment. Overall, the incidence of hepatotoxicity was higher in the HIV-infected patients than in population of the TBTC-S26 main study, but this difference was specific only to the 9INH arm.

Hypersensitivity

Patients were monitored during the TBTC-S26 main study and sub-studies for signs and symptoms of allergic drug reactions. The case definition of possible hypersensitivity was patients who developed a Grade 2, 3, or 4 AE (except isolated hepatotoxicity) that was considered by the Investigator to be study drug-related, and for which there was no other known explanation. Cases were to be subsequently categorized into one of the following 3 categories. Persons who developed either:

1. One of the following, occurring in temporal relation to taking study drug on at least one occasion:
   hypotension, urticarial, angioedema: (or angioneurotic edema), acute bronchospasm, or conjunctivitis
2. At least four of the following symptoms (at least one of which was reported as an AE of >grade 2) that occurred in relation to taking study drug: weakness, fatigue, nausea, vomiting, headache, fevers, aches, sweats, dizziness, shortness of breath, flushing, or chills.

3. An AE attributable to study drug that resulted in permanent or temporary drug discontinuation and for which there was no other known explanation.

The incidence of patients in the TBTC-S26 main study who met the case definition of possible hypersensitivity was higher in the 3RPT/INH arm compared with the 9INH arm (3.8% versus 0.5%). The majority of the possible hypersensitivity events resulted in permanent discontinuation from treatment. A total of 14 cases of possible hypersensitivity (or drug reaction) events in the 3RPT/INH arm and 1 case in the 9INH arm were considered life-threatening (Grade 4) or was reported as a serious adverse event (SAE). Based on an ad hoc analysis performed by CDC on possible hypersensitivity reactions or other drug related reactions, possible hypersensitivity in the 3RPT/INH arm presented by clinical syndrome included mainly flu-like syndrome defined as presence of fever or chills and weakness, fatigue or muscle pain, and aches, syncope, heart rate >100 bpm, palpitations, flushing, dizziness, red eyes, or sweats; and cutaneous syndrome defined as angioedema, urticarial, rash and itching.

The incidence of possible hypersensitivity events was lower in the paediatric population compared with the TBTC-S26 main study, occurring in 1.3% of children in the 3RPT/INH arm and in no children in the 9INH arm in the TBTC-S26 paediatric sub-study. Most of the children with possible hypersensitivity were 12 to 17 years of age. All events were considered either related to study drug by the Investigator and most were mild or moderate in severity. Four of 7 children discontinued treatment permanently due to this event.

In the TBTC-S26 HIV sub-study, 2 patients (1.0%) in the 3RPT/INH arm and no patients in the 9INH arm had an event that met the case definition of possible hypersensitivity. This incidence was lower than that observed in the TBTC-S26 main study (3.8%). The 2 cases of possible hypersensitivity were both considered probably related to study drug by the Investigator and both resulted in permanent discontinuation from study treatment.

**Serious adverse events**

In the TBTC-S26 main study, the overall incidence of SAEs was low. SAEs were reported in 2.7% of patients in the 9INH arm and 1.5% of patients in the 3RPT/INH arm. The most frequently reported SAEs in the 9INH arm were chest pain (7 patients, 0.19%) and hernia repair, cellulitis, pneumonia, abdominal pain, depression, hepatitis, hypertension, and anaemia (in 3 patients each, 0.08%). In the 3RPT/INH arm, the only SAE that occurred in more than 2 patients was hypersensitivity (8 patients, 0.20%).
In the TBTC-S26 paediatric sub-study, SAEs were reported in 6 children (1.2%), all of whom were in the 9INH arm and none were treatment related. SAEs included asthma, bronchial hyper-reactivity, vomiting, ankle fracture, depression, and Kawasaki’s disease.

In the TBTC-S26 HIV sub-study, SAEs were reported in 10.8% of 9INH patients and 3.9% of 3RPT/INH patients. The most frequently reported SAEs in the 9INH treatment arm were anemia, suicide attempt, and hepatitis (only the cases of hepatitis were considered related to treatment). No individual SAE in the 3RPT/INH arm occurred in more than 1 patient.

Withdrawals due to adverse events

In the TBTC-S26 main study, the incidence of patients who permanently discontinued treatment due to a treatment-related TEAE was higher in the 3RPT/INH arm (4.9%) than in the 9INH arm (3.8%). The most frequent treatment-related TEAE leading to discontinuation was hepatitis for the 9INH arm (2.0%) and hypersensitivity for 3RPT/INH (3.0%). All other treatment-related TEAEs resulting in permanent discontinuation were reported in ≤0.5% of patients.

In the TBTC-S26 paediatric sub-study, the incidence of permanent discontinuations due to treatment-related TEAEs was generally lower than that observed in the main study. TEAEs resulting in permanent discontinuation included hypersensitivity, skin reaction, pruritic rash, asthenia, drug intolerance, influenza-like illness, vomiting, and decreased appetite. Most events were reported in only 1 patient each. Permanent discontinuation due to hypersensitivity was reported in 4 patients in the 3RPT/INH treatment arm. In fact, in the 3RPT/INH arm, all of the TEAEs resulting in permanent discontinuation were signs and symptoms of drug intolerance/hypersensitivity.

The incidence of permanent treatment discontinuation due to treatment-related TEAEs was similar in the HIV-infected population compared with the TBTC-S26 main study (3.38% of HIV-infected patients in the 3RPT/INH arm and 4.30% of HIV-infected patients in the 9INH arm). All of the discontinuations in the 9INH arm were due to hepatitis, while 2 patients discontinued due to hepatitis in the 3RPT/INH arm.

Deaths

A total of 70 patients died during the TBTC-S26 main study, including 39 (1.0%) in the 9INH treatment arm and 31 (0.8%) in the 3RPT/INH treatment arm. Eleven of these deaths (7 in the 9INH treatment arm and 4 in the 3RPT/INH treatment arm) occurred while on therapy or within 60 days of last dose. In the 9INH arm, the most frequent cause of death (by International Classification of Disease [ICD9] category) was malignant neoplasms (cancer), followed by intentional injuries. In the 3RPT/INH arm, again the most frequent cause of death (by ICD9 category) was malignant neoplasms (cancer) and disease of heart, followed by chronic liver disease/ or cirrhosis or cerebrovascular diseases. Deaths related to intentional injuries were reported more frequently in the 9INH treatment arm (6 patients) than in the 3RPT/INH
The most frequent cause of death overall was lung cancer, reported in 7 patients, including 5 in the 9INH arm and 2 in the 3RPT/INH arm.

Two paediatric patients enrolled in the TBTC-S26 paediatric sub-study died. One death was due to malignant arrhythmia (16 year old girl) and the second was due to a gunshot wound (16 year old boy). Both patients were in the 9INH treatment group.

A total of 11 patients enrolled in the TBTC-S26 HIV sub-study died; 5 patients were in the 9INH arm and 6 patients were in the 3RPT/INH arm. Only one of the deaths was reported within 60 days of the last study dose (chronic liver disease in the 9INH arm).

Both paediatric patients and 4 of the 11 HIV-infected patients who died, had been enrolled in the TBTC-S26 main study and are included in the 70 deaths counted for that study. Thus, a total of 77 deaths were reported during TBTC-S26 main study and substudies: 41 deaths in 9INH arm versus 36 deaths in 3RPT/INH arm. None of the reported deaths were considered related to treatment with study medication or were attributed to TB disease.

Clinical laboratory data

In TBTC-S26 main study serum laboratory testing was performed within 60 days of enrolment for the first 644 patients (322 per treatment arm) enrolled. Evaluations included AST, alanine aminotransferase (ALT), total bilirubin, alkaline phosphatase, creatinine, haematocrit, haemoglobin, and complete blood count (CBC) with platelets. These laboratory tests were also performed on all HIV-infected persons and those patients with known liver disease or at risk for same. The AST was repeated after 1 month of study treatment if the baseline results were above the ULN. The AST and total bilirubin were also drawn at any time during the Treatment Phase if the patient developed symptoms of hepatitis. The CBC with platelets was repeated if there was clinical evidence of anaemia or petechiae.

There were no clinically significant changes in haematology parameters noted for the first 644 patients or in high-risk patients evaluated during the TBTC-S26 main study.

Among HIV-infected patients evaluated in the TBTC-S26 HIV sub-study, there were likewise no clinically significant changes in haematology parameters noted. For most clinical chemistry parameters, the number of HIV-infected patients who exhibited a shift from “normal” to “abnormal” was similar between treatment arms. In this analysis, abnormal was defined as any value greater than 1 unit ULN. For AST, 22 patients (of 186 evaluated) in the 9INH arm shifted from normal to abnormal after 1 month, compared with 18 patients (of 207) in the 3RPT/INH arm. Seven patients in the 9INH arm and 1 patient in the 3RPT/INH arm experienced a shift in AST from normal at baseline to >5 x ULN at any assessment during treatment. For ALT, 15 patients in each treatment arm shifted from normal to abnormal after 1 month. Three patients in the 9INH arm and no patients in the 3RPT/INH arm experienced a shift in ALT from normal at baseline.
to >5 x ULN at any assessment during treatment. An additional 2 patients in the 9INH arm and 1 patient in the 3RPT/INH arm had a post-baseline ALT value >5 x ULN, but the baseline assessments were missing. For the parameter of bilirubin, the number of patients with a shift was lower for the 9INH arm, where 2 (of 186) in the 9INH arm shifted from normal to abnormal at 1 month, compared to 7 (of 207) in the 3RPT/INH arm.

There was no notable pattern of change in CD4 count in either treatment group.

**Safety in supportive studies**

In an early clinical trial a regimen of once-weekly doses of directly observed RPT and INH (900 mg each once a week) for 12 weeks was compared with self-administered rifampin and pyrazinamide for two months for the treatment of LTBI in 399 TST-positive, adult, largely HIV-negative household contacts in Brazil [44]. The RPT/INH regimen was associated with significantly less toxicity than rifampin and pyrazinamide. Grade 3 (AST or ALT 5–10 times the UNL) or 4 (AST or ALT > 10 times UNL) hepatotoxicity occurred in 2 of 206 (1%) participants assigned to RPT/INH versus 20 of 193 (10%) participants assigned to rifampicin and pyrazinamide (p < 0.001).

In the Martinson study, rates of serious adverse events (grade 3 or 4 toxic effects, death, and active tuberculosis) while patients were receiving the study drugs were 8.7 per 100 person-years in the RPT/INH group, 10.6 per 100 person-years in the rifampicin/INH group, 18.4 per 100 person-years in the continuous-isoniazid group, and 15.4 per 100 person-years in the 6-month–isoniazid group (P>0.05 for all comparisons with the 6-month–isoniazid group) [36]. There were no deaths attributed to a study drug. A grade 3 or 4 elevation in the aspartate or alanine aminotransferase level occurred during the treatment phase in 1.5%, 2.4%, 28.0%, and 5.5% of patients in the RPT/INH, rifampicin/INH, continuous-INH, and 6-month–INH groups, respectively (P<0.001 for the comparison of continuous INH with 6-month INH).

Hypersensitivity has not been reported in the studies by Martinson and Schechter that used the same 3RPT/INH treatment regimen.

**Data from pharmacovigilance**

Priftin® 150 mg tablets has been registered and marketed in the USA as of June 1998 for the treatment of active TB in combination of one or more anti-TB drugs as part of a standard regimen. According to the prescribing information RPT was not recommended in children <12 years of age and in HIV-infected patients for the treatment of active TB.
A cumulative search in the Sanofi pharmacovigilance database from registration on 22 June 1998 to 01 December 2013 revealed a total of 6 spontaneous reports and 54 solicited cases involving RPT as suspect drug regardless of indication.

All 6 spontaneous reports originated from health care professionals including 1 literature case. Four were non-serious cases. Two cases were serious including a hypersensitivity reaction and a respiratory failure due likely to lorazepam intake.

- Hypersensitivity reaction occurred in a 49 year-old female after 4 doses of RPT 600 mg once weekly + INH. Symptoms including pyrexia, vomiting and body aches resolved with IV fluids and diphenhydramine. Positive re-challenges were noted with RPT + INH combination then with INH alone, (each time in association with diphenhydramine).
- Fatal acute respiratory failure occurred in a 65 year-old male patient with uremia for 3 years (on maintenance with hemodialysis), renal anemia for 3 years, hypertension for 7 years, type 2 diabetes for 7 years, and paroxysmal chest distress who had discontinued anti TB treatment with INH, ethambutol and RPT (dosages unspecified) after less than 2 months due to onset of numbness in lower limbs and bilateral blurred vision. Citalopram (hold for a few days then resumed at a higher dose), melitracen, flupentixol, and olanzapine had been recently introduced and the patient died from respiratory failure, a few weeks after discontinuation of anti TB treatment, and after addition of a unique dose of lorazepam (which was the subject of this article). No autopsy information was provided.

A total of 54 solicited reports (8 non-serious and 46 serious, including 12 with fatal outcomes) have been received. None of the deaths were related to RPT by the Investigators. The review of solicited cases did not revealed any new safety issues.

Summary on safety

In conclusion, the results of the WHO commissioned metanalysis of published data and the TBTC-S26 registration study show that 3RPT/INH is well tolerated when used for the treatment of LTBI, including children (2 to 17 years old) and HIV-infected and HIV-non infected adults. The 3RPT/INH regimen is associated with less hepatotoxicity and more possible hypersensitivity reactions than the standard LTBI therapy, 6- or 9INH.
In the TBTC-S26 main study, the frequency of patients reporting at least one TEAE or SAE was lower in the 3RPT/INH arm compared with the 9INH treatment arm, while the incidence of treatment-related TEAEs was higher in the 3RPT/INH treatment arm. This finding may be due to factors related to the drugs but could also be related to more frequent interaction between subjects and study staff in the combination-therapy group (weekly DOT plus monthly visits during treatment) and the open-label use of a new combination-therapy regimen.

No differences were observed in the frequency of Grade 3 or 4 AEs. Rates of death were low (approximately 1%) in both arms with none considered related to study drug(s) or attributed to TB disease. The safety pattern observed in the TBTC-S26 main study was generally consistent with the profile previously described and established for RPT USA labelling.

In both the WHO metanalysis and the TBTC-S26 study, hepatotoxicity events occurred with a higher incidence in the 9INH arm compared with the 3RPT/INH arm (3.0% and 0.6%, respectively). Most events of hepatotoxicity were reported with a maximum toxicity of Grade 3. Although the incidence of hepatotoxicity was lower in 3RPT/INH arm, monitoring of treatment-associated adverse events (eg, icterus, tenderness of the liver, or elevated serum transaminases (ALT/AST) should be carried out with use of the RPT/INH regimen. If signs of liver disease occur or worsen, RPT should be discontinued.

Possible hypersensitivity events (by case definition) were more frequent in the 3RPT/INH treatment arm than the 9INH arm (3.8% and 0.5%, respectively). The definition of possible hypersensitivity was intentionally broad and included hypotension, urticaria, angioedema, acute bronchospasm, or conjunctivitis occurring in relation to study drug; or ≥4 of the following (1 of which had to be ≥Grade 2) that occurred in relation to study drug: weakness, fatigue, nausea, vomiting, headache, fever, aches, sweats, dizziness, shortness of breath, flushing, or chills. HIV-infected patients presented with less hypersensitivity than the main study population.

“Flu-like syndrome” or hypersensitivity has been associated with rifamycins since they were first used in the early 1970’s [45]. A flu-like syndrome consisting of attacks of fever, chills and malaise, sometimes with headache, dizziness or bone pain, has been associated with intermittent rifampicin administration. It rarely occurs when rifampicin is given daily. With intermittent treatment regimens, it usually appears in the third to sixth months. Whether similar toxicities will occur with RPT remains to be seen. INH can also cause a hypersensitivity reaction, but it is characterized by fever, skin eruptions, lymphadenopathy, and vasculitis. Rarely, INH can cause a flu-like syndrome (predominantly fever, but rash and eosinophilia are also possible).

Based on the results of TBTC-S26 which allowed a better estimation and characterization of hypersensitivity, the Priftin labelling update for sNDA includes hypersensitivity reactions as common adverse drug reactions associated with the use of the 3RPT/INH regimen in LTBI patients. In addition, a
Routine Pharmacovigilance Plan along with a Medication Guide without Risk Evaluation and Mitigation Strategies, has been proposed as part of minimization risk guidance for physicians and in the leaflet for patients. In patients treated for LTBI, careful monitoring of signs and symptoms of possible hypersensitivity reactions should be carried out with the use of 3RPT/INH regimen. If signs of hypersensitivity syndrome occur or worsen, RPT/INH should be discontinued.

The AE profile among HIV-infected patients in the TBTC-S26 HIV sub-study was generally similar to that observed in the main study. However, the overall incidence or TEAEs and SAEs in the HIV sub-study was higher than that observed in the TBTC-S26 main study. A comparison of TEAE profile for 3RPT/INH in the HIV-infected population was generally similar to the TBTC-S26 main study. A notable exception is that possible hypersensitivity was one of the most frequently reported TEAEs in the main study population and only occurred in 2 HIV-infected patients in the 3RPT/INH arm. Hepatotoxicity was more frequently reported in HIV infected patients treated with 9INH as compared to the 9INH arm of the main study.
12. Summary of available data on comparative cost and cost-effectiveness within the pharmacological class or therapeutic group

Costs

RPT is sold in the private sector in the USA at the market prices of US $121.55 per 32-tablet blister pack. A full course for preventive therapy requires, in adults, 72 tablets of 150 mg (one dose of 6 tablets per week over a 12 week period). Hence, in this setting, one preventive therapy course of RPT will cost to the individual US $273.

SANOFI made an agreement with the USA Government to sell RPT at a reduced price of US $32/box of 32 tablets to accredited clinics or centers having an agreement with the government (eligible organizations/covered entities enrolled in the 340B Program) [46]. Moreover a discount price of $70/box of 32 tablets is also offered to Veterans Affairs Federal Supply Schedule Services.

The SANOFI Access to Medicines Department applies a tiered pricing policy to facilitate affordability of the medicine in resource constraint settings as well. Under this program, rifapentine would be provided to public sector and nongovernmental organizations outside the USA at a price which is at maximum equal to the US federal price of $32/box of 32 tablets.

Modified packaging is being developed by SANOFI in order to match the number of tablets of the blister pack with the number of tablets required for a preventive treatment course (adult dose) that would be 3 boxes of 24 tablets. It is estimated that the cost of one preventive therapy course (adult dose, reduced price) would therefore be US $72 at maximum.

The final real cost of RPT in countries outside the USA is currently difficult to predict as it will depend on the concerted agreement between SANOFI and national Health Authorities at the moment RPT will be registered in the country.

Cost-effectiveness

To assess the cost-effectiveness profile of the RPT/INH preventive therapy regimen a simulation computational model was designed using as comparator the 9H regimen [47]. Costs and health outcomes were estimated to determine the incremental costs per active TB case prevented and per quality-adjusted life year (QALY) gained by 3RPT/INH compared to 9H. Over a 20-year period, treatment of LTBI with 3RPT/INH rather than 9INH resulted in 5.2 fewer cases of TB and 25 fewer lost QALYs per 1000 individuals treated. From the societal perspective, which includes costs to the health system as well as
direct costs to patients and the economic value of lost patient productivity, 3RPT/INH is cost-saving compared to 9H at the lower RPT price [47] [using the 2014 reduced RPT price: $6.00 per 900 mg dose rather than $12.31][46]. This model includes directly observed administration of 3RPT/INH. If the results of a study being conducted by the TBTC to assess the adherence to the 3RPT/INH regimen given by self-administered will confirm that efficacy is maintained at levels achieved by DOT, then 3RPT/INH would be cost-saving compared to 9INH from both a health system and a societal perspective.

13. Summary of regulatory status of the medicine

RPT has been registered and marketed in USA since 1998 (Priftin®), in the treatment of active pulmonary TB caused by *Mycobacterium tuberculosis*. For this indication the drug must always be used in combination with one or more antituberculosis drugs to which the isolate is susceptible depending on the phase of treatment. The product indication, contraindications, warnings and precautions, dosage and administration are available through the approved US labeling [19].

In November 2014 the FDA approved a new indication for RPT, in combination with INH, for the treatment of LTBI in patients 2 years of age and older at high risk of progression to TB disease [20]. The new indication approved in the USA labeling is as following:

*PRIFTIN is indicated in adults and children 2 years and older for the treatment of latent tuberculosis infection caused by Mycobacterium tuberculosis in patients at high risk of progression to tuberculosis disease (including those in close contact with active tuberculosis patients, recent conversion to a positive tuberculin skin test, HIV-infected patients, or those with pulmonary fibrosis on radiograph).*

**Limitations of Use:**

- *Active tuberculosis disease should be ruled out before initiating treatment for latent tuberculosis infection.*
- *PRIFTIN must always be used in combination with isoniazid as a 12-week once-weekly regimen for the treatment of latent tuberculosis infection.*
- *PRIFTIN in combination with isoniazid is not recommended for Individuals presumed to be exposed to rifamycin- or -isoniazid resistant M. tuberculosis.*
14. Availability of pharmacopoeial standards

None.

Sanofi has planned to propose Drug Substance and Drug Product monographs at the USP.

15. Proposed text that could be included in a revised WHO Model Formulary

<table>
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<th>6.2.4 Antituberculosis medicines</th>
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Rifapentine is recommended in association with isoniazid for the treatment of latent tuberculosis infection in patients at high risk of progression to tuberculosis disease (including people living with HIV, adult and child contacts of pulmonary TB cases, patients initiating anti-tumor necrosis factor (TNF) treatment, patients receiving dialysis, patients preparing for organ or hematologic transplantation and patients with silicosis).

In adults (weight ≥ 50 kg or more) the dose of rifapentine is 900 mg (approximately equivalent to 15 mg/kg) (6 tablets of 150 mg) once weekly for 12 weeks in association with isoniazid 15 mg/kg (900 mg maximum).

In children ≥ 2 years, the recommended dose of rifapentine should be determined based on weight of the child to approximate 25 mg/kg (900 mg maximum), in association with isoniazid 25 mg/kg (900 mg maximum).
References


32. Farenc C, Doroumian S, Cantalloube C, Perrin L, Esposito V, Cierien-Puiseux I, Boulenc X, Maroni M. Rifapentine Once-Weekly Dosing Effect On Efavirenz, Emtricitabine and Tenofovir PKs. 2014 Conference on Retroviruses and Opportunistic Infections; 2014 March 5; Boston, MA. Abs # 493


Annexes
