<u>เอกสารกำกับยาภาษาอังกฤษ</u>

Priftin®

SANOFI

1.Name of the Medicinal Product

1.1Product Name

Priftin®

1.2Strength

Each tablet contains 150 mg of rifapentine.

1.3Pharmaceutical Dosage Form

Film-coated tablet

2.Qualitative and Quantitative Composition

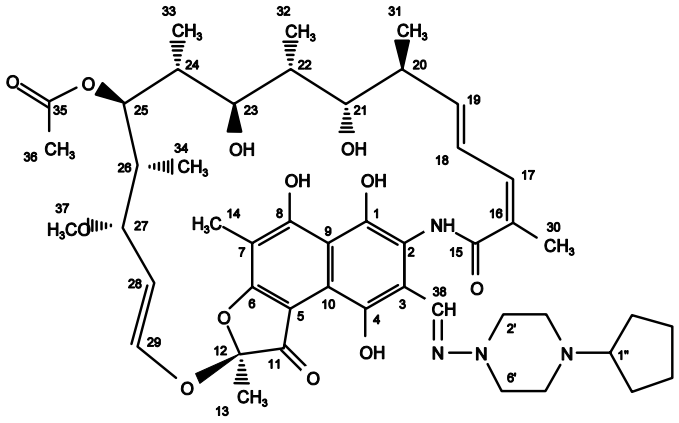
2.1Qualitative Declaration

Rifapentine is a rifamycin derivative antimicrobial and has a similar profile of microbiological activity to rifampicin. The molecular weight is 877.04.

The molecular formula is $C_{47}H_{64}N_4O_{12}$.

The chemical name for rifapentine is rifamycin, 3-[[(4-cyclopentyl-1-piperazinyl)imino]methyl]-

or 3-[N-(4-Cyclopentyl-1-piperazinyl)formimidoyl] rifamycin or 5,6,9,17,19,21-hexahydroxy-23-methoxy-2,4,12,16,18,20,22-heptamethyl-8-[N-(4-cyclopentyl-l-piperazinyl)-formimidoyl]-2,7-(epoxypentadeca[1,11,13]trienimino)naphtho[2,1-b]furan-1,11(2H)-dione 21-acetate. It has the following structure:



2.2 Quantitative Declaration

Each tablet contains 150 mg rifapentine.

3. Pharmaceutical Form

Round, dark pink, normal convex film coated tablets, engraved “F” on one side

4. Clinical Particulars

4.1 Therapeutic Indication

Priftin is indicated for the treatment of latent tuberculosis infection caused by *Mycobacterium tuberculosis* in adults and children 2 years and older who are 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).

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.

4.2Posology and Method of Administration

Priftin should be administered once-weekly in combination with isoniazid for 12 weeks as directly observed therapy.

Adults and children 12 years and older: The recommended dose of Priftin should be determined based on weight of the patient up to a maximum of 900 mg once-weekly (see Table 1). The recommended dose of isoniazid is 15 mg/kg (rounded to the nearest 50 mg or 100 mg) up to a maximum of 900 mg once-weekly for 12 weeks.

Children 2 - 11 years: The recommended dose of Priftin should be determined based on weight of the patient up to a maximum of 900 mg once- weekly (see Table 1). The recommended dose of isoniazid is 25 mg/kg (rounded to the nearest 50 mg or 100 mg) up to a maximum of 900 mg once-weekly for 12 weeks.

Table 1 - Weight based dose of Priftin in the treatment of latent tuberculosis infection

Weight range	Priftin dose	Number of Priftin tablets
10 - 14 kg	300 mg	2
14.1 - 25 kg	450 mg	3
25.1 - 32 kg	600 mg	4
32.1 - 50 kg	750 mg	5
> 50 kg	900 mg	6

Special Populations

Pediatric patients: The youngest patient included in the clinical efficacy trial was 2 years. No data are available for patients below 2 years old.

Elderly patients: No dose adjustment required.

Hepatic impairment: No dose adjustment required.

Renal impairment: No dose adjustment required.

Patients should be informed that adherence to the treatment regimen for rifapentine and other substances is essential for effective treatment, and the importance of not missing any doses must be stressed.

Priftin should be given with food. For patients with a propensity to nausea, vomiting or gastrointestinal upset, administration with food may be even useful.

For patients who cannot swallow tablets, the tablets may be crushed and added to a small amount of semi-solid food, all of which should be consumed immediately (see 5.2 Pharmacokinetic Properties).

Interactions with antacids have not been studied. However, in the clinical efficacy study, patients were advised to take Priftin at least 1 hour before or 2 hours after the ingestion of antacids.

4.3 Contraindications

Priftin is contraindicated in patients with hypersensitivity to rifapentine or any of the other rifamycins (e.g. rifampicin and rifabutin), or to any of the tablet excipients.

4.4 Special Warnings and Precautions for Use

Warnings

Hepatotoxicity

Antitubercular multidrug treatments including the rifamycin class may cause serious hepatic reactions.

Patients with abnormal liver tests and/or liver disease should only be given Priftin if absolutely necessary, and then with caution and under strict medical supervision.

In such patients, careful monitoring of liver parameters (especially serum transaminases and bilirubin) should be carried out prior to therapy and then every 2 to 4 weeks during therapy. If there are indications of a liver reaction or of the hepatic condition worsening, Priftin should be discontinued. Hepatotoxicity of other antituberculosis drugs (e.g., isoniazid, pyrazinamide) used in combination with rifapentine should also be taken into account.

Hypersensitivity and related reactions

Hypersensitivity reactions may occur in patients receiving Priftin. Signs and symptoms of these reactions may include hypotension, urticaria, angioedema, acute bronchospasm, conjunctivitis, thrombocytopenia, neutropenia or flu-like syndrome (weakness, fatigue, muscle pain, nausea, vomiting, headache, fever, chills, aches, rash, itching, sweats, dizziness, shortness of breath, chest pain, cough, syncope, palpitations) (see 4.8 Undesirable Effects)

Monitor patients receiving Priftin therapy for signs and/or symptoms of hypersensitivity reactions. If these symptoms occur, administer supportive measures and discontinue Priftin.

Drug interactions

Rifapentine is an inducer of CYP3A4 and CYP2C8/9. Concomitant use of rifapentine with other drugs metabolized by these enzymes,

such as protease inhibitors, certain reverse transcriptase inhibitors, and hormonal contraception may cause a significant decrease in plasma concentrations and loss of therapeutic effect (see 4.5 Interaction with Other Medicinal Products and Other Forms of Interactions and 5.2 Pharmacokinetic Properties).

Rifapentine has also been shown to inhibit and to induce P-gp which could modify plasma exposure of digoxin (a P-gp substrate with narrow therapeutic index). Appropriate monitoring and dose adjustment of digoxin may be necessary in case of co-administration with rifapentine (see 4.5 Interaction with Other Medicinal Products and Other Forms of Interactions and 5.2 Pharmacokinetic Properties).

Severe Cutaneous Adverse Reaction

Severe Cutaneous Adverse Reaction (SCARs) such as Stevens-Johnson Syndrom (SJS) and Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) syndrome have been reported in association with the use of rifapentine treatment regimen. Patients should be informed about the signs and symptoms of serious skin manifestations. Treatment should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

Precautions

Clostridium difficile-associated diarrhea

Pseudomembranous colitis has been reported to occur with various antibiotics, including other rifamycins. Diarrhea, particularly if severe and/or persistent, occurring during treatment or in the initial weeks

following treatment may be symptomatic of *Clostridium difficile*-associated disease, the most severe form of which is pseudomembranous colitis. If pseudomembranous colitis is suspected, Priftin should be stopped immediately and the patient treated appropriately without delay. Medications inhibiting the peristalsis are contraindicated in this clinical situation.

Discoloration of body fluids

Priftin may produce a predominantly red-orange discoloration of body tissues and/or fluids (e.g., skin, teeth, tongue, urine, feces, saliva, sputum, tears, sweat, and cerebrospinal fluid).

Contact lenses or dentures may become permanently stained.

Porphyria

Porphyria has been reported in patients receiving rifampicin, attributed to induction of delta amino levulinic acid synthetase. Because Priftin may have similar enzyme induction properties, avoid the use of Priftin in patients with porphyria.

4.5 Interaction with Other Medicinal Products and Other Forms of Interactions

Effect of Rifapentine on Other Medicinal Products

Effect on medicinal products metabolized by CYP3A4 and CYP2C8/9

Rifapentine is an inducer of CYP3A4 and CYP2C8/9.

Therefore, rifapentine may increase the metabolism of other coadministered drugs that are metabolized by these enzymes. Appropriate monitoring and dosage adjustment may be necessary if drugs metabolized by CYP 3A4 or CYP 2C8/9 are coadministered with Priftin.

Induction of enzyme activities by rifapentine occurred after the first dose of rifapentine. Enzyme activities returned to baseline levels in general 14 days after discontinuing rifapentine.

Examples of such substances include:

- Antiretroviral drugs:
  - Protease inhibitors: indinavir, darunavir, lopinavir, saquinavir, ritonavir
  - Non Nucleoside Reverse Transcriptase Inhibitors: rilpirivine, delaviridine
  - Nucleoside Reverse Transcriptase Inhibitor: zidovudine
- Antifungals: itraconazole, ketoconazole, voriconazole
- Narcotics analgesics: methadone, alfentanil, buprenorphine
- Antiarythmic: dronedarone, quinidine
- Hypoglycemic agents: repaglinide, tolbutamide
- Calcium channel blockers: felodipine, nicardipine, diltiazem, verapamil, nifedipine
- Alpha/Beta Adrenergic Antagonists: propranolol
- Ergo alkaloids derivates: ergotamine, dihydroergotamine
- Oral anti-Vit K anticoagulant: warfarin
- Hormonal contraceptives: oral, transdermal, and implant
- Immunosuppressants: cyclosporine, tacrolimus, sirolimus, voclosporin.

Effect of rifapentine on transporter substrates

In vitro, rifapentine has been shown to inhibit and to induce P-gp which could modify plasma exposure of digoxin (P-gp substrate) (see 5.2 Pharmacokinetic Properties).

Because of narrow therapeutic index of digoxin, appropriate monitoring and dose adjustment of digoxin may be necessary in case of co-administration with rifapentine.

Effect of rifapentine on Antiretroviral drugs

- *Protease Inhibitors and certain Reverse Transcriptase Inhibitors*
  Concomitant use of rifapentine with Protease Inhibitors and certain Reverse Transcriptase Inhibitors, metabolized by CYP3A4 or CYP2C8/9, may cause a significant decrease in plasma concentrations and loss of therapeutic effect of these drugs.
- *Fixed dose combination of Efavirenz, Emtricitabine and Tenofovir*
  Once-weekly co-administration of 900 mg Priftin with the antiretroviral fixed dose combination of efavirenz 600 mg, emtricitabine 200 mg and tenofovir disoproxyl fumarate 300 mg in HIV- infected patients did not result in any substantial change in steady state exposures of efavirenz, emtricitabine, and tenofovir. No clinically significant change in CD4 cell counts or viral loads were noted.
  No need for dose adjustment of fixed dose combination of Efavirenz, Emtricitabine and Tenofovir, if coadministered with Priftin 900 mg once-weekly.
- *Raltegravir*
  Once-weekly co-administration of 900 mg Priftin with raltegravir resulted in a 71% mean increase in raltegravir AUC_{0-12}, and an 89% increase in C_{max}. The increased raltegravir exposure was safe and tolerable. No need for dose adjustment of raltegravir, if coadministered with Priftin 900 mg once-weekly.

Hormonal contraceptives

Priftin may reduce the effectiveness of hormonal contraceptives. Women taking oral contraceptions, transdermal patch, or other systemic hormonal contraceptives who need Priftin therapy should discuss with their physician regarding the use of an additional non-hormonal means of contraception or the change of their contraceptive pill.

Effect of Other Drugs on Rifapentine

Potential drug interaction with CYP450 inducer/inhibitor drugs, as well as with transporters inhibitor/inducer drugs are not expected (see 5.2 Pharmacokinetic Properties).

Since rifapentine is highly bound to albumin, drug displacement interactions with NSAIDs, sulfonylureas, and oral anticoagulants may also occur.

Interferences with Laboratory and Diagnostic Test

Therapeutic concentrations of rifampin have been shown to inhibit standard microbiological assays for serum folate and Vitamin B12. Similar interferences should be considered for rifapentine. Therefore, alternative assay methods should be considered.

4.6 Pregnancy and Lactation

Pregnancy

Animal data

Animal studies have shown reproductive toxicity in rats and rabbits. A complete reproductive toxicity program was conducted with rifapentine showing drug-related adverse effects in rats and rabbits at

40 mg/kg/day leading to recommendation for use in pregnant and lactating women (see 5.3 Preclinical Safety Data).

Human data

In the clinical trial that compared the safety and effectiveness of rifapentine in combination with isoniazid to isoniazid alone for the treatment of latent tuberculosis infection (TBTC-S26 study), a total of 46 pregnancies were reported in the rifapentine/isoniazid arm. There were 31 live births, six elective abortions, seven spontaneous abortions, and two unknown outcomes. Of the 31 live infants, 21 were reported healthy while in the other ten cases no further details were available. No congenital anomalies were reported. The rate of spontaneous abortion (15%) did not represent an increase over the background rate of 15 to 20 percent reported in the general population. Further interpretation of these results is limited by the quality of adverse event reporting.

In the absence of adequate and well-controlled studies in pregnant women, Priftin should be used during pregnancy only if the potential benefit outweighs the potential risk to the fetus.

Rifampicin is known to cause postnatal hemorrhages in the mother and infant when taken during the last few weeks of pregnancy. Since rifapentine might have a similar effect, appropriate coagulation testing should be performed when the drug is used during late pregnancy. Treatment with Vitamin K may be indicated.

Lactation

It is not known whether rifapentine is excreted in human milk.

Animal data have shown compound-related effects in nursing offspring (see 5.3 Preclinical Safety Data).

A decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Since rifapentine may produce a red-orange discoloration of body fluids, the potential for discoloration of breast milk should be remembered.

4.7 Effects on Ability to Drive and Use Machine

No information in this section.

4.8 Undesirable Effects

The following CIOMS frequency rating is used, when applicable: Very common ≥ 10%; Common ≥ 1 and < 10%; Uncommon ≥ 0.1 and < 1%;

Rare ≥ 0.01 and < 0.1%; Very rare < 0.01%; Not known (cannot be estimated from available data).

Clinical trials experience

The safety profile of rifapentine in combination with isoniazid given once-weekly is based on the study TBTC-S26. In this study, rifapentine in combination with isoniazid given once-weekly for 3 months (3RPT/INH) was compared to isoniazid given once daily for 9 months (9INH) in an open-label, randomized trial in patients with a positive tuberculin skin test, and at high risk for progression from latent tuberculosis infection to active tuberculosis disease.

A total of 4040 patients received at least one dose of the 3RPT/INH regimen, including 348 children 2 - 17 years of age and 105 HIV-

infected individuals. A total of 3759 received at least one dose of the 9INH regimen, including 342 children 2 years - 17 years of age and 95 HIV-infected individuals.

Patients were followed for 33 months from the time of enrollment (see 5.1 Pharmacodynamic Properties).

Table 2 - Adverse drug reactions (i.e. considered by the investigator to be possibly, probably, or definitely related to the medicinal product) reported in at least 3 patients treated with 3RPT/INH*

System Organ Class	Frequency	*3RPT/INH*	*9INH*
Infections and infestations			
Influenza	Uncommon	8 (0.2)	1 (0.03)
Immune system disorders			
Hypersensitivity	Common	160 (3.96)	18 (0.48)
Nervous System Disorders			
Headache	Uncommon	14 (0.35)	10 (0.27)
Gastrointestinal Disorders			
Nausea	Uncommon	11 (0.3)	6 (0.2)
Abdominal pain upper	Uncommon	3 (0.07)	2 (0.05)
Hepatobiliary Disorders			
Hepatitis	Uncommon	18 (0.45)	103 (2.74)
Skin and Subcutaneous Tissue Disorders			

System Organ Class	Frequency	*3RPT/INH*	*9INH*
Skin reaction	Uncommon	31 (0.77)	21 (0.56)
Musculoskeletal and Connective Tissue Disorders			
Myalgia	Uncommon	4 (0.1)	0
General Disorders and Administration Site Conditions			
Influenza-like illness	Uncommon	8 (0.2)	0
Fatigue	Uncommon	4 (0.1)	6 (0.16)
Chills	Uncommon	4 (0.1)	0
Pyrexia	Uncommon	4 (0.1)	1 (0.03)
Asthenia	Rare	3 (0.07)	0

*Includes events reported through 60 days after last dose of study drug

The following adverse drug reactions were reported in less than 3 patients (frequency: rare): pancreatitis, oesophageal irritation, pneumonia.

Pediatric population

Six-hundred and ninety children 2 years - 17 years of age received at least one dose of study drugs in the main study. An additional 342 children 2 years - 17 years of age received at least one dose in the pediatric extension study (total 1032 children; 539 received 3RPT/INH and 493 received 9INH).

No children in either treatment arm developed hepatotoxicity. Children in the 3RPT/INH group experienced less rifamycin hypersensitivity reaction (7 (1.3%)) than adults. Adverse reactions in

children 2 years - 11 years of age and 12 years - 17 years of age were similar.

HIV population

Two-hundred HIV-infected patients with latent tuberculosis infection received at least one dose of study drugs in the main study and an additional 193 patients received at least one dose in the extension study (total of 393; 207 received 3RPT/INH and 186 received 9INH). Compared to the HIV-negative patients enrolled in the main study, a higher proportion of HIV-infected patients in each treatment arm experienced a treatment emergent adverse reaction, including a higher incidence of hepatotoxicity. Hepatotoxicity occurred less frequently in patients in the 3RPT/INH arm (3/207 (1.5%)) than in the 9INH arm (14/186 (7.5%)).

Rifamycin hypersensitivity occurred in only one HIV-infected patient in 3RPT/INH arm.

Postmarketing

Skin and subcutaneous tissue disorders

Not known: Severe Cutaneous Adverse Reactions (SCARs) such as Steven-Johnson Syndrome (SJS) and Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) syndrome (See 4.4 Special Warnings and Precautions for Use).

4.9 Overdose

Signs and Symptoms

No case of an acute overdose with Priftin has been reported.

In pharmacokinetic trials, eight healthy male volunteers were given single oral doses of Priftin up to 1200 mg. Adverse events were mild and well tolerated (mainly headache and gastrointestinal upset).
Out of 32 patients (20 to 74 years) who accidentally received continuous daily doses of 600 mg rifapentine for up to 20 days, one patient experienced a transient elevation in SGPT and glucose and a second patient experienced slight pruritus.

Management

While there is no experience in the treatment of overdose with Priftin, clinical experience with rifamycins suggest that gastric lavage to evacuate gastric contents (within a few hours of overdose), followed by instillation of an activated charcoal slurry into the stomach, may help adsorb any remaining drug from the gastrointestinal tract.
Rifapentine and 25-desacetyl rifapentine are highly plasma protein bound and have limited urinary excretion. Therefore, neither hemodialysis nor forced diuresis is expected to enhance the systemic elimination.

5.Pharmacological Properties

5.1Pharmacodynamic Properties

Mode of Action/Pharmacodynamic Characteristics

Mechanism of action

Rifapentine belongs to the rifamycin class of antibiotics which exert their antibacterial action by selectively inhibiting the DNA-dependent RNA polymerase of susceptible bacteria.
It forms a stable complex with bacterial DNA-dependent RNA polymerase, leading to repression of RNA synthesis and cell death.

Rifapentine and its 25-desacetyl metabolite accumulate in human monocyte-derived macrophages and are bactericidal to both intracellular and extracellular *Mycobacterium tuberculosis* organisms at concentrations achievable by the recommended oral dosing regimens. 25-desacetyl rifapentine, the active metabolite, is almost as active as rifapentine.
In vitro studies showed rifapentine to be highly concentrated within cells after brief incubation periods in media containing the antibiotic.
Antibacterial spectrum
In addition to its activity against most strains of *Mycobacterium tuberculosis*, rifapentine exhibits in vitro activity against most of the following microorganisms, however, the safety and effectiveness of rifapentine in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials.

Aerobic gram-positive microorganisms:
Staphylococcus aureus (including some strains of methicillin-resistant *S. aureus* / MRSA)
Staphylococcus epidermidis (including some strains of methicillin-resistant *S. epidermidis* / MRSE)

Other coagulase-negative staphylococci

Aerobic gram-negative microorganisms:
Neisseria gonorrhoeae

Anaerobic microorganisms:
Bacteroides fragiles

"Other" microorganisms:

Mycobacterium avium-intracellulare complex

ß-Lactamase production should have no effect on rifapentine activity.

Breakpoints

The following rifapentine Minimum Inhibitor Concentration (MIC) breakpoint (for active Tuberculosis), separating susceptible from resistant *M. tuberculosis* strains is proposed: susceptible < 0.5 mg/L, resistant > 0.5 mg/L.

This breakpoint has been determined using the Agar Proportion Method in 7H10 or 7H11 agar medium and the Radiometric Proportion Method in liquid 7H12 Middlebrook (12B) medium (using the BACTEC 460 instrument). The rifapentine critical concentration is 0.5 mg/L for both methods.

Susceptibility test results obtained by the two different methods can only be compared if the appropriate antibiotic concentration is used for each test method as indicated above. The use of two quality control strains, H37Rv (ATCC 27294) and H37RvSCC (ATCC 700457) is suggested for both procedures. Susceptibility of the H37Rv strain (ATCC 27294) should be completely obvious at 0.5 mg/L of rifapentine and resistance of the H37RvSCC strain (ATCC 700457) to the same concentration of rifapentine by the same method should also be completely obvious.

In a recent clinical trial conducted in South Africa, Canada and the United States, radiometric MIC values for susceptible strains of *M. tuberculosis* were ≤ 0.25 mg/l rifapentine (n = 830), while MIC values for rifamycin-resistant isolates were > 8 mg/L.

Susceptible microorganisms

Susceptible

*Mycobacterium tuberculosis**

Rifapentine shows cross-resistance with rifampicin.

* Clinical efficacy has been demonstrated for susceptible isolates.

Susceptible (based on in vitro data)

Staphylococcus species

Bordetella pertussis

Chlamydia pneumoniae

Haemophilus influenzae

Legionella pneumophila

Moraxella catarrhalis

Streptococcus pneumoniae, peni-S/I/R

Not Susceptible (based on in vitro data)

Klebsiella pneumoniae

Mycoplasma pneumoniae

S = Sensitive I = Intermediate R = Resistant ß= ß-lactamase

Resistance

Most organisms resistant to other rifamycins are likely to be resistant to rifapentine. In the treatment of tuberculosis, the small number of resistant bacilli present within large populations of susceptible bacilli can rapidly become predominant. In addition, resistance to rifamycin antibiotics has been determined to occur as a single step mutation of the gene that encodes for the beta subunit of the DNA-dependent RNA polymerase. However, other mechanisms of rifamycin

resistance observed among certain organisms, such as Nocardia and mycobacteria other than *M. tuberculosis* cannot be ruled out. Appropriate susceptibility tests should be performed in the event of persistently positive cultures.

Clinical Efficacy/Clinical Studies

Summary of the TBTC-S26 Phase 3 clinical study

The pivotal TBTC-S26 study was a multicenter, prospective, randomized, open-label trial conducted among more than 8000 high-risk tuberculin skin test (TST) reactors (i.e., household and other close contacts of active tuberculosis cases, recent [within 2 years] tuberculin converters, persons with fibrotic lesions on chest X-ray [CXR], HIV-infected persons, and young children), who required treatment of latent tuberculosis infection (LTBI) to prevent tuberculosis (TB) disease. Close contacts were defined as persons spending ≥ 4 hours in a shared airspace during a 1-week period with a person with sputum culture-confirmed TB disease. This included household and non-household contacts. In group settings such as households, group homes, or shelters, all patients were placed on the same regimen as the first patient in the group i.e., clusters. Close contacts were randomized by household (clusters); others were randomized individually.

The primary objective of the study was to evaluate the effectiveness of weekly rifapentine in combination with isoniazid for 3 months (3RPT/INH) given by directly-observed therapy (DOT) versus daily self-administered isoniazid for 9 months (9INH) in preventing TB disease in high-risk tuberculin reactors.

In addition to the main study, two sub-studies one each in pediatric population (2 - 17 years) and HIV-infected patients with LTBI at high risk of progression to active TB disease were nested in the main study and continued beyond the completion of enrollment in the main study to recruit additional patients in these subgroups.

Table 3 - LTBI study treatment doses and durations

3RPT/INH (by DOT)	9INH (self-administered)
RPT dose: 900 mg for patients > 50 kg and weight-based incremental dosing for patients ≤ 50 kg (dose range 300 - 750 mg) INH dose: 2 - 11 years: 25 mg/kg (900 mg maximum) ≥ 12 years: 15 mg/kg (900 mg maximum)	INH dose: 2 - 11 years: 10 - 15 mg/kg (300 mg maximum) ≥ 12 years: 5 mg/kg (300 mg maximum)
3RPT/INH duration: Once weekly dosing for 12 weeks (12 doses)	9INH duration: Daily dosing for 9 months (270 doses)

The primary endpoint used to determine effectiveness was the development of active TB disease confirmed by sputum culture for *M. tuberculosis* in adults (i.e., ≥ 18 years of age) and culture-confirmed

or clinical TB disease in children less than 18 years of age, at 33 months after enrollment in the study.

The Table 4 below shows that in the modified intention-to-treat (MITT) analysis for the main study, TB disease developed in 7 of 3986 patients in the 3RPT/INH group (cumulative rate, 0.19%) versus 15 of 3745 patients in 9INH group (cumulative rate, 0.43%), for a difference of 0.24 percentage points.

Rates of treatment completion were 82.1% in the 3RPT/INH group and 69.0% in the 9INH group (p<0.001). Rates of permanent drug discontinuation due to an adverse event were 4.9% in the 3RPT/INH and 3.7% in the INH therapy group (p = 0.009).

Table 4 - Number of tuberculosis cases and event rates by treatment group: LTBI Main study (MITT population, 33 month analysis)

Study Treatment Arm	N	TB Cases	TB per 100 p-y	Cumulative TB Rate (%)	Difference in Cumulative TB Rate (%)	Upper bound of 95% CI* (%)
Main study						
9INH	3745	15	0.16	0.43	-0.24	0.01
3RPT/INH	3986	7	0.07	0.19		

Abbreviations: p-y: patient-years; N: number of patients; CI: confidence interval; MITT: modified intention-to-treat; TB: tuberculosis; 9INH: 9-month (270-dose) regimen of daily INH; 3RPT/INH: 3-month (12-dose) regimen of weekly RPT and INH

* 95% CI for the difference in cumulative TB disease rates (%).
The difference in cumulative TB disease rate is the rate in the 3RPT/INH group minus the rate in the 9INH group.

The incidence of drug resistance was low and similar between the 2 treatment groups. In the 9INH treatment group, 2 cases were found to be INH-monoresistant. Both cases developed in patients with unknown HIV status. In the 3RPT/INH treatment group, 1 case was found to be RIF- and PZA-resistant, INH-susceptible *M. bovis* infection. This case was reported in a patient with HIV infection who had treatment interruptions and completed therapy late. Another case in the 3RPT/INH treatment group was found to be PZA monoresistant.

Pediatric Sub-study

RPT dosing in 12 to 17 year-old children enrolled in the 3RPT/INH group was identical to adults (12 weekly doses of RPT 900 mg or 750 mg if less than 50 kg). For children aged 2 to 11 years, the dose of RPT given in combination with INH was based on the weight at enrollment (Table 3) without exceeding 900 mg. The dose of INH in the 3RPT/INH arm was adjusted for age: 15 mg/kg for children ≥12 years old (rounded up to nearest 50 or 100 mg; 900 mg maximum) and 25 mg/kg for those 2 to -11 years (rounded up to nearest 50 or 100 mg; 900 mg maximum). The dose of INH in the 9INH group was: 5 mg/kg for children ≥12 years old (rounded up to nearest 50 or 100 mg, 300 mg maximum) and 10-15 mg/kg for those 2 to -11 years (rounded up to nearest 50 or 100 mg, 300 mg maximum).

Approximately 67% of the enrolled children were included in the analysis for the LTBI main study. Three children in the 9INH group developed tuberculosis (Table 5) including one INH-monoresistant, there were no TB cases reported in the 3RPT/INH. The treatment completion rate in the MITT population was statistically significantly higher among children in the 3RPT/INH group than in children in the 9INH group: 88.1% versus 81.0%, respectively, (p=0.003).

Table 5 - Number of tuberculosis cases and event rates by treatment group: Pediatric substudy (MITT population, 33 month analysis)

Study Treatment Arm	N	TB Cases	TB per 100 p-y	Cumulative TB Rate (%)	Difference in Cumulative TB Rate (%)	Upper bound of 95% CI* (%)
Pediatric substudy**						
9INH	436	3	0.27	0.78	-0.78	0.44
3RPT/INH	472	0	0.00	0.0		

Abbreviations: p-y: patient-years; N: number of patients; CI: confidence interval; MITT: modified intention-to-treat; TB: tuberculosis; 9INH: 9-month (270-dose) regimen of daily INH; 3RPT/INH: 3-month (12-dose) regimen of weekly RPT and INH

* 95% CI for the difference in cumulative TB disease rates (%).

** All 3 children who developed TB in the pediatric substudy had participated in the main study and are also counted in number of TB cases for the main study.

HIV Substudy

In the HIV substudy MITT population at 33 months after study enrollment, TB disease developed in 2 of 206 patients in the 3RPT/INH group (cumulative rate, 1.01%) and in 6 of 193 patients in the 9INH group (cumulative rate, 3.50%), for a difference of -2.49% with an upper limit of the 95% CI of +0.60% . The TB event rate in the HIV substudy was higher than that observed in the main study, which included mostly non-infected patients (see Table 6). Four of the 8 HIV-infected patients who developed TB (2 patients in the 3RPT/INH group including one PZA-Rif resistant strain and 2 patients in the 9INH group) were enrolled in the main study and are also included in the results for the main study. One patient in the 9INH group developed a multiresistant TB (RIF-INH-Streptomycin) during the extension phase. The treatment completion rate was statistically significantly higher among HIV-infected patients in the 3RPT/INH group than in the 9INH HIV-infected patients: 88.8% versus 63.7%, respectively, ($p \leq 0.0001$).

Table 6 Number of tuberculosis cases and event rates by treatment group: HIV substudy (MITT population, 33 month analysis)

Study Treatment Arm	N	TB Cases	TB per 100 p-y	Cumulative TB Rate (%)	Difference in Cumulative TB Rate (%)	Upper bound of 95% CI* (%)

HIV substudy**						
9INH	193	6	1.25	3.50	-2.49	0.60
3RPT/INH	206	2	0.39	1.01		

Abbreviations: p-y: patient-years; N: number of patients; CI: confidence interval; MITT: modified intention-to-treat; TB: tuberculosis; 9INH: 9-month (270-dose) regimen of daily INH; 3RPT/INH: 3-month (12-dose) regimen of weekly RPT and INH

* 95% CI for the difference in cumulative TB disease rates (%).

** 4 of the 8 patients who developed culture-confirmed TB in the HIV substudy had participated in the main study and are also counted in number of TB cases for the main study.

5.2Pharmacokinetic Properties

When 600 mg oral doses of rifapentine were administered once daily or once every 72 hours to healthy volunteers for 10 days (4 doses), mean $C_{through}$ were below the limit of quantification suggesting no accumulation, moreover single dose AUC $_{(0-\infty)}$ of rifapentine was similar to its $AUC_{ss(0-72h)}$ values after 4 repeated dose, suggesting no significant auto-induction effect.

Based on the data observed after a single oral dose of 900 mg in healthy subjects, no plasma accumulation of rifapentine and 25-desacetyl rifapentine (active metabolite) is expected after once weekly administration of Priftin.

The pharmacokinetic parameters of rifapentine and 25-desacetyl rifapentine on day 10 following oral administration of 600 mg Priftin every 72 hours to healthy volunteers are described in Table 7.

Table 7 Pharmacokinetics of Rifapentine and 25-Desacetyl Rifapentine in Healthy Volunteers

Parameter	Rifapentine	25-desacetyl Rifapentine
	Mean ± SD	
C_{max} (µg/mL)	15.05 ± 4.62	6.26 ± 2.06
AUC $_{(0\text{-}72h)}$ (µg*h/mL)	319.54 ± 91.52	215.88 ± 85.96
$T_{1/2}$ (h)	13.19 ± 1.38	13.35 ± 2.67
T_{max} (h)	4.83 ± 1.80	11.25 ± 2.73
Cl/F (L/h)	2.03 ± 0.60	--

The pharmacokinetic parameters of rifapentine and 25-desacetyl rifapentine following single-dose oral administration of 900 mg Priftin in combination with 900 mg isoniazid in fed conditions are described in Table 8.

Table 8 - Mean ± SD Pharmacokinetic Parameters of Rifapentine and 25-Desacetyl Rifapentine in Healthy Volunteers When Priftin is Co-administered with Isoniazid under Fed Conditions (N=16)

Parameter	Rifapentine	25-desacetyl Rifapentine
C_{max} (µg/mL)	25.8± 5.83	13.3 ± 4.83
AUC (µg*h/mL)	817 ± 128	601 ± 187
$T_{1/2}$(h)	16.6 ± 5.02	17.5 ± 7.42
T_{max} (h)*	8 (3-10)	24 (10-36)
Cl/F (L/h)	1.13 ± 0.174	NA**

*Median (Min - Max)
**Not Applicable

Absorption

The absolute bioavailability of rifapentine has not been determined.

Based on mass balance study, absorption was estimated as almost complete.

Rifapentine bioavailability is affected by food.

When the tablet is administered with food the bioavailability of rifapentine and its active metabolite increases by 40% to 50%. This increase in bioavailability is not affected by the meal composition including the amount of lipids.

Rifapentine should be taken with food in order to maximize rifapentine and 25-desacetyl rifapentine exposures and reduce inter-subject variability.

In contrast, the ingestion of the meal decreases isoniazid exposures (C_{max} and AUC by 46% and of 23%, respectively with the low fat, high carbohydrate breakfast).

Distribution

In healthy volunteers, rifapentine and 25-desacetyl rifapentine were highly 97.7% and 93.2% bound to plasma proteins, respectively.

Similar extent of protein binding was observed in healthy volunteers, asymptomatic HIV-infected subjects and hepatically impaired subjects.

Following oral dosing of rifapentine in fed condition, the apparent volume of distribution is 32 L.

The intrapulmonary distribution was studied in healthy subjects who received a single oral dose of rifapentine (600 mg). The peak concentrations in plasma, in epithelial lining fluid, and in alveolar cells were 26.2, 3.7, and 5.3 µg/mL, respectively. Although the intrapulmonary RPT concentrations were less than the plasma RPT concentrations at all time periods, they remained above the RPT and 25-DRPT MIC for the 48-h observation period.

Metabolism

Rifapentine was hydrolyzed by an esterase enzyme to form a single microbiologically active metabolite 25-desacetyl rifapentine.
This metabolite represents 60 to 70% of rifapentine AUC.

Elimination

After administration of 14C-rifapentine, the majority of the dose is excreted in feces (70%), while urine is a minor pathway for excretion (17%). Oral plasma clearance of rifapentine is low with values in the range of 1.5 to 2 L/h. The apparent elimination of rifapentine and 25-desacetyl rifapentine are monophasic with a terminal half-life ranging from 13 to 17h.
The main elimination pathways are metabolism for rifapentine and biliary excretion in feces for both rifapentine and its metabolite 25-desacetyl rifapentine. Renal clearance is a minor pathway of excretion for rifapentine and its metabolite.

Drug Interactions

Potential of rifapentine to affect other drugs

- Cytochromes P450 substrates

In vitro, rifapentine and its metabolite (25-desacetyl-rifapentine) are potent inducer of CYP3A4. In vivo in human, rifapentine has also been shown to be a potent CYP3A4 inducer: rifapentine daily (from 5 mg/kg) decreased midazolam exposure by 90%, rifapentine 600 mg twice weekly dosing reduced indinavir (protease inhibitor substrate of CYP3A4) exposure by 70%. There is no clinical data evaluating drug-drug interaction between CYP3A substrate and rifapentine at dosing regimen recommended for LTBI (900 mg weekly dosing). However, rifapentine is also predicted a potent inducer at this dosing regimen.

In vitro, rifapentine is an inducer of CYP2C8 and CYP2C9 and its metabolite (25-desacetyl-rifapentine) is a potential inhibitor of CYP2C8. No clinical interaction study was performed to assess in vivo potential of RPT to interact with drugs metabolized by CYP2C8/C9 but the risk of interaction is likely. The in vivo net effect, resulting from induction and inhibition of CYP2C8 was not evaluated but a higher impact of induction can be predicted.

In vitro studies showed that rifapentine and its metabolite (25-desacetyl-rifapentine) are inducers of CYP2B6 and that rifapentine is an inhibitor of CYP2B6. Interaction with CYP2B6 substrate was evaluated in one clinical study with efavirenz which is known as a very sensitive CYP2B6 substrate. After a single and repeated weekly administration of rifapentine 900 mg, no or minor modification (≤15%) of steady-state exposure of efavirenz was observed.

In vitro, rifapentine and its metabolite are not inducer of CYP1A2.

Based on in vitro data, it is predicted that rifapentine and its metabolite have no potential to inhibit CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A4 and CYP2E1, in vivo in human.

- Transporter substrates

  In vitro, rifapentine has been shown to inhibit several transporters (P-gp, BCRP and OATP1B1/B3, OCT1). However, the risk of clinically significant interaction resulting from inhibition of BCRP, OATP1B1/B3, evaluated using a mechanistic static approach, was considered as minimal. Moreover, rifamycins are known to induce some of these transporters (such as P-gp, OATP1B1/OATP1B3) via activation of PXR and could balance the inhibition effect. For P-gp, interactions have been evaluated in human with 2 substrates of P-gp, raltegravir and tenofovir suggesting a limited effect. However, because of narrow therapeutic index of digoxin (P-gp substrate), appropriate monitoring and dose adjustment of digoxin may be necessary in case of co-administration with rifapentine (see 4.5 Interaction with Other Medicinal Products and Other Forms of Interactions).

Potential of other drugs to affect rifapentine

Rifapentine is metabolized by esterases and its main metabolite, 25-desacetyl-rifapentine, is not metabolized. There is lack of risk of interaction with CYP450 inducer and as well as inhibitor drugs (such as triazole antifungal agents frequently coadministered in HIV-infected patients). Similarly, taking into account the high passive diffusion component in the hepatocyte uptake or the good intestinal

permeability, potential drug interaction with transporters inhibitor/inducer drugs are not expected.

Special Populations

Gender

PK profiles in healthy young women and young men did not evidence any gender effect for rifapentine or 25-desacetyl-rifapentine.
Gender was also investigated as covariates of population PK model and was not associated with rifapentine PK variability.

Elderly patients

In elderly (≥ 65 years), following single oral administration of 600 mg, mean rifapentine and 25-desacetyl-rifapentine exposures were increased (41% for rifapentine AUC, 58% for 25-desacetyl-rifapentine) compared to healthy young subjects (historical comparison). However no dose adjustments were recommended for elderly subjects based on safety results in elderly healthy subjects and elderly patients with LTBI.

Pediatric patients

In healthy adolescents, rifapentine and 25-desacetyl-rifapentine PK were not different from those observed in healthy adults.
In pediatrics (younger than 12-years old), a significant correlation was observed between clearance and age: clearance adjusted to body weight increased when decreasing age.
Based on these findings, a weight band dosing (Table 1) was selected for rifapentine in children with LTBI and validated with PK and safety data in this population.

In children (2 - 12 years of age) receiving doses based on weight , while the mean rifapentine dosages in mg/kg were 2-fold higher than in adults (23 versus 11 mg/kg), exposures were 31% and 41% higher than adults for rifapentine and 25-desacetyl-rifapentine respectively, exposures that in adults have been associated with successful treatment of LTBI. Among children, exposure was about 25% lower in those who could not swallow the whole tablets and received crushed tablets but still higher than in adults. Despite the generally increased exposure observed in children, higher mg/kg Priftin doses were well tolerated.

Hepatic impairment

Following oral administration of a single 600 mg dose of Priftin to mild to severe hepatic impaired patients, the pharmacokinetics of rifapentine and 25-desacetyl metabolite were similar in patients with various degrees of hepatic impairment. In comparison to healthy subjects, rifapentine and 25-desacetyl-rifapentine exposure (AUC) were increased in subjects with hepatic impairment by 19% to 25% and 77% to 99%, respectively.

Renal impairment

The pharmacokinetics of rifapentine have not been evaluated in renal impaired patients. However, the risk of an impact of impaired renal function on PK is considered as minimal only about 17% of an administered dose is excreted via the kidneys. The clinical significance of impaired renal function on the disposition of rifapentine and its 25-desacetyl metabolite is not known.

Asymptomatic HIV-Infected Volunteers

In asymptomatic HIV-infected subjects, rifapentine and 25-desacetyl metabolite PK profiles were not significantly different from those observed in healthy subjects. The safety and PK results indicated that no dose adjustment for Priftin is necessary for asymptomatic HIV-infected patients.

5.3 Preclinical Safety Data

Carcinogenicity

A two-year carcinogenicity in NMRI mice (Harlan Winklemann) was carried out with rifapentine at oral dose levels of 5, 20 and 80 mg/kg/d. At histological examination, a statistically significant higher incidence of hepatocellular carcinomas was seen in all treated male groups, but not in females. Dose-related pre-neoplastic eosinophilic foci of hepatocellular alterations were also detected in mid and high dose males. In addition, treatment-related centrilobular fatty changes occurred in high dose males. Rifapentine elicits an increase of the number of both liver tumors and altered cell foci in the mouse. Overall, it is assumed that rifapentine causes liver tumors in mice through a mechanism, which is not relevant to humans.

A two-year carcinogenicity study was carried out in Wistar rats with rifapentine at the dose levels of 2.5, 10 and 40 mg/kg/d. Tumors were limited to nasal turbinates and were all benign in nature. Because observed tumors location was limited to nasal cavity, were exclusively benign in nature and because of the specificities of nasal turbinates in the rat, it is considered that RPT-induced higher (than control) incidence of nasal adenomas is a rat specific effect.

Genotoxicity

A whole battery of *in vitro* and *in vivo* tests was carried out, both with rifapentine and with 25-DRPT. All data taken together – gene mutation in bacteria or eukaryote cells, chromosomal aberration tests or *in vivo* assays - it was concluded that both rifapentine and its human metabolite 25-DRPT do not represent a genotoxic risk to humans.

Rifapentine was negative in the following genotoxicity tests: in vitro gene mutation assay in bacteria (Ames test); in vitro point mutation test in *Aspergillus nidulans*; in vitro gene conversion assay in *Saccharomyces cerevisiae*; host-mediated (mouse) gene conversion assay with *Saccharomyces cerevisiae*; in vitro Chinese hamster ovary cell/hypoxanthineguanine- phosphoribosyl transferase (CHO/HGPRT) forward mutation assay; in vitro chromosomal aberration assay utilizing rat lymphocytes; and in vivo mouse bone marrow micronucleus assay.

The 25-desacetyl metabolite of rifapentine was positive in the in vitro mammalian chromosome aberration test in V79 Chinese Hamster cells, but was negative in the in vitro gene mutation assay in bacteria (Ames test), the in vitro Chinese hamster ovary cell/hypoxanthine-guanine- phosphoribosyl transferase (CHO/HGPRT) forward mutation assay, and the in vivo mouse bone marrow micronucleus assay.

Teratogenicity

In rats, given oral rifapentine during organogenesis at 40 mg/kg/day, there was an increase in resorption rate; litter and mean fetus weight were 20% lower than that of controls. Major malformations were

observed including mainly cleft palate and right aortic arch. Minor anomalies or variations at the external, visceral and skeletal examinations were also found increased.

In dams allowed to deliver and rear their pups, a slight decrease in litter size and mean litter weight, an increase in number of stillborn and mortality during lactation were noted at 40 mg/kg/day.

In rabbits, on gestational day 29, litter size and weight were slightly lower at 10 and 40 mg/kg/day, compared to controls. Major malformations were seen in 4 fetuses, one with ovarian agenesis (10 mg/kg/day), one with pes varus (20 mg/kg/day) and 2 fetuses with arhinia, microphthalmia and irregularities of the ossified facial tissues (40 mg/kg/day).

Effect on postnatal development was noted in rats. Pup weights in the 20 mg/kg/day were significantly decreased on post-partum days 1 and 4, which returned to normal on post-partum Day 21.

Following mating of F1 generation pups, slight decreases in litter size, increases in resorption rate, and increases in pre-implantation loss were observed in the offspring of F0 mothers from the 20 mg/kg/day. One abnormal fetus (bilateral, posterior pes varus) was observed in an F1 dam descending from a 20 mg/kg/day F0 rat. (See 4.6 Pregnancy and Lactation)

Though no specific study on milk excretion was performed in animals, the toxicological data in animals have shown compound-related effects in nursing offspring (i.e., on pups' survival and pups' body weights), while no significant effects were observed in nursing mothers. (See 4.6 Pregnancy and Lactation)

Impairment of Fertility

Fertility and reproductive performance were not affected by oral administration of rifapentine to male and female rats at doses of up to 20 mg/kg/day (one-third of the human dose based on body surface area conversions) leading to margin of safety of approximately 7 in terms of AUC.

6.Pharmaceutical Particulars

6.1List of Excipient

Calcium stearate, edetate disodium, FD&C Blue No.2 aluminum lake, hydroxypropyl cellulose, hypromellose, microcrystalline cellulose, polyethylene glycol, pregelatinized starch, propylene glycol, sodium ascorbate, sodium lauryl sulfate, sodium starch glycolate, red iron oxide, titanium dioxide

6.2Incompatibilities

No information in this section.

6.3Shelf Life

36 months

6.4Special Precautions for Storage

Storage condition: Store below 30ºC

6.5Nature and Contents of Container

Aluminum blister

7.Marketing Authorization Holder

Importer: sanofi-aventis (Thailand) Ltd., Bangkok, Thailand

8.Marketing Authorization Numbers

1C 15075/61 (N)

9.Date of Authorization

16 October 2018

10. Date of Revision of the text

Rifapentine CCDS v3 (28 March 2019)