SCHEDULING STATUS S4

1. NAME OF THE MEDICINE

PRIFTIN film-coated tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 150 mg rifapentine.

Sugar free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets.

Round, dark pink, convex, engraved, film-coated tablets.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

PRIFTIN in combination with isoniazid (INH) is indicated for the treatment of latent tuberculosis infection (LTBI) 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.

4.2 Posology and method of administration

Posology

PRIFTIN should be administered once-weekly in combination with isoniazid for 12 weeks as directly observed therapy (DOT).

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 3**). 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

Paediatric 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 (see sections 4.3 and 4.4).

Renal impairment:

No dose adjustment required.

Method of administration

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

PRIFTIN, in combination with isoniazid, should be given with food.

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 section 5.2).

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's excipients.
- PRIFTIN is contraindicated in patients with porphyria. Based on experience with rifampicin, it may be assumed that rifapentine can also induce delta-aminolevulinic acid synthetase and therefore cause an acute attack of porphyria.
- Acute or chronic liver disease.

4.4 Special warnings and precautions for use

- **Hepatotoxicity**

PRIFTIN may cause serious hepatic disease/injury.

Patients with abnormal liver tests and/or liver disease should only be given PRIFTIN if no safer alternative is available, and then with caution and under strict medical supervision (see section 4.3).

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 medicines (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 section 4.8).

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

- **Medicine interactions**

PRIFTIN is an inducer of CYP3A4 and CYP2C8/9. Concomitant use of rifapentine with other medicines metabolised 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 of these medicines (see sections 4.5 and 5.2).

PRIFTIN 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 sections 4.5 and 5.2).

- **Severe cutaneous adverse reactions**

Severe cutaneous adverse reactions (SCARs) such as Stevens-Johnson syndrome (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.

- ***Clostridium difficile*-associated diarrhoea**

Pseudomembranous colitis has been reported to occur with rifamycins such as PRIFTIN. Diarrhoea, 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. Medicines inhibiting the peristalsis are contraindicated in this clinical situation.

Discolouration of body fluids

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

Contact lenses or dentures may become permanently stained.

4.5 Interaction with other medicines and other forms of interaction

Effect of PRIFTIN on other medicines

- ***Effect on medicines metabolised by CYP3A4 and CYP2C8/9***

PRIFTIN is an inducer of CYP3A4 and CYP2C8/9. Therefore, PRIFTIN may increase the metabolism of other co-administered medicines that are metabolised by these enzymes. Appropriate monitoring and dosage adjustment may be necessary if medicines metabolised by CYP3A4 or CYP2C8/9 are co-administered with PRIFTIN.

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

Examples of such substances include:

- Antiretroviral medicines:
  - Protease inhibitors: indinavir, darunavir, lopinavir, saquinavir, ritonavir
  - Non-nucleoside reverse transcriptase inhibitors: rilpivirine
  - Nucleoside reverse transcriptase inhibitor: zidovudine
- Antifungals: itraconazole, ketoconazole, voriconazole
- Narcotic analgesics: methadone, alfentanil, buprenorphine

- Hypoglycaemic medicines: repaglinide
- Calcium channel blockers: felodipine, diltiazem, verapamil, nifedipine
- Alpha/Beta adrenergic antagonists: alfuzosin, propranolol
- Ergot alkaloid derivatives: ergotamine
- Oral anti-vitamin K anticoagulant: warfarin
- Hormonal contraceptives: oral, transdermal and implant
- Immunosuppressants: ciclosporin, tacrolimus, sirolimus
- Benzodiazepines: midazolam.

- ***Effect of PRIFTIN on transporter substrates***

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

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

- ***Effect of PRIFTIN on antiretroviral medicines***

- *Protease inhibitors and certain reverse transcriptase inhibitors*

Concomitant use of rifapentine with protease inhibitors and certain reverse transcriptase inhibitors, metabolised by CYP3A4 or CYP2C8/9, may cause a significant decrease in plasma concentrations and loss of therapeutic effect of these medicines.

- *Fixed dose combination of efavirenz, emtricitabine and tenofovir*

Once-weekly co-administration of 900 mg PRIFTIN with the antiretroviral fixed dose combination of 600 mg efavirenz, 200 mg emtricitabine and 300 mg tenofovir disoproxyl fumarate 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 co-administered 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}. No need for dose adjustment of raltegravir, if co-administered with PRIFTIN 900 mg once-weekly.

- ***Hormonal contraceptives***

PRIFTIN may reduce the effectiveness of hormonal contraceptives.
Women taking oral contraception, using a transdermal patch, or other systemic hormonal contraceptives who need PRIFTIN therapy should discuss the use of an additional non-hormonal means of contraception or the change of their contraceptive pill with their medical practitioner.

Effect of other medicines on PRIFTIN

Potential interaction with CYP450 inducer/inhibitor medicines, as well as with transporters inhibitor/inducer medicines are not expected (see section 5.2).
Since PRIFTIN is highly bound to albumin, medicine displacement interactions with non-steroidal anti-inflammatory drugs (NSAIDs), sulfonylureas and oral anticoagulants may also occur.

Interferences with laboratory and diagnostic tests

Therapeutic concentrations of rifampin have been shown to inhibit standard microbiological assays for serum folate and vitamin B_{12}. Similar interferences should be considered for PRIFTIN. Therefore, alternative assay methods should be considered.

4.6 Fertility, pregnancy and lactation

Pregnancy

Safety in pregnancy and lactation has not been established. Women who are pregnant should not be treated with PRIFTIN.

Human data:

Rifampicin is known to cause postnatal haemorrhages in the mother and infant when taken during the last few weeks of pregnancy. Since PRIFTIN might have a similar effect, appropriate coagulation testing should be performed when pregnant women are inadvertently exposed to PRIFTIN during late pregnancy. Treatment with vitamin K may be indicated.

Breastfeeding

Mothers on treatment with PRIFTIN should not breastfeed their babies. It is not known whether PRIFTIN is excreted in human milk.

PRIFTIN may produce a red-orange discolouration of body fluids, including breast milk.

4.7 Effects on ability to drive and use machines

Do not drive or operate machines if you experience any side effects of PRIFTIN which could adversely affect your ability to drive or use machines.

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 %)*; frequency not known (*frequency cannot be estimated from available data).

Clinical trials experience:

The safety profile of PRIFTIN in combination with isoniazid given once-weekly is based on the study TBTC-S26. In this study, PRIFTIN in combination with isoniazid given once-weekly for 3 months (3RPT/INH) was compared to a comparator given once daily for 9 months in an open-label, randomised 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 4 040 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 3 759 received at least one dose of the comparator regimen, including 342 children 2 years to 17 years of age and 95 HIV-infected individuals. Patients were followed for 33 months from the time of enrolment.

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

System organ class	**Frequency**	***3RPT/INH patients (%)***	***Comparator patients (%)***
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)
Upper abdominal pain	Uncommon	3 (0,07)	2 (0,05)
Hepatobiliary disorders			

Hepatitis	Uncommon	18 (0,45)	103 (2,74)
Skin and subcutaneous tissue disorders			
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 medicine.

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

Paediatric population:

Six-hundred and ninety children 2 years – 17 years of age received at least one dose of study medicines in the main study. An additional 342 children 2 years – 17 years of age received at least one dose in the paediatric extension study (total 1 032 children; 539 received 3RPT/INH and 493 received the comparator).

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 medicines in the main study and an additional 193 patients received at least one dose in the extension study (total of 393; 207 received 3 RPT/INH and 186 received comparator). 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 comparator arm (14/186 [7,5 %]).

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

Post-marketing

Skin and subcutaneous tissue disorders

Not known: Severe cutaneous adverse reactions (SCARs) such as Stevens-Johnson syndrome (SJS) and drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome (see section 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to:

- The Pharmacovigilance Unit at Sanofi: za.drugsafety@sanofi.com (email) or 011 256 3700 (tel), or
- SAHPRA via the **"6.04 Adverse Drug Reactions Reporting Form"** found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose

Signs and symptoms

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

An overdose may precipitate side effects and increase the severity thereof.

Treatment

Treatment should be symptomatic and supportive.

While there is no experience in the treatment of overdose with PRIFTIN, clinical experience with rifamycins suggests 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 medicine from the gastrointestinal tract.

Rifapentine and 25-desacetyl rifapentine are highly plasma protein bound and have limited urinary excretion. Therefore, neither haemodialysis nor forced diuresis is expected to enhance the systemic elimination.

5. PHARMACOLOGICAL PROPERTIES

Category and class: A 20.2.3 Tuberculostatics

5.1 Pharmacodynamic properties

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.

Susceptible microorganisms:

Mycobacterium tuberculosis

Rifapentine shows cross-resistance with rifampicin.

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.

5.2 Pharmacokinetic 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_{trough} were below the limit of quantification suggesting no accumulation; moreover, single dose $AUC_{(0-\infty)}$ of rifapentine was similar to its $AUC_{ss\ (0\text{-}72\ h)}$ values after 4 repeated doses, 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 3**.

Table 3: 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 $_{(0\text{-}72\ h)}$ (µg•h/mL)	319,54 ± 91,52	215,88 ± 85,96
T½ (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 4**.

Table 4: 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
Cmax (µg/mL)	25,8 ± 5,83	13,3 ± 4,83
AUC (µg•h/mL)	817 ± 128	601 ± 187
T½ (h)	16,6 ± 5,02	17,5 ± 7,42
Tmax (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 maximise 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 23 %, respectively, with the low fat, high carbohydrate breakfast).

Distribution

In healthy volunteers, rifapentine and 25-desacetyl rifapentine were 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 litres.

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 rifapentine (RPT) concentrations were less than the plasma RPT concentrations at all time periods, they remained above the RPT and 25-desacetyl rifapentine (25-DRPT) minimum inhibitor concentration (MIC) for the 48-hour observation period.

Biotransformation

Rifapentine was hydrolysed 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 ^{14}Crifapentine, the majority of the dose is excreted in faeces (70 %), while urine is a minor pathway for excretion (17 %). Plasma clearance after oral administration 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 is monophasic with a terminal half-life ranging from 13 to 17 hours.

The main elimination pathways are metabolism for rifapentine and biliary excretion in faeces for both rifapentine and its metabolite 25-desacetyl rifapentine. Renal clearance is a minor pathway of excretion for rifapentine and its metabolite.

Medicine interactions:

Potential of rifapentine to affect other medicines

- Cytochrome P450 substrates

In vitro, rifapentine and its metabolite (25-desacetyl-rifapentine) are potent inducers of CYP3A4. *In vivo* in humans, 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 are no clinical data evaluating the interaction between CYP3A substrate and rifapentine at the dosing regimen recommended for latent tuberculosis infection (LTBI) (900 mg weekly dosing). However, rifapentine is also predicted to be 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 rifapentine to interact with medicines metabolised 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. Interactions 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 inducers 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 humans.

- 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 and/or 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 humans with 2 substrates of P-gp, raltegravir and tenofovir, suggesting a limited effect.

However, because of the 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 section 4.5).

Potential of other medicines to affect rifapentine

Rifapentine is metabolised by esterases and its main metabolite, 25-desacetyl-rifapentine, is not metabolised. There is a lack of risk of interaction with CYP450 inducer and as well as inhibitor medicines (such as triazole antifungal agents frequently co-administered in HIV-infected patients). Similarly, taking into account the high passive diffusion component in the hepatocyte uptake or the good intestinal permeability, potential interaction with transporters inhibitor/inducer medicines are not expected.

Special populations:

Elderly patients

In elderly patients (≥ 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.

Paediatric patients

In healthy adolescents, rifapentine and 25-desacetyl-rifapentine PK were not different from those observed in healthy adults.

In paediatric patients (younger than 12 years old), a significant correlation was observed between clearance and age: clearance adjusted to body weight increased with 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 in 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 hepatically 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 renally 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

No further information of relevance available.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Calcium stearate, microcrystalline cellulose, pregelatinised starch, sodium ascorbate, sodium lauryl sulphate and sodium starch glycolate.

Tablet film-coat: disodium edetate, hydroxypropyl cellulose, hypromellose, indigo carmine (FD&C Blue No. 2 aluminium lake), polyethylene glycol, propylene glycol, red iron oxide, sodium ascorbate and titanium dioxide.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

- Store at or below 30 °C.
- Protect from excessive heat and humidity.
- Keep blister strips in outer carton until required for use.

6.5 Nature and contents of container

24 tablets packed in grey aluminium formable foil blister strips (3 blister strips x 8 tablets) in cardboard cartons.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

sanofi-aventis south africa (pty) ltd

Hertford Office Park, Building I, 5th Floor

90 Bekker Road, Vorna Valley, Midrand 2196

South Africa

8. REGISTRATION NUMBER

51/20.2.3/1081

9. DATE OF FIRST AUTHORISATION

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