SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Rifapentine Tablets 300 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 300 mg of rifapentine

For the full list of excipients, see Section 6.1.

3. PHARMACEUTICAL FORM:

Film-coated Tablets

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Active pulmonary tuberculosis

Rifapentine Tablets is indicated in adults and children 12 years and older for the treatment of active pulmonary tuberculosis (TB) caused by Mycobacterium tuberculosis. Rifapentine must always be used in combination with one or more antituberculosis (anti-TB) drugs to which the isolate is susceptible.

Limitations of use

Do not use Rifapentine Tablets monotherapy in either the initial or the continuation phases of active anti-tuberculous treatment.

Rifapentine Tablets should not be used once-weekly in the continuation phase regimen in combination with isoniazid (INH) in HIV-infected patients with active pulmonary tuberculosis because of a higher rate of failure and/or relapse with rifampin (RIF)-resistant organisms.

Rifapentine Tablets has not been studied as part of the initial phase treatment regimen in HIV- infected patients with active pulmonary tuberculosis.

Latent tuberculosis infection

Rifapentine Tablets 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. Rifapentine Tablets must always be used in combination with isoniazid as a 12-week once-weekly regimen for the treatment of latent tuberculosis infection.

- Rifapentine Tablets in combination with isoniazid is not recommended for Individuals presumed to be exposed to rifamycin- or - isoniazid resistant M. tuberculosis.

4.2 Dose and method of administration

Posology

Active pulmonary tuberculosis

Rifapentine is only recommended for the treatment of active pulmonary tuberculosis caused by drug-susceptible organisms as part of regimens consisting of a 2-month initial phase followed by a 4-month continuation phase.

Rifapentine should not be used in the treatment of active pulmonary tuberculosis caused by rifampin-resistant strains.

Initial phase (2 Months)

Rifapentine Tablets should be administered at a dose of 600 mg twice weekly for two months as directly observed therapy (DOT), with an interval of no less than 3 consecutive days (72 hours) between doses, in combination with other anti- tuberculosis drugs as part of an appropriate regimen which includes daily companion drugs such as isoniazid (INH), ethambutol (EMB) and pyrazinamide (PZA).

Continuation phase (4 Months)

Following the initial phase (2 months), continuation phase (4 months) treatment consists of Rifapentine Tablets 600 mg once-weekly for 4 months in combination with isoniazid or another appropriate anti-tuberculosis agent for susceptible organisms administered as directly observed therapy.

Latent tuberculosis infection

Rifapentine Tablets should be administered once-weekly in combination with isoniazid for 12 weeks as directly observed therapy. For age and weight-based dose please refer Table 1.

Table 1: Age and weight-based dose of rifapentine in the treatment of latent tuberculosis infection

Regimen	**Dose by age and weight band**					
Three months of Rifapentine plus high dose isoniazid weekly (3HP)	**Age 2 – 14 years**					
	Medicine, formulation	10-15 kg	16-23 kg	24-30 kg	31-34 kg	>34 kg
	Rifapentine 300 mg tablet	1	1.5	2	2.5	2.5
	Age >14 years					

	Medicine, formulation	30-35 kg	36-45 kg	46-55 kg	56-70 kg	>70 kg
	Rifapentine 300 mg tablet	3	3	3	3	3

Method of administration

Oral use.

Take Rifapentine Tablets 300 mg tablets with meals. Administration of rifapentine with a meal increases oral bioavailability and may reduce the incidence of gastrointestinal upset, nausea, and/or vomiting.

4.3 Contraindications

Rifapentine is contraindicated in patients with a history of hypersensitivity to rifamycins.

4.4 Special warnings and precautions for use

Hepatotoxicity

Elevations of liver transaminases may occur in patients receiving rifapentine (see section 4.8). Patients on rifapentine should be monitored for symptoms of liver injury.

Patients with abnormal liver tests and/or liver disease or patients initiating treatment for active pulmonary tuberculosis should only be given rifapentine in cases of necessity and under strict medical supervision. In such patients, obtain serum transaminase levels prior to therapy and every 2-4 weeks while on therapy. Discontinue rifapentine if evidence of liver injury occurs.

Hypersensitivity and related reactions

Hypersensitivity reactions may occur in patients receiving rifapentine. 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). There have been reports of anaphylaxis.

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

Relapse in the treatment of active pulmonary tuberculosis

Rifapentine has not been evaluated as part of the initial phase treatment regimen in HIV-infected patients with active pulmonary TB.

Do not use rifapentine as a once-weekly continuation phase regimen in HIV-infected patients with active pulmonary tuberculosis because of a higher rate of failure and/or relapse with rifampin-resistant organisms (see section 5.2).

Higher relapse rates may occur in patients with cavitary pulmonary lesions and/or positive sputum cultures after the initial phase of active tuberculosis treatment and in patients with evidence of bilateral pulmonary disease. Monitor for signs and symptoms of TB relapse in these patients (see section 5.2).

Poor adherence to therapy is associated with high relapse rate. Emphasize the importance of compliance with therapy.

Drug interactions

Rifapentine is an inducer of CYP450 enzymes. 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 sections 4.5 and 5.2).

Discoloration of body fluids

Rifapentine may produce a 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.

Clostridium difficile-associated diarrhea

Clostridium difficile-associated diarrhea (CDAD) has been reported with the use of nearly all systemic antibacterial agents, including rifapentine, with severity ranging from mild diarrhea to fatal colitis. Treatment with antibacterial agents can alter the normal flora of the colon and may permit overgrowth of *C. difficile*.

C. difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibacterial use. Careful medical history is necessary because CDAD has been reported to occur over two months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, discontinue antibacterial use not directed against *C. difficile* if possible. Institute appropriate measures such as fluid and electrolyte management, protein supplementation, antibacterial treatment of *C. difficile*, and surgical evaluation as clinically indicated.

Porphyria

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

Pediatric patients

The safety and effectiveness of rifapentine in the treatment of active pulmonary tuberculosis have not been established in pediatric patients under the age of 12.

The safety and effectiveness of rifapentine in combination with isoniazid once-weekly regimen has been evaluated in pediatric patients (2–17 years of age) for the treatment of latent tuberculosis infection. In

clinical studies, the safety profile in children was similar to that observed in adult patients (see sections 4.8 and 5.2).

As per literature data from a pharmacokinetic study conducted in 2 year to 11 year-old pediatric patients with latent tuberculosis infection, rifapentine was administered once-weekly based on weight (15 mg/kg to 30 mg/Kg, up to a maximum of 900 mg). Exposures (AUC) in children 2 years–11 years with latent tuberculosis infection were higher (average 31%) than those observed in adults receiving rifapentine 900 mg once-weekly (see sections 4.2 and 5.2).

Elderly patients

Clinical studies with rifapentine did not include sufficient numbers of subjects aged 65 years and over to determine whether they respond differently from younger subjects. In a pharmacokinetic study with rifapentine, no substantial differences in the pharmacokinetics of rifapentine and 25-desacetyl metabolite were observed in the elderly compared to younger adults (see section 5.2).

Labor or delivery

When administered during the last few weeks of pregnancy, rifampin, another rifamycin product, may increase the risk for maternal postpartum hemorrhage and bleeding in the exposed neonate. Monitor prothrombin time of pregnant women and neonates, who are exposed to rifapentine during the last few weeks of pregnancy. Treatment with Vitamin K may be indicated.

4.5 Interaction with other medicinal products and other forms of interaction

Protease inhibitors and reverse transcriptase inhibitors

Rifapentine is an inducer of CYP450 enzymes. Concomitant use of rifapentine with other drugs metabolized by these enzymes, such as protease inhibitors and certain reverse transcriptase inhibitors, may cause a significant decrease in plasma concentrations and loss of therapeutic effect of the protease inhibitor or reverse transcriptase inhibitor (see sections 4.4 and 5.2).

Fixed dose combination of efavirenz, emtricitabine and tenofovir

Once-weekly co-administration of 900 mg rifapentine with the antiretroviral fixed dose combination of efavirenz 600 mg, emtricitabine 200 mg and tenofovir disoproxyl fumarate 300mg 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 (see section 5.2).

Hormonal contraceptives

Rifapentine may reduce the effectiveness of hormonal contraceptives. Therefore, patients using oral, transdermal patch, or other systemic hormonal contraceptives should be advised to change to nonhormonal methods of birth control.

Cytochrome P450 3A4 and 2C8/9

Rifapentine is an inducer of cytochromes P4503A4 and P4502C8/9. Therefore, rifapentine may increase the metabolism of other co-administered drugs that are metabolized by these enzymes. Induction of enzyme

activities by rifapentine occurred within 4 days after the first dose. Enzyme activities returned to baseline levels 14 days after discontinuing rifapentine.

Rifampin has been reported to accelerate the metabolism and may reduce the activity of the following drugs; hence, rifapentine may also increase the metabolism and decrease the activity of these drugs. Dosage adjustments of the drugs in Table 2 or of other drugs metabolized by cytochrome P4503A4 or P4502C8/9 may be necessary if they are given concurrently with rifapentine.

Table 2. Drug Interactions with rifapentine: Dosage adjustment may be necessary

Drug Class	Examples of drugs within class
Antiarrhythmics	Disopyramide, mexiletine, quinidine, tocainide
Antibiotics	Chloramphenicol, clarithromycin, dapsone, doxycycline; Fluoroquinolones (such as ciprofloxacin)
Oral Anticoagulants	Warfarin
Anticonvulsants	Phenytoin
Antimalarials	Quinine
Azole Antifungals	Fluconazole, itraconazole, ketoconazole
Antipsychotics	Haloperidol
Barbiturates	Phenobarbital
Benzodiazepines	Diazepam
Beta-Blockers	Propanolol
Calcium Channel Blockers	Diltiazem, nifedipine, verapamil
Cardiac Glycoside Preparations	Digoxin
Corticosteroids	Prednisone
Fibrates	Clofibrate
Oral Hypoglycemics	Sulfonylureas (e.g., glyburide, glipizide)
Hormonal Contraceptives/ Progestins	Ethinyl estradiol, levonorgestrel
Immunosuppressants	Cyclosporine, tacrolimus
Methylxanthines	Theophylline
Narcotic analgesics	Methadone
Phophodiesterase-5 (PDE-5) Inhibitors	Sildenafil
Thyroid preparations	Levothyroxine
Tricyclic antidepressants	Amitriptyline, nortriptyline

Other interactions

The conversion of rifapentine to 25-desacetyl rifapentine is mediated by an esterase enzyme. There is minimal potential for rifapentine metabolism to be inhibited or induced by another drug, based upon the characteristics of the esterase enzymes.

Since rifapentine is highly bound to albumin, drug displacement interactions may also occur [see section 5.2).

Interactions with laboratory tests

Therapeutic concentrations of rifampin have been shown to inhibit standard microbiological assays for serum folate and Vitamin B_{12}. Similar drug-laboratory interactions should be considered for rifapentine; thus, alternative assay methods should be considered.

4.6 Fertility, pregnancy, and lactation

Pregnancy

Pregnancy Category C

There are no adequate and well controlled trials of rifapentine in pregnant women; however, there are limited pregnancy outcome data reported from women enrolled in clinical trials of various rifapentine treatment regimens for active tuberculosis and latent tuberculosis infection. The reported rate of spontaneous abortion following rifapentine exposure did not represent an increase over the background rate of spontaneous abortion reported in the general population. Further interpretation of these data is limited by the quality of clinical trial adverse event reporting. In animal reproduction and developmental toxicity studies, rifapentine produced fetal harm and was teratogenic at doses less than and similar to the recommended human dose. Because animal studies are not always predictive of human response, rifapentine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Fourteen patients with active tuberculosis treated with multiple anti-tuberculosis drugs including rifapentine became pregnant during clinical studies. Six delivered normal infants; four had first trimester spontaneous abortions (of these, one patient abused ethanol and another patient was HIV-infected); one had an elective abortion; and outcome was unknown in three patients. These data are, however, limited by the quality of reporting and confounded by co-morbid medical conditions and multiple antituberculosis drug exposures.

In the trial that compared the safety and effectiveness of rifapentine in combination with isoniazid to isoniazid alone for the treatment of latent tuberculosis infection, a total of 45 (2.5%) women in the rifapentine /isoniazid arm and 71 (4.1%) women in the isoniazid arm became pregnant. Among the 46 total pregnancies 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 in the rifapentine /isoniazid arm (15%), and the rate of spontaneous abortion in the isoniazid arm (19%), 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.

Breast-feeding

It is not known whether rifapentine is present in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother (see section 5.3). Since rifapentine may produce a red-orange discoloration of body fluids, there is a potential for discoloration of breast milk.

A slight increase in rat pup mortality was observed during lactation when dams were dosed late in gestation through lactation.

Fertility

There are no studies conducted in human. Fertility and reproductive performance were not affected by oral administration of rifapentine to male and female rats (see section 5.3).

4.7 Effects on ability to drive and use machines

The effect of Rifapentine Tablets on ability to drive or use machinery has not been studied.

4.8 Undesirable effects

The following serious and otherwise important adverse drug reactions are discussed in greater detail in other sections of labeling:

- Hepatotoxicity (see section 4.4)
- Hypersensitivity (see sections 4.3 and 4.4)
- Discoloration of body fluids (see section 4.4)
- Clostridium difficile-associated diarrhea (see section 4.4)
- Porphyria (see section 4.4)

Clinical trials experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Active pulmonary tuberculosis

As per literature data, rifapentine was studied in a randomized, open label, active-controlled trial of HIV-negative patients with active pulmonary tuberculosis. The population consisted of primarily of male subjects with a mean age of 37 ± 11 years. In the initial 2-month phase of treatment, 361 patients received rifapentine 600 mg twice a week in combination with daily isoniazid, pyrazinamide, and ethambutol and 361 subjects received rifampin in combination with isoniazid, pyrazinamide and ethambutol all administered daily. Ethambutol was discontinued when drug susceptibly testing was known. During the 4-month continuation phase, 317 patients in the rifapentine group continued to receive rifapentine 600 mg dosed once-weekly with isoniazid and 304 patients in the rifampin group received twice weekly rifampin and isoniazid. Both treatment groups received pyridoxine (Vitamin B6) over the 6-month treatment period.

Because rifapentine was administered as part of a combination regimen, the adverse reaction profile reflects the entire regimen.

Twenty-two deaths occurred in the study, eleven in the rifampin combination therapy group and eleven in the rifapentine combination therapy group. 18/361 (5%) rifampin combination therapy patients discontinued the study due to an adverse reaction compared to 11/361 (3%) rifapentine combination therapy patients. Three patients (two rifampin combination therapy patients and one rifapentine combination therapy patient) were discontinued in the initial phase due to hepatotoxicity. Concomitant medications for all three patients included isoniazid, pyrazinamide, ethambutol, and pyridoxine. All three recovered without sequelae.

Five patients had adverse reactions associated with rifapentine overdose. These reactions included hematuria, neutropenia, hyperglycemia, ALT increased, hyperuricemia, pruritus, and arthritis.

Table 3 presents selected treatment-emergent adverse reactions associated with the treatment regimens which occurred in at least 1% of patients during treatment and post-treatment through the first three months of follow-up.

Table 3: Selected treatment emergent adverse reactions during treatment of active pulmonary tuberculosis and through three months follow-up

	*Initial Phase**		*Continuation Phase†*	
System Organ Class Preferred Term	***Rifapentine Combination (N=361) N (%)***	***Rifampin Combination (N=361) N (%)***	***Rifapentine Combination (N=317) N (%)***	***Rifampin Combination (N=304) N (%)***
BLOOD AND LYMPHATICS				
Anemia	41 (11.4)	41 (11.4)	5 (1.6)	10 (3.3)
Lymphopenia	38 (10.5)	37 (10.2)	10 (3.2)	9 (3)
Neutropenia	22 (6.1)	21 (5.8)	27 (8.5)	24 (7.9)
Leukocytosis	6 (1.7)	13 (3.6)	5 (1.6)	2 (0.7)
Thrombocytosis	20 (5.5)	13 (3.6)	1 (0.3)	0 (0.0)
Thrombocytopenia	6 (1.7)	6 (1.7)	4 (1.3)	6 (2)
Lymphadenopathy	4 (1.1)	2 (0.6)	0 (0.0)	2 (0.7)
Nonprotein Nitrogen Increased	4 (1.1)	3 (0.8)	10 (3.2)	15 (4.9)
EYE				
Conjunctivitis	8 (2.2)	2 (0.6)	1 (0.3)	1 (0.3)
GASTROINTESTINAL				
Dyspepsia	6 (1.7)	11 (3)	4 (1.3)	6 (2)
Vomiting	6 (1.7)	14 (3.9)	3 (0.9)	3 (1)
Nausea	7 (1.9)	3 (0.8)	2 (0.6)	1 (0.3)
Diarrhea	5 (1.4))	2 (0.6)	2 (0.6)	0 (0.0)
GENERAL				
Back Pain	15 (4.2)	11 (3)	11 (3.5)	4 (1.3)
Abdominal Pain	3 (0.8)	3 (0.8)	4 (1.3)	4 (1.3)
Fever	5 (1.4)	7 (1.9)	1 (0.3)	1 (0.3)
Anorexia	14 (3.9)	18 (5)	8 (2.5)	6 (2)
HEPATIC & BILIARY				
ALT Increased	18 (5)	23 (6.4)	7 (2.2)	10 (3.3)
AST Increased	15 (4.2)	18 (5)	7 (2.2)	8 (2.6)
MUSCULOSKELETAL				
Arthralgia	13 (3.6)	13 (3.6)	3 (0.9)	5 (1.6)
NEUROLOGIC				
Headache	11 (3)	13 (3.6)	3 (0.9)	7 (2.3)
Dizziness	5 (1.4)	5 (1.4)	1 (0.3)	1 (0.3)
RESPIRATORY				
Hemoptysis	27 (7.5)	20 (5.5)	6 (1.9)	6 (2)
Coughing	21 (5.8)	8 (2.2)	9 (2.8)	11 (3.6)
SKIN				
Rash	15 (4.2)	26 (7.2)	8 (2.5)	8 (2.6)
Sweating Increased	19 (5.3)	18 (5)	5 (1.6)	4 (1.3)
Pruritus	10 (2.8)	16 (4.4)	3 (0.9)	0 (0.0)
Rash Maculopapular	6 (1.7)	3 (0.8)	0 (0.0)	1 (0.3)

*Initial phase consisted of therapy with either rifapentine twice weekly or rifampin daily combined with daily isoniazid, pyrazinamide, and ethambutol for 60 days.
†Continuation phase consisted of therapy with either rifapentine once weekly or rifampin twice weekly combined with daily isoniazid for 120 days.

The following selected treatment-emergent adverse reactions were reported in less than 1% of the rifampin combination therapy patients during treatment and post-treatment through the first three months of follow-up.

Blood and lymphatics: lymphocytosis, hematoma, purpura, thrombosis.

Cardiovascular: syncope, tachycardia, palpitation, orthostatic hypotension, pericarditis.

Metabolic & nutritional: BUN increased, alkaline phosphatase increased.

Gastrointestinal: gastritis, esophagitis, pancreatitis, salivary gland enlargement.

General: asthenia, facial edema.

Hepatobiliary: bilirubinemia, hepatomegaly, jaundice.

Infectious disease: infection fungal.

Musculoskeletal: myalgia, myositis.

Neurologic: somnolence, dysphonia.

Pregnancy, puerperium and perinatal conditions: abortion

Psychiatric: anxiety, confusion

Reproductive disorders: vaginitis, vaginal hemorrhage, leukorrhea.

Respiratory: dyspnea, pneumonitis, pulmonary fibrosis, asthma, bronchospasm, laryngeal edema, laryngitis.

Skin: urticaria, skin discoloration,

In another randomized, open-label trial, 1075 HIV non-infected and infected patients with active pulmonary tuberculosis who had completed an initial 2-month phase of treatment with 4 drugs were randomly assigned to receive either rifapentine 600 mg and isoniazid once weekly or rifampin and isoniazid twice weekly for the 4 month continuation phase. 502 HIV non-infected and 36 HIV-infected patients were randomized to receive the rifapentine regimen and 502 HIV-noninfected and 35 HIV-infected patients were randomized to receive the rifampin regimen.

The death rate was 6.5% for the rifapentine combination regimen compared to 6.7% for the rifampin combination regimen.

Latent tuberculosis infection

Main study

According to the literature data, 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. Rifapentine was dosed by weight, and isoniazid mg/kg dose was determined according to age (see section 4.2) to a maximum of 900 mg each.

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. Treatment-emergent adverse reactions were defined as those occurring during treatment and 60 days after the last dose of treatment. 161 (4%) 3RPT/INH subjects had a rifamycin hypersensitivity reaction, defined as either: a) one of the following: hypotension, urticaria, angioedema, acute bronchospasm, or conjunctivitis occurring in relation to study drug or b) at least four of the following symptoms occurring in relation to the study drug, with at least one symptom being CTCAE Grade 2 or higher: weakness, fatigue, nausea, vomiting, headache, fever, aches, sweats, dizziness, shortness of breath, flushing or chills. No specific definition was used for isoniazid hypersensitivity; 18 (0.5%) 9INH subjects were classified as having a hypersensitivity reaction. Hepatotoxicity was defined as AST≥3× upper limit of normal in the presence of specific signs and symptoms of hepatitis, or AST>5× upper limit of normal regardless of signs or symptoms. 113 (3%) 9INH subjects and 24 (0.6%) 3RPT/INH subjects developed hepatotoxicity.

196 subjects (4.9%) in the 3RPT/INH arm discontinued treatment due to a treatment related adverse reaction patients and 142 (3.8%) in the 9INH arm discontinued treatment due to a treatment related adverse reaction. In the 3RPT/INH group, the most frequent treatment related adverse reaction resulting in treatment discontinuation was hypersensitivity reaction, occurring in 120 (3%) patients. In the 9INH group, the most frequent treatment related adverse reaction resulting in treatment discontinuation was hepatotoxicity, occurring in 76 (2%) patients.

Seventy-one deaths occurred, 31/4040, 0.77% in the 3RPT/INH group and 40/3759 (1.06%) in the 9INH group) during the 33-month study period. During the treatment emergent period, 11 deaths occurred, 4 in the 3RPT/INH group and 7 in the 9INH group. None of the reported deaths were considered related to treatment with study drugs or were attributed to tuberculosis disease.

Table 4 presents select adverse reactions that occurred during the treatment emergent period in the main study in LTBI patients treated with 3RPT/INH or 9INH at a frequency greater than 0.5%.

Table 4 Select adverse reactions occurring in 0.5% or greater of patients[*] in the latent tuberculosis infection main study

System Organ Class *Preferred Term*	*3RPT/INH* *(N=4040)* *N (%)*	*9INH* *(N=3759)* *N (%)*
Immune system disorders		
Hypersensitivity	161 (4)	18 (0.5)
Hepatobiliary dis orders		
Hepatitis	24 (0.6)	113 (3)
Nervous system disorders		
Headache	26 (0.6)	17 (0.5)

Skin and subcutaneous tissue disorders		
Skin reaction	31 (0.8)	21 (0.6)

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

Pediatric sub-study

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. Using the same definition for rifamycin hypersensitivity reaction as in the main study, 7 (1.3%) of children in the 3RPT/INH group experienced a rifamycin hypersensitivity reaction. Adverse reactions in children 2 years-11 years of age and 12 years-17 years of age were similar.

HIV sub-study

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 in 3/207 (1.5%) patients in the 3RPT/INH arm and in 14/186 (7.5%) in the 9INH arm. Rifamycin hypersensitivity occurred in only one HIV-infected patient.

Eleven deaths occurred during the 33month follow up period (6/207 in the 3RPT/INH group and 5/186 in the 9INH group) including one death in the 9INH arm during the treatment emergent period. None of the reported deaths were considered related to treatment with study drugs or tuberculosis disease.

Selected treatment-emergent adverse reactions reported during treatment and 60 days post-treatment in less 0.5% of the 3RPT/INH combination-therapy group in the main study are presented below by body system.

Eye disorders: conjunctivitis.

Blood and lymphatic system disorders: leukopenia, anemia, lymphadenopathy, neutropenia.

Gastrointestinal disorders: nausea, diarrhea, vomiting, abdominal pain constipation, dry mouth, dyspepsia, esophageal irritation, gastritis, pancreatitis.
General disorders and administration site conditions: fatigue, pyrexia, asthenia, chest pain, chills, feeling jittery.

Infections and infestations: pharyngitis, viral infection, vulvovaginal candidiasis.

Metabolism and nutrition disorders: hyperglycemia, gout, hyperkalemia, decreased appetite, hyperlipidemia.

Musculoskeletal and connective tissue disorders: arthralgia, myalgia, back pain, rhabdomyolysis.

Nervous system disorders: dizziness, convulsion, paresthesia, headache, neuropathy peripheral, syncope.

Psychiatric disorders: depression, anxiety, disorientation, suicidal ideation.

Renal and urinary disorders: azotemia.

Reproductive system and breast disorders: vulvovaginal pruritus.

Respiratory, thoracic and mediastinal disorders: cough, dyspnea, oropharyngeal pain, asthma, bronchial hyperactivity, epistaxis.

Skin and subcutaneous issue disorders: rash, hyperhidrosis, pruritus, urticaria.

Reporting suspected adverse effects

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions to the respective drug regulatory authorities

4.9 Overdose

While there is no experience with the treatment of acute overdose with rifapentine, 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 drug from the gastrointestinal tract.

Rifapentine and 25-desacetyl rifapentine are 97.7% and 93.2% plasma protein bound, respectively. Rifapentine and related compounds excreted in urine account for only 17% of the administered dose, therefore, neither hemodialysis nor forced diuresis is expected to enhance the systemic elimination of unchanged rifapentine from the body of a patient with rifapentine overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

Rifapentine, a cyclopentyl rifamycin, is an antimycobacterial agent. Rifapentine, a cyclopentyl rifamycin, inhibits DNA-dependent RNA polymerase in susceptible strains of Mycobacterium tuberculosis but does not affect mammalian cells at concentrations that are active against these bacteria. At therapeutic levels, rifapentine inhibits RNA transcription by preventing the initiation of RNA chain formation. 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 *M. tuberculosis* bacilli.

Mechanism of resistance

The mechanism of resistance to rifapentine appears to be similar to that of rifampin. Bacterial resistance to rifapentine is caused by an alteration in the target site, the beta subunit of the DNA-dependent RNA polymerase, caused by a one-step mutation in the rpoβ gene. The incidence of rifapentine resistant mutants in an otherwise susceptible population of *M. tuberculosis* strains is approximately one in 10^7 to 10^8 bacilli.

Rifapentine resistance appears to be associated with monotherapy. Therefore, rifapentine should always be used in combination with other antituberculosis drugs.

Cross resistance

M. tuberculosis organisms resistant to other rifamycins are likely to be resistant to rifapentine. A high level of cross-resistance between rifamycin and rifapentine has been demonstrated with M. tuberculosis strains. Cross-resistance between rifapentine and non-rifamycin antimycobacterial agents has not been identified in clinical isolates.

Susceptibility test methods

In vitro susceptibility tests should be performed according to published methods[1]. Susceptibility test interpretive criteria and quality control ranges for in vitro susceptibility testing of Rifapentine have not been established.

Clinical trials

Active pulmonary tuberculosis

Rifapentine was studied in two randomized, open label controlled clinical trials in the treatment of active pulmonary tuberculosis.

The first trial was an open-label, prospective, parallel group, active controlled trial in HIV-negative patients with active pulmonary tuberculosis. The population mostly comprised Black (approximately 60%) or multiracial (approximately 31%) patients. Treatment groups were comparable for age and sex and consisted primarily of male subjects with a mean age of 37 ± 11 years. In the initial 2-month phase of treatment, 361 patients received rifapentine 600 mg twice a week in combination with daily isoniazid, pyrazinamide, and ethambutol and 361 subjects received rifampin600 mg in combination with isoniazid, pyrazinamide and ethambutol all administered daily. The doses of the companion drugs were the same in both treatment groups during the initial phase: isoniazid 300 mg, pyrazinamide 2000 mg, and ethambutol 1200 mg. For patients weighing less than 50 kg, the doses of rifampin (450 mg), pyrazinamide (1500 mg) and ethambutol (800 mg) were reduced. Ethambutol was discontinued when isoniazid and rifampin susceptibility testing results were confirmed. During the 4-month continuation phase, 317 patients in the rifapentine group continued to receive rifapentine 600 mg dosed once weekly with isoniazid 300 mg and 304 patients in the rifampin group received twice weekly rifampin and isoniazid 900 mg. For patients weighing less than 50 kg, the doses of rifampin (450 mg) and isoniazid (600 mg) were reduced. Both treatment groups received pyridoxine (Vitamin B6) over the 6-months treatment period. Treatment was directly observed. 65/361 (18%) of patients in the rifapentine group and 34/361 (9%) in the rifampin group received overdoses of one or more of the administered study medications during the initial or continuation phase of treatment. Seven of these patients had adverse reactions reported with the overdose (5 in the rifapentine group and 2 in the rifampin group).

Table 5 below contains assessments of sputum conversion at end of treatment (6 months) and relapse rates at the end of follow-up (24 months).

Table 5. Clinical outcome in HIV negative patients with active pulmonary tuberculosis (Trial 1)

	Rifapentine Combination Treatment % and (n/N*)	**Rifampin Combination Treatment % and**

		(n/N*)
Status at End of 6 months of Treatment		
Converted	87% (248/286)	80% (226/283)
Not Converted	1% (4/286)	3% (8/283)
Lost to Follow-up	12% (34/286)	17% (49/283)
Status Through 24 Month Follow-up†:		
Relapsed	12% (29/248)	7% (15/226)
Sputum Negative	57% (142/248)	64% (145/226)
Lost to Follow-up	31% (77/248)	29% (66/226)

*All data for patients with confirmed susceptible *M. tuberculosis* (rifapentine combination treatment, N=286; rifampin combination treatment, N=283).
† Twenty-two (22) deaths occurred during the study; 11 in each treatment group

Risk of relapse was greater in the group treated with the rifapentine combination. Higher relapse rates were associated with a lower rate of compliance as well as a failure to convert sputum cultures at the end of the initial 2-month treatment phase. Relapse rates were also higher for males in both regimens. Relapse in the rifapentine group was not associated with development of mono-resistance to rifampin.

The second trial was randomized, open-label performed in 1075 HIV-negative and positive patients with active pulmonary tuberculosis. Patients with culture-positive, drug-susceptible pulmonary tuberculosis who had completed the initial 2-month phase of treatment with 4 drugs (rifampin, isoniazid, pyrazinamide, and either ethambutol or streptomycin) under direct observation were randomly assigned to receive either rifapentine 600 mg and isoniazid 15 mg/kg (max 900 mg) once-weekly or rifampin 10 mg/kg (max 600 mg) and isoniazid 15 mg/kg (max 900 mg) twice weekly for the 4-month continuation phase. Study drugs were given under direct observation therapy in both groups.

In the rifapentine group, 502 HIV-negative and 36 HIV-positive patients were randomized and in the rifampin group 502 HIV-negative and 35 HIV-positive patients were randomized to treatment. Enrollment of HIV-infected patients was stopped when 4 of 36 patients in the rifapentine combination group relapsed with isolates that were rifampin resistant.

Table 6 below contains assessments of sputum conversion at the end of treatment (6 months total: 2 months of initial and 4 months of randomized continuation treatment) and relapse rates at the end of follow-up (24 months) in all HIV-negative patients randomized to treatment. Positive culture was based on either one sputum sample with >10 colonies on solid media OR at least 2 positive sputum samples on liquid or solid media. However, only one sputum sample was collected at each visit in a majority of patients.

Table 6. Clinical outcome in HIV negative patients with active pulmonary tuberculosis (Trial 2)

	Rifapentine Combination Treatment % (n/N)	**Rifampin Combination Treatment % (n/N)**
Status at End of 4 Months Continuation Phase		
Treatment Response*	93.8% (471/502)	91% (457/502)
Not Converted	1% (5/502)	1.2% (6/502)
Did Not Complete Treatment†	4.2% (21/502)	7% (35/502)
Deaths	1 % (5/502)	0.8% (4/502)
Status Through 24 Month Follow-up†:		
Relapsed	8.7% (41/471)	4.8% (22/457)
Sputum Negative	79.4% (374/471)	80.1% (366/457)
Lost to Follow-up	7.9% (37/471)	9.8% (45/457)

Deaths	4% (19/471)	5.3% (24/457)

*Treatment response was defined as subjects who had two negative sputum cultures after 16 doses of rifampin and isoniazid or after 8 doses of rifapentine and isoniazid, and remained sputum negative through the end of continuation phase therapy.
† Due to drug toxic effects, non-adherence, withdrawal of consent, receipt of non-study regimen, other.

In HIV-negative patients, higher relapse rates were seen in patients with a positive sputum culture at 2 months (i.e., at the time of study randomization), cavitation on chest x-ray, and bilateral pulmonary involvement.

Sixty-one HIV-positive patients were assessed for relapse. The rates of relapse were 16.7% (5/30) in the rifapentine group and 9.7% (3/31) in the rifampin group. In HIV-positive patients, 4 of the 5 relapses in the rifapentine combination group involved M. tuberculosis strains with rifampin monoresistance. No relapse strain in the twice weekly rifampin / isoniazid group acquired drug resistance.

The death rate among all study participants did not differ between the two treatment groups.

Latent tuberculosis infection

According to the literature data, a multi-center, prospective, open-label, randomized, active-controlled trial compared the effectiveness of 12 weekly doses of rifapentine in combination with isoniazid (3RPT/INH arm) administered by directly observed therapy to 9 months of self-administered daily isoniazid (9INH arm). The trial enrolled patients two years of age or older with positive tuberculin skin test and at high risk for progression to tuberculosis disease. Enrolled patients included those having close contact with a patient with active tuberculosis disease, recent (within two years) conversion to a positive tuberculin skin test, HIV-infection, or fibrosis on chest radiograph. rifapentine was dosed by weight, for a maximum of 900 mg weekly. Isoniazid mg/kg dose was determined by age, for a maximum of 900 mg weekly in the 3RPT/INH arm and 300 mg daily in the 9INH arm (see section 4.2).

The outcome measure was the development of active tuberculosis disease, defined as culture confirmed tuberculosis in adults and culture-confirmed or clinical tuberculosis in children less than 18 years of age, at 33 months after trial enrollment. Patients who were found after enrollment to be ineligible because they had active tuberculosis disease, were contacts of a source case with culture-negative or drug-resistant tuberculosis disease cases or no information regarding susceptibility of *M. tuberculosis*, and young children lacking a positive TST on initial and repeat testing were excluded from the analysis.

Active tuberculosis disease developed in 5 of 3074 randomized patients in the 3RPT/INH group (0.16%) versus 10 of 3074 patients in 9INH group (0.32%), for a difference in cumulative rates of 0.17%, 95% CI (-0.43, 0.09) (Table 7).

Table 7. Outcomes in randomized patients at 33-months post-enrollment*

Outcome	3RPT/INH (n=3074)	9INH (n=3074)	Difference†, 95% CI
Tuberculosis n (%)	5 (0.16)	10 (0.32)	-0.16 (-0.42, 0.01)
Cumulative TB Rate (%)	0.17	0.35	-0.17 (-0.43, 0.09)
Deaths	22 (0.72)	35 (1.14)	-0.42 (-0.91, 0.06)
Lost to Follow-Up	320 (10.41)	357 (11.61)	-1.20 (-2.77, -0.36)

*Similar results were observed when all enrolled patients were included in the analysis.
†Rate in the 3RPT/INH group minus the rate in the 9INH group.

The proportion of patients completing treatment was 81.2% in the 3RPT/INH group and 68.3% in the 9INH group for a difference (3RPT/INH-9INH) of 12.8% 95% CI (10.7, 15.0).

In the 9INH treatment group, two of the thirteen culture-confirmed cases were found to be isoniazid-monoresistant. In the 3RPT/INH treatment group, one of the seven cases was rifampin-resistant, isoniazid-susceptible *M. bovis* infection.

Pediatric sub-study

Enrollment of children was extended after the overall target number of patients was attained in the main study. Data from both the main study and the extension were pooled resulting in an eligible population for analysis of 375 children in the 3RPT/INH arm and 367 in the 9INH arm.

One child in the 9INH group developed tuberculosis (1/367, cumulative rate 0.32%) versus zero tuberculosis cases in the 3RPT/INH group (0/375) at 33 months post-enrollment. The proportion of patients completing treatment in the 3RPT/INH and the 9INH groups was 87.5% and 79.6% respectively for a difference of 7.9%, 95% CI (2.5, 13.2).

HIV sub-study

Enrollment of HIV-positive patients was extended after the overall target number of patients was attained in the main study. Data from both the main study and the extension were pooled resulting an eligible population for analysis of 206 patients in the 3RPT/INH group and 193 in the 9INH group. Tuberculosis disease developed in 2/206 patients in the 3RPT/INH group (cumulative rate, 1.01%) and in 6/193 patients in the 9INH group (cumulative rate, 3.45%). The proportion of patients completing treatment in the 3RPT/INH and 9INH groups was 88.8% and 63.7%, respectively for a difference of 25.1%, 95% CI (16.8, 32.9).

5.2 Pharmacokinetic properties

Oral doses of rifapentine were administered once daily or once every 72 hours to healthy volunteers for 10 days, single dose $AUC_{(0-\infty)}$ of rifapentine was similar to its steady-state $AUC_{ss\ (0-24h)}$ or $AUC_{ss\ (0-72h)}$ values, suggesting no significant auto-induction effect on steady-state pharmacokinetics of rifapentine. Steady-state conditions were achieved by day 10 following daily administration of rifapentine 600 mg. No plasma accumulation of rifapentine and 25-desacetyl rifapentine (active metabolite) is expected after once weekly administration of rifapentine.

The pharmacokinetic parameters of rifapentine and 25-desacetyl rifapentine on day 10 following oral administration of 600 mg rifapentine every 72 hours to healthy volunteers are described in Table 8.

Table 8. Pharmacokinetics and rifapentine and 25-desacetyl rifapentine in healthy volunteers

Parameter	Rifapentine	25-desacetyl Rifapentine
	Mean ± SD (n=12)	
C_{max} (µg/mL)	15.05 ± 4.62	6.26 ± 2.06
$AUC_{(0-72h)}$ 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 rifapentine in combination with 900 mg isoniazid in fed conditions are described in Table 9.

Table 9. Mean ± SD pharmacokinetic parameters of rifapentine and 25- desacetyl rifapentine in healthy volunteers when rifapentine is Co-administered with isoniazid under fed conditions (N=16).

Parameter	Rifapentine	25-desacetyl Rifapentine
	Mean ± SD (n=12)	
C_{max} (µg/mL)	25.8± 5.83	13.3 ± 4.83
AUC $_{(0-72h)}$ 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. The relative bioavailability (with an oral solution as a reference) of rifapentine after a single 600 mg dose to healthy adult volunteers was 70%. The maximum concentrations were achieved from 5 hours to 6 hours after administration of the 600 mg rifapentine dose.

The administration of rifapentine with a high fat meal increased rifapentine C_{max} and AUC by 40% to 50% over that observed when rifapentine was administered under fasting conditions.

The administration of rifapentine (900 mg single dose) and isoniazid (900 mg single dose) with a low fat, high carbohydrate breakfast, led to a 47% and 51% increase in rifapentine C_{max} and AUC, respectively. In contrast, the ingestion of the same meal decreased isoniazid C and AUC by 46% and of 23%, respectively.

Distribution

In a population pharmacokinetic analysis in 351 tuberculosis patients who received 600 mg rifapentine in combination with isoniazid, pyrazinamide and ethambutol, the estimated apparent volume of distribution was 70.2 ± 9.1 L. In healthy volunteers, rifapentine and 25-desacetyl rifapentine were 97.7% and 93.2% bound to plasma proteins, respectively. Rifapentine was mainly bound to albumin. Similar extent of protein binding was observed in healthy volunteers, asymptomatic HIV-infected subjects and hepatically impaired subjects.

Metabolism/Excretion

Following a single 600 mg oral dose of radiolabeled rifapentine to healthy volunteers (n=4), 87% of the total ^{14}C rifapentine was recovered in the urine (17%) and feces (70%). Greater than 80% of the total ^{14}C rifapentine dose was excreted from the body within 7 days. Rifapentine was hydrolyzed by an esterase enzyme to form a microbiologically active 25-desacetyl rifapentine. Rifapentine and 25-desacetyl rifapentine accounted for 99% of the total radioactivity in plasma. Plasma $AUC_{(0-\infty)}$ and C_{max} values of the 25-desacetyl rifapentine metabolite were one-half and one-third those of the rifapentine, respectively. Based upon relative in vitro activities and $AUC_{(0-\infty)}$ values, rifapentine and 25-desacetylrifapentine potentially contributes 62% and 38% to the clinical activities against *M. tuberculosis*, respectively.

Specific populations

Gender

In a population pharmacokinetics analysis of sparse blood samples obtained from 351 tuberculosis patients who received 600 mg rifapentine in combination with isoniazid, pyrazinamide and ethambutol, the estimated apparent oral clearance of rifapentine for males and females was 2.51 ± 0.14 L/h and 1.69 ± 0.41 L/h, respectively. The clinical significance of the difference in the estimated apparent oral clearance is not known.

Elderly

As per literature data, following oral administration of a single 600 mg dose of rifapentine to elderly (65 years and older) male healthy volunteers (n=14), the pharmacokinetics of rifapentine and 25-desacetyl metabolite were similar to that observed for young (18 to 45 years) healthy male volunteers (n=20).

Pediatric

In a pharmacokinetic study in pediatric patients (age 2 to 12 years), a single oral dose of 150 mg rifapentine was administered to those weighing less than 30 kg (n=11) and a single oral dose of 300 mg was administered to those weighing greater than30kg (n=12). The mean estimates of AUC and C_{max} were approximately 30% to 50% lower in these pediatric patients than those observed in healthy adults administered single oral doses of 600 mg and 900 mg.

A study compared the pharmacokinetics of rifapentine in pediatric patients (age 2 years to 11 years) with latent tuberculosis infection (n=80) receiving rifapentine once weekly based on weight (15 mg/kg–30 mg/kg, up to a maximum of 900 mg, see Table 1) to that of adults (n=77) receiving rifapentine 900 mg once weekly. Children who could not swallow whole tablets were administered crushed tablets mixed in soft food. Overall, the geometric mean AUC of rifapentine in this age group was 31% higher compared to adult patients receiving 900 mg rifapentine once weekly (720 versus 551 mcg*h/mL). The geometric mean AUC of rifapentine was 60% higher in children administered whole tablets (884 versus 551 mcg*h/mL) and 19% higher in children administered crushed tablets (656 versus 551 mcg*h/mL), as compared to exposures in adults. Pediatric patients administered crushed rifapentine tablets had 26% lower rifapentine exposures compared to those pediatric patients who were given whole tablets.

Population pharmacokinetic analysis showed that rifapentine clearance adjusted to body weight decreased with increasing age of pediatric patients (2–18 years).

In another pharmacokinetics study of rifapentine in healthy adolescents (age 12 to 15 years), 600 mg rifapentine was administered to those weighing ≥45 kg (n=10) and 450 mg was administered to those weighing less than 45 kg (n=2). The pharmacokinetics of rifapentine were similar to those observed in healthy adults.

Renal impairment

The pharmacokinetics of rifapentine have not been evaluated in renal impaired patients. Although 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.

Hepatic impairment

According to the literature data, Following oral administration of a single 600 mg dose of rifapentine to mild to severe hepatic impaired patients (n=15), the pharmacokinetics of rifapentine and 25-desacetyl metabolite were similar in patients with various degrees of hepatic impairment and to that observed in another study for healthy volunteers (n=12).

Asymptomatic HIV-infected volunteers

As per the literature data Following oral administration of a single 600 mg dose of rifapentine to asymptomatic HIV-infected volunteers (n=15) under fasting conditions, mean C_{max} and $AUC_{(0-\infty)}$ of rifapentine were lower (20%–32%) than that observed in other studies in healthy volunteers (n=55). In a cross-study comparison, mean C_{max} and AUC values of the 25-desacetyl rifapentine, when compared to healthy volunteers were higher (6%–21%) in one study (n=20), but lower (15%–16%) in a different study (n=40). The clinical significance of this observation is not known. Food (850 total calories: 33 g protein, 55 g fat, and 58 g carbohydrate) increases the mean AUC and C_{max} of rifapentine observed under fasting conditions in asymptomatic HIV-infected volunteers by about 51% and 53%, respectively.

Drug-Drug Interactions

Isoniazid: Co-administration of rifapentine (900 mg single dose) and isoniazid (900 mg single dose), in fasted condition, did not result in any significant change in the exposure of rifapentine and isoniazid compared to when administered alone in fasted condition.

Rifapentine is an inducer of cytochrome P4503A4 and 2C8/9. Therefore, it may increase the metabolism and decrease the activity of other co-administered drugs that are metabolized by these enzymes. Dosage adjustments of the co-administered drugs may be necessary if they are given concurrently with rifapentine (see section 4.5).

Indinavir: In a study in which 600 mg rifapentine was administered twice weekly for 14 days followed by rifapentine twice weekly plus 800 mg indinavir 3 times a day for an additional 14 days, indinavir C_{max} decreased by 55% while AUC reduced by 70%. Clearance of indinavir increased by 3-fold in the presence of rifapentine while half-life did not change. But when indinavir was administered for 14 days followed by co-administration with rifapentine for an additional 14 days, indinavir did not affect the pharmacokinetics of rifapentine (see sections 4.4 and 4.5).

Fixed dose combination of efavirenz, emtricitabine and tenofovir: Once-weekly co-administration of 900 mg rifapentine with the antiretroviral fixed dose combination of efavirenz 600 mg, emtricitabine 200 mg and tenofovir disoproxyl fumarate 300mg in HIV- infected patients did not result in any substantial change in steady state exposures of efavirenz, emtricitabine, and tenofovir (Table 10). A 15% decrease in efavirenz C_{min} and AUC and a 13% decrease in tenofovir C_{min} were observed with repeated weekly doses of rifapentine (Table 10). No clinically significant change in CD4 cell counts or viral loads were noted.

Table 10. Treatment ratio estimates (with versus without repeated once-weekly (rifapentine 900 mg) with 90% confidence intervals for efavirenz, emtricitabine and tenofovir pharmacokinetic parameters

Parameter	Efavirenz Point Estimates (90% CI)	Emtricitabine Point Estimates (90% CI)	Tenofovir Point Estimates (90% CI)
C_{max}	0.92 (0.82 –1.03)	0.95 (0.81– 1.10)	1.00 (0.82 –1.22)
C_{min}	0.85 (0.79– 0.93)	0.97 (0.90– 1.05)	0.87(0.73 – 1.05))
$AUC_{(0-24h)}$	0.86 (0.79– 0.93)	0.93 (0.89– 0.98)	0.91(0.85 –0.98)

5.3 Preclinical safety data

Animal studies in rats and rabbits revealed embryofetal toxicity in both species. Pregnant rats given oral rifapentine during organogenesis at 40 mg/kg/day (0.6 times the human dose of 600 mg based on body surface area), produced pups with cleft palates, right aortic arch, increased incidence of delayed ossification, and increased numbers of ribs. When rifapentine was administered orally to mated female rats late in gestation, at 20 mg/kg/day (0.3 times the human dose based on body surface area), pup weights and gestational survival (live pups born/pups born) were reduced compared to controls. Increased resorptions and post implantation loss decreased mean fetal weights, increased numbers of stillborn pups, and slightly increased pup mortality during lactation were also noted. When pregnant rabbits received oral rifapentine at 10 mg/kg to 40 mg/kg (0.3 times to 1.3 times the human dose based on body surface area), major fetal malformations occurred including: ovarian agenesis, pes varus, arhinia, microphthalmia, and irregularities of the ossified facial tissues. At the higher dose, there were increases in post-implantation loss and the incidence of stillborn pups.

Carcinogenesis, mutagenesis, impairment of fertility

Hepatocellular carcinomas were increased in male NMRI mice (Harlan Winklemann) which were treated orally with rifapentine for two years at or above doses of 5 mg/kg/day (0.04 times the recommended human dose based on body surface area conversions). In a 2-year rat study, there was an increase in nasal cavity adenomas in Wistar rats treated orally with rifapentine at 40 mg/kg/day (0.6 times human dose based on body surface area conversions).

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.

As per literature data, 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. 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).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline Cellulose, Sodium Starch Glycolate, Pregelatinized Starch, Hydroxypropyl Cellulose, Sodium Ascorbate, Sodium Lauryl Sulfate, Disodium Edetate, Colloidal Silicon Dioxide, Calcium Stearate, Opadry 03G565009 Brown

6.2 Incompatibilities

Not applicable

6.3 Shelf life
24 Months

6.4 Special precautions for storage
Do not store above 30°C. Protect from excessive heat and moisture

6.5 Nature and contents of container

Packs	Description
10's Aluminium Strip	10 Tablets shall be packed per strip using plain strip aluminium foil 0.04 mm as base material and printed strip aluminium foil 0.04 mm as a lidding material
12's Aluminium Strip	12 Tablets shall be packed per strip using plain strip aluminium foil 0.04 mm as base material and printed strip aluminium foil 0.04 mm as a lidding material
14's Aluminium Strip	14 Tablets shall be packed per strip using plain strip aluminium foil 0.04 mm as base material and printed strip aluminium foil 0.04 mm as a lidding material
10's Alu-Alu Blister	10 Tablets shall be packed per Blister using cold form Alu-Alu blister foil as base material and 0.03 mm thick blister hard tampered heat seal lacquer coated printed Aluminium foil as a lidding material
12's Alu-Alu Blister	12 Tablets shall be packed per Blister using cold form Alu-Alu blister foil as base material and 0.03 mm thick blister hard tampered heat seal lacquer coated printed Aluminium foil as a lidding material
14's Alu-Alu Blister	14 Tablets shall be packed per Blister using cold form Alu-Alu blister foil as base material and 0.03 mm thick blister hard tampered heat seal lacquer coated printed Aluminium foil as a lidding material

6.6 Special precautions for disposal
No special requirements. Any unused product or waste material should be disposed of in accordance with local requirements.

7. Supplier
Lupin Ltd
Kalpataru Inspire
3rd Floor, Off Western Express Highway
Santacruz (East)
Mumbai 400055, India

8. WHO REFERENCE NUMBER (PREQUALIFICATION PROGRAMME)

9. DATE OF FIRST PREQUALIFICATION /RENEWAL OF THE PREQUALIFICATION

10. DATE OF REVISION OF THE TEXT

References:

1. Clinical and Laboratory Standards Institute. M24-A Susceptibility Testing of Mycobacteria, Nocardiae, and Other Aerobic Actinomycetes; Approved Standard. 23 ed. 2003. Clinical Laboratory Standards Institute, Wayne, PA.