SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Rifapentine and isoniazid 300 mg/300 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 300 mg of rifapentine and 300 mg of isoniazid

For the full list of excipients, see Section 6.1.

3. PHARMACEUTICAL FORM:

Tablets

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Rifapentine and isoniazid tablet is indicated for the treatment of active pulmonary tuberculosis, caused by *Mycobacterium tuberculosis*.

Consideration should be given to official treatment guidelines for tuberculosis, e.g those of WHO when initiating treatment.

4.2 Dose and method of administration

Posology

Active pulmonary tuberculosis

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

Initial phase (2 Months)

Rifapentine and isoniazid tablet 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 ethambutol (EMB) and pyrazinamide (PZA).

Continuation phase (4 Months)

Following the initial phase (2 months), continuation phase (4 months) treatment consists of and isoniazid tablet 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 and isoniazid tablet should be administered once-weekly for 12 weeks as directly observed therapy.

Adults and children 12 years and older

The recommended dose of Rifapentine and isoniazid tablet 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 100mg) up to a maximum of 900 mg once-weekly for 12 weeks.

Children 2–11 years

The recommended dose of Rifapentine and isoniazid tablet 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 100mg) up to a maximum of 900 mg once weekly for 12 weeks.

Table 1: Weight based dose of rifapentine in the treatment of latent tuberculosis infection

Weight range	Rifapentine dose	Number of tablets
10–14 kg	300 mg	1
14.1–25 kg	450 mg	3
25.1– 32 kg	600 mg	2
32.1–50 kg	750 mg	5
> 50 kg	900 mg	3

Method of administration

Oral use.

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

4.3 Contraindications

Rifapentine and isoniazid tablets are contraindicated in patients with:

- hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- patients with a history of hypersensitivity to rifamycins.
- acute liver disease of any etiology.
- drug induced hepatic disease.
- previous isoniazid-associated hepatic injury or
- previous severe adverse reactions such as drug fever, chills or arthritis.

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.

Severe and sometimes fatal hepatitis associated with isoniazid therapy has been reported. The majority of cases occur within the first three months of therapy, but hepatotoxicity may also develop after a longer duration of treatment. Therefore, patients should be carefully monitored and interviewed at monthly intervals.

Patients should be instructed to immediately report signs or symptoms consistent with liver damage or other adverse effects.

These include any of the following: unexplained anorexia, nausea, vomiting, dark urine, icterus, rash, persistent paraesthesia of the hands and feet, persistent fatigue, weakness of greater than 3 days duration and/or abdominal tenderness, especially of the right upper quadrant.

If these symptoms appear or if signs suggestive of hepatic damage are detected, isoniazid should be discontinued promptly, since continued use of the drug in these cases has been reported to cause a more severe form of liver damage.

Patient groups especially at risk for developing hepatitis include
- age > 35 years
- daily users of alcohol (patients should be strongly advised to restrict intake of alcoholic beverages, see section 4.5)
- patients with active chronic liver disease and
- injection drug users.

In addition to monthly symptom reviews, hepatic enzymes (specifically AST and ALT) should be measured in these patients prior to starting isoniazid therapy and periodically throughout treatment.

Furthermore, the following patients should be carefully monitored:
- patients with concurrent use of any chronically administered medication (see section 4.5)
- existence of peripheral neuropathy or conditions predisposing to neuropathy
- pregnant patients and
- HIV infected patients.

The concentration of liver enzymes is commonly raised during therapy with isoniazid. These effects on liver function are usually mild to moderate, and will most commonly normalise spontaneously within three months, even in the presence of continued therapy.

If the concentration of liver enzymes exceeds three to five times the upper limit of normal, discontinuation of isoniazid should be strongly considered.

<u>Hypersensitivity and related reactions</u>

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.

Patients hypersensitive to ethionamide, pyrazinamide, niacin (nicotinic acid), or other chemically related medications may also be hypersensitive to this product.

Isoniazid should be used with caution in patients with pre-existing seizure disorders, a history of psychosis or hepatic impairment.

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.

Peripheral neuropathy

Peripheral neuropathy is the most common toxic effect of isoniazid (see section 4.8). The frequency depends on the dose and on predisposing conditions such as malnutrition, impaired renal function, alcoholism or diabetes. Concomitant pyridoxine administration largely reduces the risk of developing neuropathy. Therefore, pyridoxine should be co-administered routinely at doses of 10 mg per day.

Diabetes Mellitus

Patients with diabetes should be carefully monitored, since blood glucose control may be affected by isoniazid.

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).

Renal impairment

Patients with renal impairment, particularly those who are slow acetylators (see sections 4.2 and 5.2) may be at increased risk for isoniazid adverse effects such as peripheral neuropathy, and should be monitored accordingly. As in other patients, adequate supplementation with pyridoxine (see above) should be given to avoid neurotoxicity.

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.

Information about excipients

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

Inhibitor of CYP2C19 and CYP3A4

Isoniazid acts as an inhibitor of CYP2C19 and CYP3A4. Thus, it may increase exposure to drugs mainly eliminated through either of these pathways. The following list of interactions should not be considered exhaustive, but as representative of the classes of medicinal products where caution should be exercised.

Anticonvulsants

Phenytoin, carbamazepine, valproate:

Isoniazid decreases the apparent clearance of these drugs, and therefore increases drug exposure. Plasma concentrations of the anticonvulsant should be determined prior to and after initiation of isoniazid therapy; the patient should be monitored closely for signs and symptoms of toxicity and the dose of the anticonvulsant should be adjusted accordingly. Concomitant intake of phenytoin or carbamazepine may increase the hepatotoxicity of isoniazid.

Sedatives

Benzodiazepines (e.g. diazepam, flurazepam, triazolam, midazolam)

Isoniazid may decrease the hepatic metabolism of benzodiazepines, leading to increased benzodiazepine plasma concentrations. Patients should be carefully monitored for signs of benzodiazepine toxicity and the dose of the benzodiazepine should be adjusted accordingly.

Phenobarbital

Concomitant use with isoniazid may lead to increased hepatotoxicity.

Antipsychotics

Chlorpromazine

Concomitant use with isoniazid may impair the metabolism of isoniazid. Patients should be carefully monitored for isoniazid toxicity.

Haloperidol

Concomitant use with isoniazid may increase plasma levels of haloperidol. Patients should be carefully monitored for haloperidol toxicity and the dose of haloperidol should be adjusted accordingly.

Anticoagulants

Coumarin- or indandione-derivatives (e.g. warfarin and phenindione)

Concomitant use with isoniazid may inhibit the enzymatic metabolism of the anticoagulants, leading to increased plasma concentrations with an increased risk of bleeding. Therefore, INR should be closely monitored.

Opoids and anaesthetics

Alfentanil

Isoniazid may decrease the plasma clearance and prolong the duration of action of alfentanil. The dose of alfentanil may need to be adjusted accordingly.

Enflurane

Isoniazid may increase the formation of the potentially nephrotoxic inorganic fluoride metabolite of enflurane when used concomitantly.

Others

Theophylline
Concomitant use with isoniazid may reduce the metabolism of theophylline, thereby increasing its plasma levels. Therefore, theophylline plasma levels should be monitored.

Procainamide

Concomitant use with isoniazid may increase the plasma concentrations of isoniazid. Patients should be carefully monitored for isoniazid toxicity.

Corticosteroids (e.g. prednisolone)

In one study, concomitant use with isoniazid decreased isoniazid exposure by 22-30%. Isoniazid dosage adjustments may be required in rapid acetylators.

Acetaminophen, paracetamol

Concurrent use with isoniazid may increase hepatotoxicity.

Aluminium hydroxide

Impairs the absorption of isoniazid. During therapy with Isoniazid 300 mg tablets acid-suppressing drugs or antacids that do not contain aluminium hydroxide should be used. Disulfiram: concurrent use with isoniazid may result in increased incidence of effects on the central nervous system. Reduced dosage or discontinuation of disulfiram may be necessary.

Hepatotoxic medications

Concurrent use of isoniazid with other hepatotoxic medications may increase hepatotoxicity and should be avoided.

Neurotoxic medications

Concurrent use of isoniazid with other neurotoxic medications may lead to additive neurotoxicity and should be avoided.

Interactions with food and drinks

Alcohol

Concurrent daily intake of alcohol may result in an increased incidence of isoniazid induced hepatotoxicity. Patients should be monitored closely for signs of hepatotoxicity and should be strongly advised to restrict intake of alcoholic beverages (see section 4.4).

Cheese and fish (histamine- or tyramine-rich food)

Concurrent ingestion with isoniazid may lead to inhibition of mono-/diamine oxidases by isoniazid, interfering with the metabolism of histamine and tyramine. Clinically, this may result in redness or itching of the skin, hot feeling, rapid or pounding heartbeat, sweating, chills or clammy feeling, headache, or lightheadedness.

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.

Isoniazid may cause a false positive response to copper sulfate glucose tests; enzymatic glucose tests are not affected.

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

and no adverse effects of isoniazid on the fetus have been reported rifapentine/isoniazid 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; however, isoniazid passes into breast milk. No adverse effects in the baby have been reported. Concentrations in breast milk are so low, that breast-feeding cannot be relied upon for adequate tuberculosis prophylaxis or therapy for nursing infants.

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 male or female fertility. Fertility and reproductive performance were not affected by oral administration of rifapentine to male and female rats however, in animal studies, male fertility has been impaired by isoniazid (see section 5.3).

4.7 Effects on ability to drive and use machines

The effect of Rifapentine/isoniazid on ability to drive or use machinery has not been studied. Nevertheless, the clinical status of the patient and the adverse reaction profile of this medicine, especially its potential neurotoxicity, should be borne in mind when considering the patient's ability to drive or operate machinery.

4.8 Undesirable effects

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

Rifapentine

- 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.

Isoniazid

The most important adverse effects of isoniazid are peripheral and central neurotoxic effects, and severe and sometimes fatal hepatitis.

The adverse reactions considered at least possibly related to treatment with the components of Isoniazid 300 mg tablets from clinical trial and post-marketing experience are listed below by body system organ class and absolute frequency. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. Frequencies are defined as very common (≥ 1/10), common (≥ 1/100, < 1/10), uncommon (≥ 1/1,000, < 1/100), rare (≥ 1/10,000, < 1/1,000) or very rare (< 1/10,000)

including isolated reports, or not known (identified through post-marketing safety surveillance and the frequency cannot be estimated from the available data).

Nervous system disorders	
Very common	Peripheral neuropathy, usually preceded by paraesthesias of the feet and hands. The frequency depends on the dose and on predisposing conditions such as malnutrition, alcoholism or diabetes. It has been reported in 3.5 to 17% of patients treated with isoniazid. Concomitant pyridoxine administration largely reduces this risk (see section 4.4).
Uncommon	seizures, toxic encephalopathy
Not known	dizziness, headache, tremor, vertigo, hyperreflexia
Psychiatric disorders	
Uncommon	memory impairment, toxic psychosis
Not known	confusion, disorientation, hallucination
Gastrointestinal disorders	
Not known	nausea, vomiting, anorexia, dry mouth, flatulence, abdominal pain, constipation.
Hepatobiliary disorders	
Very common	Transient increases of serum transaminases
Uncommon	Hepatitis
Renal and urinary disorders	
Not known	urinary retention, nephrotoxicity including interstitial nephritis
Metabolic and nutrition disorders	
Not known	hyperglycaemia, metabolic acidosis, pellagra
General disorders	
Not known	allergic reactions with skin manifestation (exanthema, erythema, erythema multiforme), pruritus, fever, leucopenia, anaphylaxia, allergic pneumonitis, neutropenia, eosinophilia, Stevens-Johnson syndrome, vasculitis, lymphadenopathy, rheumatic syndrome, lupus–like syndrome
Blood and lymphatic systems disorders	
Not known	anaemia (haemolytic, sideroblastic, or aplastic), thrombocytopenia, leucopenia (allergic), neutropenia with eosinophilia, agranulocytosis
Respiratory, thoracic and mediastinal disorders	
Not known	pneumonitis (allergic)
Musculoskeletal disorders	
Not known	Arthritis
Eye disorders	
Not known	Optic atrophy or neuritis

For recommendations on the management of side effects related to anti-tuberculosis therapy official national and/or international guidelines should be consulted.

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

Rifapentine

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.

Isoniazid

Symptoms

Anorexia, nausea, vomiting, gastrointestinal disturbances, fever, headache, dizziness, slurred speech, hallucinations and/or visual disturbances occur within 30 minutes to 3 hours after ingestion. With marked isoniazid overdoses (≥ 80 mg/kg body weight) respiratory distress and CNS depression, progressing rapidly from stupor to profound coma, along with severe intractable seizures are to be expected. Typical laboratory findings are severe metabolic acidosis, acetonuria, and hyperglycaemia.

Treatment

Emesis, gastric lavage and activated charcoal may be of value if instituted within a few hours of ingestion. Subsequently, pyridoxine (intravenous bolus on a gram per gram basis, equal to the isoniazid dose; if latter dose is unknown an initial dose of 5 g in adults or 80 mg/kg BW in children should be considered), intravenous diazepam (in case of seizures not responding to pyridoxine) and haemodialysis may be of value. Further treatment should be supportive, with special attention to monitoring/support of ventilation and correction of metabolic acidosis. There is no specific antidote.

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.

Isoniazid is highly active against *Mycobacterium tuberculosis*. It is bactericidal *in vitro* and *in vivo* against actively dividing tubercle bacilli. Its primary action is to inhibit the synthesis of long chain mycolic acids, which are unique constituents of mycobacterial cell wall. Resistance to isoniazid occurs rapidly if it is used alone in the treatment of clinical disease due to mycobacteria.

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.

After oral administration isoniazid is rapidly absorbed with a bioavailability of ≥80%, and peak serum concentrations reached after 1-2 hours. The rate and extent of absorption are reduced when isoniazid is administered with food. Isoniazid undergoes appreciable presystemic (first pass) metabolism in the wall of small intestine and liver.

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.

As per data reported in published literature, following single dose isoniazid 300 mg administration in healthy volunteers, the mean (± SD) isoniazid C_{max} value was 8323 ng/ml (± 3637), and the corresponding value for AUC was 38063 ng.hours/ml (± 10516). The mean (± SD) isoniazid t_{max} value was 0.92 (± 0.76) hours.

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.

Isoniazid is distributed in the body with an apparent volume of distribution volume of 0.57 to 0.76 l/kg. Protein binding is very low (0-10%).

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.

Isoniazid undergoes extensive metabolism that takes place in the mucosal cells of the small intestine and in the liver. First isoniazid is inactivated through acetylation. Subsequently acetyl-isoniazid is further hydrolysed. Isoniazid acetylation is dependent on the genetically determined metabolic rate of the individual patients, who are termed either fast or slow acetylators (this is due to a genetic polymorphism in the metabolising enzyme N-acetyl transferase). Different ethnic groups contain differing proportions of acetylator phenotypes. Acetylator status is the main determinant of isoniazid exposure at a given dose. At recommended doses, exposure in fast acetylators is about half that seen in slow acetylators.

Up to 95% of ingested isoniazid is excreted in the urine within 24 hours, primarily as inactive metabolites. Less than 10% of the dose is excreted in the faeces. The main excretion products in the urine are N-acetyl isoniazid and iso nicotinic acid.

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.

The documentation of the pharmacokinetics of isoniazid and its metabolites in patients with renal impairment is incomplete. However, the half-life of isoniazid is prolonged and exposure is increased, in slow acetylators. The exposure to the (inactive) metabolites of isoniazid is likely to be increased in both fast and slow acetylators.

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).

Non-clinical data reveal no special hazard for isoniazid in humans at recommended doses based on conventional studies of safety pharmacology, repeated -dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction. In male rats spermatogenesis impairment and abnormalities in testicular histopathology was seen.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose, hydroxypropyl cellulose, pregelatinized starch, sodium ascorbate, sodium lauryl sulfate, sodium starch glycolate, Dewaxed shellac ,calcium stearate, disodium Edetate, Wincoat WT-MPAQ-01266P brown (Polyvinyl alcohol, soya lecithin, xanthan gum, talc, red iron oxide and titanium dioxide).

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 Months Proposed

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 plain 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 plain 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 plain 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

1.**WHO REFERENCE NUMBER (PREQUALIFICATION PROGRAMME)**

2.**DATE OF FIRST PREQUALIFICATION/RENEWAL OF 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.