20th December 2021

## SUMMARY OF PRODUCT CHARACTERISTIC

### 1. Name of the Medicinal Product

Rifapentine Tablets 300 mg

### 2. Qualitative and Quantitative Composition

Each film coated tablet contains:

Rifapentine …….....300mg

**For Excipients see point 6.1**

### 3. Pharmaceutical Form

Tablet

The tablet can be divided into equal doses.

### 4. Clinical Particulars

### 4.1 Therapeutic indications

***Active Pulmonary Tuberculosis***

Rifapentine is indicated in adults and children aged 12 years or older with a body weight of more than 40 kg for the treatment of Pulmonary Drug susceptible tuberculosis (DS-TB), including those who are also HIV-positive with a CD4 count of more than 100 cells/mm3 and patients with diabetes.

Limitations of Use

Rifapentine Tablet should not be used for the treatment of following patients:

- patients weighing less than 40 kg;
- patients with severe extrapulmonary TB (e.g. tuberculous meningitis, disseminated TB, osteoarticular TB or abdominal TB);
- PLHIV with a CD4 count of less than 100 cells/mm3;
- children and adolescents aged under 12 years; and
- pregnant, breastfeeding and postpartum women.

***Latent Tuberculosis Infection***

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

- Rifapentine in combination with isoniazid is not recommended for individuals presumed to be exposed to rifamycin-resistant or isoniazid-resistant M. Tuberculosis.

**4.2 Posology and method of administration**

***Dosage in Active Pulmonary Tuberculosis***

Rifapentine (P) is recommended for the treatment of pulmonary DS-TB in patients aged 12 years or older in combination with isoniazid (H), moxifloxacin (M) and pyrazinamide (Z) as a part of 4-month regimen. (2HPMZ/ 2HPM).

The first 2 months of treatment, includes four drugs i.e. isoniazid (H), Rifapentine (P), moxifloxacin (M) and pyrazinamide (Z) followed by three i.e. isoniazid (H), Rifapentine (P) and moxifloxacin (M) for remaining 2 months.

For this regimen, daily dosing is recommended.

The dose of rifapentine is 1200 mg as per below table:

| Medicine | Strength | 35 to <50 kg | 50 to <65 kg | 65 kg + |
|---|---|---|---|---|
| Rifapentine | 300mg | 4 tablets | 4 tablets | 4 tablets |

The dose of moxifloxacin is 400 mg. Other medicines i.e. isoniazid and pyrazinamide should be taken as per the standard recommended doses.

Replacement of moxifloxacin by another fluoroquinolone is not recommended.

Prolonging the regimen beyond the planned duration of 4 months is not recommended.

***Dosage in Latent Tuberculosis Infection***

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

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

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

**Weight Based Dose of RIFAPENTINE in the Treatment of Latent Tuberculosis Infection**

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

***Administration***

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

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

The tablet has a score line that can be used to divide it into equal doses.

**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. 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 to 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

**SUMMARY OF PRODUCT CHARACTERISTIC**

RIFAPENTINE

***Severe Cutaneous Adverse Reactions***

Severe cutaneous adverse reactions (SCARs) such as Stevens-Johnson syndrome (SJS) and drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome have been reported in association with the use of Rifapentine treatment regimens in patients with active and latent tuberculosis. Discontinue Rifapentine at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity

***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 rifampinresistant organisms

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

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

***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

***Clostridioides Difficile–Associated Diarrhea***

Clostridioides 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

**4.5 Interaction with other medicinal products and other forms of interaction**

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

***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

***Fixed-Dose Combination of Efavirenz, Emtricitabine, and Tenofovir***

Once-weekly coadministration of 900 mg Rifapentine with the antiretroviral fixed-dose combination of efavirenz 600 mg, emtricitabine 200 mg and tenofovir disoproxil fumarate 300 mg in HIV-infected patients did not result in any substantial change in steady state exposures of efavirenz, emtricitabine, and tenofovir. No clinically significant change in CD4 cell counts or viral loads were noted

***Hormonal Contraceptives***

Rifapentine may reduce the effectiveness of hormonal contraceptives. Patients using hormonal contraception should be advised to use an alternative non-hormonal contraceptive method or add a barrier method of contraception during treatment with Rifapentine.

***Cytochrome P450 3A4 and 2C8/9***

Rifapentine is an inducer of cytochromes P450 3A4 and P450 2C8/9. Therefore, Rifapentine may increase the metabolism of other coadministered 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 4 or of other drugs metabolized by cytochrome P450 3A4 or P450 2C8/9 may be necessary if they are given concurrently with Rifapentine.

**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 | Propranolol |
| 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 |
| Phosphodiesterase-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

***Interactions with Laboratory Tests***

Therapeutic concentrations of rifampin have been shown to inhibit standard microbiological assays for serum folate and Vitamin B12. Similar drug-laboratory interactions should be considered for RIFAPENTINE; thus, alternative assay methods should be considered

## 4.6 Pregnancy and lactation

***Pregnancy***

*Risk Summary*

Based on animal data, RIFAPENTINE may cause fetal harm when administered to a pregnant woman. Available data from clinical trials, case reports, epidemiology studies and postmarketing experience with RIFAPENTINE use in pregnant women are insufficient to establish a drug-associated risk of major birth defects, adverse maternal or fetal outcomes. In two clinical trials, a total of 59 patients who were treated with rifapentine in combination with other anti-tuberculosis drugs became pregnant. Overall, the reported rate of miscarriage following rifapentine exposure in these two clinical trials did not represent an increase over the background rate of miscarriage reported in the general population. There are risks associated with active tuberculosis during pregnancy. When administered during the last few weeks of pregnancy, RIFAPENTINE may be associated with maternal postpartum hemorrhage and bleeding in the exposed neonates

In animal reproduction and developmental toxicity studies, adverse developmental outcomes (including cleft palate or mal-positioned aortic arches) were observed following administration of rifapentine to pregnant rats and rabbits at doses approximately 0.6 and 0.3 to 1.3 times respectively of the recommended human dose based on body surface area comparisons. Based on animal data, advise pregnant women of the risk for fetal harm. As rifapentine is always used in combination with other antituberculosis drugs such as isoniazid, ethambutol, and pyrazinamide, refer to the prescribing information of the other drug(s) for more information on their associated risks of use during pregnancy.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

*Clinical Considerations*

Disease-associated maternal and/or embryo-fetal risk

Active tuberculosis in pregnancy is associated with adverse maternal and neonatal outcomes including maternal anemia, cesarean delivery, preterm birth, low birth weight, birth asphyxia and perinatal infant death.

Labor or delivery

When administered during the last few weeks of pregnancy, Rifapentine 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.

***Lactation***

*Risk Summary*

There are no data on the presence of rifapentine or its metabolite in human or animal milk, the effects on the breastfed infant, or the effects on milk production. Since RIFAPENTINE may produce a red-orange discoloration of body fluids, there is a potential for discoloration of breast milk. Monitor infants exposed to rifapentine through breast milk for signs of hepatotoxicity. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for RIFAPENTINE and any potential adverse effects on the breastfed infant from RIFAPENTINE or from the underlying maternal condition.

*Clinical Considerations*

Monitor infants exposed to rifapentine through breast milk for signs of hepatotoxicity to include irritability, prolonged unexplained crying, yellowing of the eyes, loss of appetite, vomiting, and changes in color of the urine (darkening) or stool (lightening, pale or light brown).

***Females and Males of Reproductive Potential***

Use of RIFAPENTINE may reduce the efficacy of hormonal contraceptives. Advise patients using hormonal contraceptives to use an alternative non-hormonal contraceptive method or add a barrier method of contraception during treatment with RIFAPENTINE.

***Pediatric Use***

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 to 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 .

In a pharmacokinetic study conducted in 2 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 to 11 years old with latent tuberculosis infection were higher (average 31%) than those observed in adults receiving RIFAPENTINE 900 mg once weekly.

***Geriatric Use***

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 25desacetyl metabolite were observed in the elderly compared to younger adults.

## 4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. However, patients should be informed that dizziness has been reported during treatment with Rifapentine.

## 4.8 Undesirable effects

- Hepatotoxicity
- Hypersensitivity
- Severe Cutaneous Adverse Reactions
- Discoloration of Body Fluids
- Clostridioides Difficile–Associated Diarrhea
- Porphyria

***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*

RIFAPENTINE was studied in a randomized, open label, active-controlled trial of HIV-negative patients with active pulmonary tuberculosis. The population 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 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

Below Table 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.

| **System Organ Class** Adverse Reaction | **Initial Phase1** | | **Continuation Phase2** | |
|---|---|---|---|---|
| | **RIFAPENTINE Combination (N=361) N (%)** | **Rifampin Combination (N=361) N (%)** | **RIFAPENTINE Combination (N=317) N (%)** | **RIFAPENTINE Combination (N=317) 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 (3.0) |
| 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) |
| **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 and 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) |
| **Investigations** | | | | |
| Blood urea increased | 4 (1.1) | 3 (0.8) | 10 (3.2) | 15 (4.9) |
| **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) |

1 Initial phase consisted of therapy with either RIFAPENTINE twice weekly or rifampin daily combined with daily isoniazid, pyrazinamide, and ethambutol for 60 days.
2 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 RIFAPENTINE 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:** 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

*Latent Tuberculosis Infection*

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 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 to 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 to 17 years of age and 95 HIV-infected individuals.

Below Table 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%.

| **System Organ Class**<br>Adverse Reaction | **3RPT/INH**<br>**(N=4040)**<br>**N (%)** | **9INH**<br>**(N=3759)**<br>**N (%)** |
|---|---|---|
| **Immune system disorders** | | |
| Hypersensitivity | 161 (4) | 18 (0.5) |
| **Hepatobiliary disorders** | | |
| 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) |

Selected treatment-emergent adverse reactions reported during treatment and 60 days post treatment in less than 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 Tissue Disorders:** rash, hyperhidrosis, pruritus, urticaria.

*Postmarketing Experience*

The following adverse reactions have been identified from postmarketing surveillance of rifapentine

**Skin and subcutaneous tissue disorders:** Severe cutaneous adverse reactions (SCARs) such as Stevens-Johnson syndrome (SJS) and drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome

## 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

Rifapentine, a cyclopentyl rifamycin, is an antimycobacterial agent

Mechanism of action

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.

## 5.2 Pharmacokinetic properties

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 Cmax 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 Cmax and AUC, respectively. In contrast, the ingestion of the same meal decreased isoniazid Cmax 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 14C-rifapentine was recovered in the urine (17%) and feces (70%). Greater than 80% of the total 14C-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-∞) and Cmax 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∞) values, rifapentine and 25-desacetyl rifapentine potentially contributes 62% and 38% to the clinical activities against M. tuberculosis, respectively.

### 5.3 Preclinical safety data

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 two 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/hypoxanthine-guanine phosphoribosyltransferase (CHO/HGPRT) forward mutation assay; in vitro chromosomal aberration assay utilizing rat lymphocytes; and in vivo mouse bone marrow micronucleus assay.

The 25-desacetyl metabolite of rifapentine was positive in the in vitro mammalian chromosome aberration test in V79 Chinese hamster cells but was negative in the in vitro gene mutation assay in bacteria (Ames test), the in vitro Chinese hamster ovary cell/hypoxanthine-guanine phosphoribosyltransferase (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

Core tablet: Microcrystalline Cellulose, Pregelatinized Starch, Low substituted Hydroxy propyl cellulose, Sodium Starch Glycolate, Sodium Lauryl Sulfate, Hydroxypropyl Cellulose, Disodium Edetate, Sodium Ascorbate, Colloidal Silicon Dioxide, Calcium Stearate.

Film Coat: Opadry® II 85F565338 Brown (Polyvinyl Alcohol, Polyethylene Glycol/Macrogol, Titanium Dioxide, Talc, Iron Oxide Red)

### 6.2 Incompatibilities

None

### 6.3 Shelf life

24 months from the manufacturing date.

Never use after the expiry date clearly indicated on the outer packaging.

### 6.4 Special precautions for storage

Do not store above 30°C. Protect from excessive heat and humidity. Avoid excursions above 30°C.

**SUMMARY OF PRODUCT CHARACTERISTIC**

**6.5 Nature and contents of container**

Strip pack of 10 Tablets such 3 Strips in a carton along with pack insert (3x10 tablets).

**6.6 Special Precaution for disposal**

None

**7. Supplier**

**Macleods Pharmaceuticals Ltd.**
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Andheri (East), Mumbai- 400 059, India
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sjadhav@macleodspharma.com
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**8. Who Reference Number (Prequalification Programme)**

**9. Date of first Prequalification/ last renewal**

**10. Date of Revision of the Text:**

**References:**

- https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/021024s017s018lbl.pdf
- WHO operational handbook on tuberculosis Module 4: Treatment – drug-susceptible tuberculosis treatment , May 2022, available at https://www.who.int/publications/i/item/9789240050761