

## WHO-PQ RECOMMENDED SUMMARY OF PRODUCT CHARACTERISTICS

*This summary of product characteristics focuses on uses of the medicine covered by WHO's Prequalification Team - Medicines. The recommendations for use are based on WHO guidelines and on information from stringent regulatory authorities.\**

*The medicine may be authorised for additional or different uses by national medicines regulatory authorities.*

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\*[https://extranet.who.int/prequal/sites/default/files/document\\_files/75%20SRA%20clarification\\_Feb2017\\_newtempl.pdf](https://extranet.who.int/prequal/sites/default/files/document_files/75%20SRA%20clarification_Feb2017_newtempl.pdf)

## 1. NAME OF THE MEDICINAL PRODUCT

[TB398 trade name]<sup>†</sup>

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 300 mg rifapentine.

For a full list of excipients see section 6.1.

## 3. PHARMACEUTICAL FORM

Reddish-brown, round, film-coated tablets. They are biconvex (rounded on top and bottom) with a bevelled edge. The tablets have a break line on one side with “J” debossed (stamped into the tablet) above the break line and “37” debossed below; they are plain on the other side.

The tablet can be divided into equal halves.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

[TB398 trade name] is indicated in combination with other tuberculosis medicines for the initial treatment of tuberculosis due to *Mycobacterium tuberculosis*.

It is also indicated together with other medicines for the prevention of tuberculosis in persons at risk.

Treatment and prophylaxis regimens should follow the most recent WHO guidelines, supplemented by other authoritative guidelines.

### 4.2 Posology and method of administration

Use of [TB398 trade name] should be initiated and monitored by a health care provider experienced in the management and prevention of *Mycobacterium tuberculosis* infection.

Patients should be advised to take [TB398 trade name] exactly as prescribed and to complete the full course.

#### **Posology**

##### **Treatment**

For the treatment of drug-susceptible tuberculosis, [TB398 trade name] should be given to patients aged 12 years and older once daily for a period of 4 months, as part of a regimen with isoniazid, moxifloxacin and pyrazinamide.

The daily dose of [TB398 trade name] is 1,200 mg (4 tablets) once daily.

##### **Prophylaxis**

Patients aged 2 -14 years may be given [TB398 trade name] with isoniazid **once weekly** for a period of 3 months, i.e., 12 doses, as follows:

Body weight	Number of tablets	Dose of rifapentine
10 to less than 16 kg	1	300 mg
16 to less than 24 kg	1½	450 mg
24 to less than 31 kg	2	600 mg
31 kg and over	2½	750 mg

<sup>†</sup> Trade names are not prequalified by WHO. This is the national medicines regulatory agency's responsibility.

A dispersible formulation may be preferred where available and suitable.

*Patients aged over 14 years* and weighing at least 30 kg may be given 3 tablets of [TB398 trade name] (rifapentine 900 mg) weekly with isoniazid for 3 months.

*In patients aged 13 years and older*, [TB398 trade name] may also be used as part of a **daily** prophylactic regimen with isoniazid, given for one month. The recommended dose is rifapentine 600 mg (2 tablets) daily.

### **Special populations**

#### *People living with HIV*

The 4-month treatment regimen with rifapentine, isoniazid, moxifloxacin and pyrazinamide has been shown to be effective in patients with drug-sensitive TB who are also HIV-positive. However, the evidence on the use of this 4-month regimen in people with HIV was limited to those with a CD4 count of above 100 cells/mm<sup>3</sup>. An alternative regimen is recommended in patients with CD4 counts below this value.

#### *Elderly*

Caution should be exercised in such patients especially if there is evidence of hepatic impairment.

#### *Hepatic impairment*

Use should be carefully monitored in patients with chronic liver disease.

#### *Renal impairment*

There are no pharmacokinetic data for rifapentine in patients with renal impairment.

### **Missed doses and vomiting after a dose**

It is important that the patient takes the medicine regularly as prescribed.

If the patient forgets to take a **daily** dose and there are more than 6 hours till their next dose, they should take the missed dose as soon as possible. Then they should continue their treatment as before. If there are less than 6 hours till their next dose, the missed dose should be skipped. A double dose should not be taken to make up for a missed dose.

If a **weekly** dose is missed but it is remembered within the next 2 days, the patient can take the dose immediately and continue the schedule as originally planned. If the missed dose is remembered more than 2 days later, the person can take the missed dose immediately and change the schedule for weekly intake to the day the missed dose was taken until treatment completion.

If 4 or more weekly doses are missed, consideration should be given to restarting the full preventive treatment.

If a patient vomits within 1 hour of taking [TB398 trade name], the dose should be repeated.

### **Method of administration**

[TB398 trade name] should be taken orally with a meal.

For young children or patients not able to swallow the tablets whole, the tablets may be crushed and added to a small amount of semi-solid food or liquid, all of which should be consumed immediately.

### **4.3 Contraindications**

- Hypersensitivity to any rifamycin or to any of the excipients listed in section 6.1.
- Acute liver disease, icterus or severe liver impairment.
- History of liver damage or other severe side effects such as drug fever or chills that is linked to rifapentine.

- Co-administration of [TB398 trade name] with HIV protease inhibitors, elvitegravir/cobicistat, nevirapine, rilpivirine, etravirine, doravirine, bictegravir/emtricitabine/tenofovir alafenamide, artemisinin & its derivatives, or direct-acting antivirals for chronic Hepatitis C (see section 4.4).

#### **4.4 Special warnings and precautions for use**

##### *Hypersensitivity*

Rifamycins such as rifapentine may cause a hypersensitivity syndrome including ‘flu-like’ symptoms and/or organ manifestation. The risk is higher in intermittent therapy or if treatment is resumed after discontinuation. If severe, acute signs of rifapentine hypersensitivity do appear (e.g., thrombocytopenia, purpura, haemolytic anaemia, dyspnoea, shock or acute renal failure), then [TB398 trade name] should immediately be discontinued. Such patients should not be rechallenged with 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 some patients taking rifapentine. [TB398 trade name] should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

##### *Hepatotoxicity*

[TB398 trade name] may cause hepatotoxicity (see section 4.8). Therefore, patients should be carefully monitored at monthly intervals. In addition to monthly symptom reviews, hepatic enzymes (specifically AST and ALT) should be measured prior to starting therapy with [TB398 trade name] and periodically throughout treatment.

[TB398 trade name] can also cause cholestasis and elevated transaminases. These effects on liver function tests are usually mild to moderate, and will most commonly normalise spontaneously within 3 months, even with continued therapy.

If abnormalities of liver function exceed 3 to 5 times the upper limit of normal, discontinuation of [TB398 trade name] should be strongly considered.

Particular care may be needed in patients with pre-existing liver disease. The contribution of other potentially hepatotoxic medicines used with [TB398 trade name] in combination TB regimens should be taken into consideration.

Patients should be instructed to immediately report signs or symptoms consistent with liver damage or other adverse effects. If these appear, [TB398 trade name] should be discontinued promptly, since continued use in these cases may cause a more severe form of liver damage.

##### *Hyperbilirubinaemia*

A rifapentine-induced, moderate rise in bilirubin is not in itself an indication for interrupting treatment; rather, the decision should be made after repeating the tests, noting trends in the levels and considering them in conjunction with the patient’s clinical condition.

##### *Drug interactions*

Rifapentine is an inducer of CYP450 enzymes. Concomitant use of [TB398 trade name] with other drugs metabolized by these enzymes, such as protease inhibitors and reverse transcriptase inhibitors, may cause a significant decrease in plasma concentrations and loss of their therapeutic effect (see Section 4.5).

For the effect of rifapentine on oral contraceptives and corticosteroids, see also under the headings ‘Contraception’ and ‘Addison’s disease’ below.

##### *Haematological toxicity*

Rifapentine may be associated with haemolytic anaemia, leucopenia and thrombocytopenia; full blood count should be monitored regularly throughout therapy with [TB398 trade name]. In case of severe haematological disturbances, [TB398 trade name] must be discontinued.

### *Clostridioides difficile-associated colitis*

*C. difficile* infection may develop after rifapentine administration. Patients should be evaluated for *C. difficile*-associated colitis if they have moderate to severe diarrhoea, fever, bloody stools and abdominal pain that last more than 2 days.

### *Contraception*

Oral contraceptives do not provide adequate protection against conception when co-administered with [TB398 trade name]. This probably also pertains to other forms of hormonal contraceptives (e.g. patches, transdermal implants). Barrier or other non-hormonal methods of contraception should be used.

### *Addison's disease*

[TB398 trade name] may reduce the efficacy of corticosteroids in Addison's disease and induce an Addisonian crisis (see section 4.5).

### *Porphyria*

[TB398 trade name] should be used with caution in patients with porphyria, since the enzyme induction by rifapentine may cause symptoms.

### *Discolouration of body fluids*

[TB398 trade name] may cause a reddish-orange discolouration of body fluids and/or fluids, e.g., skin, teeth, tongue, urine, feces, saliva, sputum, tears, sweat, and cerebrospinal fluid. This is due to rifapentine, and does not require medical attention. In addition, contact lenses or dentures may be permanently stained red-orange.

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

Like other rifamycins, rifapentine is a potent inducer of the hepatic and intestinal cytochrome P-450 enzyme system, as well as of glucuronidation and the P-glycoprotein transport system. In vitro and in vivo enzyme induction studies have suggested rifapentine induction potential may be less than rifampicin but more potent than rifabutin.

Administration of rifapentine with drugs that undergo biotransformation through these metabolic pathways is likely to accelerate elimination of co-administered drugs. To maintain optimum therapeutic blood levels, dosages of drugs metabolised by these enzymes may require adjustment when starting or stopping administration of [TB398 trade name]. This must be taken into account when giving [TB398 trade name] with other medicines.

The effects of rifapentine on biotransformation approach their maximum after about 10 days of treatment, and gradually return to normal within 2 or more weeks after discontinuation. The magnitude of enzyme induction by rifapentine is dependent on dose and dosing frequency; less enzyme induction occurred with rifapentine doses of 600 mg every 72 hours versus the same dose daily.

The following list of drug interactions with [TB398 trade name], based largely on what is known of the properties of rifapentine and experience with other rifamycins such as rifampicin, is not exhaustive, but is a selection of interactions of putative importance. The scope of the table is largely based on the WHO Essential Medicines List.

Drugs by Therapeutic Area	Interaction	Recommendations concerning co-administration
<b>ANTI-INFECTIVES</b>		
<i>Antiretrovirals</i>		
<i>Nucleoside/nucleotide reverse transcriptase inhibitors</i> <b>Didanosine</b> <b>Lamivudine</b> <b>Emtricitabine</b> <b>Stavudine</b>	No interaction expected.	No dose adjustment required.

Drugs by Therapeutic Area	Interaction	Recommendations concerning co-administration
<b>Zidovudine</b>		
<b>Abacavir</b>	Empirical data are lacking, but rifapentine may decrease abacavir exposure through induction of glucuronidation.	Efficacy of abacavir should be closely monitored in co-treatment.
<b>Tenofovir alafenamide</b>	Co-administration with rifapentine, a P-gp inducer, may decrease tenofovir alafenamide plasma concentrations, which may result in loss of therapeutic effect and development of resistance.	Additional monitoring, alteration of tenofovir drug dosage or timing of administration may be required.
<b>Bictegravir/ emtricitabine/ tenofovir alafenamide</b>	Interaction not studied. Co-administration of rifapentine, a P-gp inducer, may decrease bictegravir and tenofovir alafenamide plasma concentrations, which may result in loss of therapeutic effect and development of resistance.	Co-administration with [TB398 trade name] is contraindicated.
<i>Non-nucleoside reverse transcriptase inhibitors</i> <b>Doravirine</b>	Significant decrease in doravirine concentration.	Co-treatment of [TB398 trade name] and doravirine is contraindicated.
<b>Efavirenz</b>	Potential interaction likely to be of weak intensity.	Additional action/monitoring or dosage adjustment is unlikely to be required.
<b>Etravirine</b>	Rifapentine significantly reduces exposure to etravirine.	Co-treatment of [TB398 trade name] and etravirine is contraindicated.
<b>Nevirapine</b>	Rifapentine will decrease the level or effect of nevirapine by altering drug metabolism	Co-administration of [TB398 trade name] with nevirapine is contraindicated..
<b>Rilpivirine</b>	Significant decrease in rilpivirine concentration	Co-treatment of [TB398 trade name] and rilpivirine is contraindicated.
<i>Protease inhibitors</i> <b>Atazanavir</b> <b>Darunavir</b> <b>Fosamprenavir</b> <b>Lopinavir</b> <b>Ritonavir</b> <b>Tipranavir</b>	Protease inhibitor exposure will be reduced to subtherapeutic level due to interaction with rifapentine. Attempts to dose adjust by increased doses, or an increase in ritonavir-boosting, have been ineffective or ill-tolerated with a high rate of hepatotoxicity.	Co-administration with [TB398 trade name] is contraindicated.
<i>Integrase inhibitors</i> <b>Dolutegravir</b>	Dolutegravir AUC ↓	A dose adjustment of dolutegravir to 50 mg twice daily is recommended when co-administered with [TB398 trade name] in the absence of integrase class resistance. In the presence of integrase class resistance this combination should be avoided.
<b>Elvitegravir/cobicistat</b>	Co-administration has not been studied. Rifapentine is a potent inducer of CYP450 metabolism and may cause significant decrease	Co-administration is contraindicated.

Drugs by Therapeutic Area	Interaction	Recommendations concerning co-administration
	in the plasma concentration of elvitegravir and cobicistat resulting in loss of therapeutic effect.	
<b>Raltegravir</b>	Raltegravir AUC ↑	Once weekly rifapentine can be used with raltegravir without dose adjustment. However, a dosing strategy of daily rifapentine (for treatment of active TB) is still under clinical investigation.
<i>CCR5 inhibitors</i> <b>Maraviroc</b>	Maraviroc AUC ↓	Co-treatment should be avoided. If deemed necessary, the maraviroc dose should be increased to 600 mg b.i.d.
<i>Antivirals Hepatitis C-infection</i>		
<b>Daclatasvir</b> <b>Elbasvir/Grazoprevir</b> <b>Glecaprevir/Pibrentasvir</b> <b>Ledipasvir/Sofosbuvir</b> <b>Ombitasvir/paritaprevir/ritonavir (with or without dasabuvir)</b> <b>Sofosbuvir (with or without velpatasvir with or without voxilaprevir)/</b>	Co-administration has not been studied but is expected to decrease concentrations of these HCV-antivirals due to induction of CYP3A4 by rifapentine and hence to reduce their therapeutic effect. Rifapentine will decrease the level or effect of sofosbuvir, ledipasvir/sofosbuvir by affecting how the drug is eliminated via what is known as the P-glycoprotein [MDR1 transporter)	Co-administration of [TB398 trade name] with these antivirals is contraindicated.
<i>Antifungals</i>		
<b>Fluconazole</b>	Fluconazole AUC ↓	Monitor therapeutic effect. An increased dose of fluconazole may be required.
<b>Itraconazole</b>	Itraconazole AUC ↓	Co-administration should be avoided.
<b>Ketoconazole</b>	Ketoconazole AUC ↓	Co-administration should be avoided. If deemed necessary, a dose increase of ketoconazole may be required.
<b>Voriconazole</b>	Based on interaction data from rifabutin and rifampicin, it is expected for expected for voriconazole plasma concentrations to significantly decrease.	Concomitant use of [TB398 trade name] and voriconazole should be avoided.
<i>Antibacterials/TB medicines</i>		
<b>Bedaquiline</b>	Co-administration with rifamycins, including rifapentine, significantly reduces concentrations of bedaquiline (<50%).	Co-administer with caution and dose adjustment of bedaquiline.
<b>Chloramphenicol</b>	Reduction of chloramphenicol exposure.	Co-administration should be avoided.
<b>Clarithromycin</b>	Clarithromycin mean serum concentration ↓. 14-OH clarithromycin levels unchanged.	Co-administration should be avoided.
<b>Dapsone</b>	Co-administration has not been studied, but based on experience with rifampicin,	Dosage of dapsone may require adjustment when starting or stopping

Drugs by Therapeutic Area	Interaction	Recommendations concerning co-administration
	exposure to dapsone may be reduced.	concomitantly administered [TB398 trade name].
<b>Doxycycline</b>	Doxycycline AUC ↓	If co-treatment is considered necessary, the dose of doxycycline should be doubled.
<b>Ethionamide</b>	Empirical data are not available.	Rifapentine and ethionamide should not be co-administered, due to a possible increased risk of hepatotoxicity.
<b>Fluoroquinolones</b>	Empirical data are not available.	Dosage of fluoroquinolone may require adjustment when starting or stopping concomitantly administered [TB398 trade name].
<b>Metronidazole</b>	Metronidazole AUC i.v. ↓	The clinical relevance of the interaction is unknown. No dose adjustment is routinely recommended. Efficacy should be monitored.
<b><i>p</i>-aminosalicylic acid</b>	Co-administration has not been studied, but based on experience with rifampicin, <i>p</i> -aminosalicylic acid granules may reduce absorption of rifapentine if given concomitantly.	If <i>p</i> -aminosalicylic acid and rifapentine are both included in the treatment regimen, they should be given not less than 8 hours apart to ensure satisfactory blood levels.
<b>Sulfamethoxazole</b>	Sulfamethoxazole AUC may decrease	Interaction probably not clinically significant. Efficacy of sulfamethoxazole should be monitored.
<b>Trimethoprim</b>	Trimethoprim AUC may decrease	A dose increase of trimethoprim may be required. Efficacy should be monitored.
<i>Antimalarials</i>		
<b>Amodiaquine</b>	Empirical data are not available. Since amodiaquine undergoes hepatic metabolism, it is likely that clearance is increased when co-treating with rifapentine.	Co-administration should be avoided.
<b>Artemisinin and its derivatives</b>	Artemether AUC ↓ Dihydroartemisinin AUC ↓	Co-administration is contraindicated.
<b>Atovaquone</b>	Empirical data are not available but based on experience with rifampicin and atovaquone, it is likely that: Atovaquone AUC ↓ Rifapentine AUC ↑	Co-administration should be avoided.
<b>Chloroquine</b>	Empirical data are not available. Since chloroquine undergoes polymorphic hepatic metabolism, lower levels are likely during rifapentine co-therapy.	Co-administration should be avoided.
<b>Lumefantrine</b>	Empirical data are not available but based on data on rifampicin and lumefantrine, it is likely that:	Co-administration should be avoided.



Drugs by Therapeutic Area	Interaction	Recommendations concerning co-administration
	Lumefantrine AUC ↓	
<b>Mefloquine</b>	Rifapentine may modify the metabolism of mefloquine, leading to an increase or decrease in mefloquine plasma concentration.	The clinical consequences of these effects are unknown and a close clinical surveillance is warranted. Co-administration should be avoided.
<b>Quinine</b>	Quinine AUC ↓. This has been associated with significantly higher recrudescence rates.	Co-administration should be avoided. If co-administration is deemed necessary, an increased dose of quinine should be considered.
<i>Anthelmintics</i>		
<b>Praziquantel</b>	Therapeutically effective plasma levels of praziquantel may not be achieved when co-administered with rifapentine.	Co-administration should be avoided.
<b>ANALGESICS, ANTIPYRETICS, NON-STEROIDAL ANTI-INFLAMMATORY DRUGS</b>		
<b>Codeine</b>	Plasma levels of morphine, the active moiety of codeine, are likely to be substantially reduced.	Efficacy should be monitored and codeine dose increased if necessary.
<b>Methadone</b>	Methadone AUC expected to decrease when co-administered with rifapentine.	Patients should be monitored for possible withdrawal effects, and methadone dose increased as appropriate (up to 2-3 fold).
<b>Morphine</b>	Morphine AUC decreased with reduced analgesic effect.	Co-treatment should be avoided. If deemed necessary, efficacy should be monitored and the dose may need to be increased.
<b>Paracetamol</b>	Rifapentine may increase the glucuronidation of paracetamol and decrease the efficacy. There may be an increased risk of hepatotoxicity on co-administration, but data are inconclusive.	Co-administration of [TB398 trade name] and acetaminophen (paracetamol) should be avoided.
<b>ANTICONVULSANTS</b>		
<b>Carbamazepine</b>	Rifapentine is expected to decrease the serum concentration of carbamazepine. The risk of hepatotoxicity increases when co-treating with carbamazepine.	Co-administration of [TB398 trade name] and carbamazepine should be avoided.
<b>Lamotrigine</b>	Empirical data are not available but based on data on rifampicin and lamotrigine co-administration, it is likely that: Lamotrigine AUC ↓	Co-treatment should be avoided. If deemed necessary, lamotrigine dose should be increased as appropriate.
<b>Phenobarbital</b>	Phenobarbital and rifapentine are both strong hepatic enzyme inducers, and each drug may lower the plasma concentrations of the other.	Co-administration of [TB398 trade name] and phenobarbital should be undertaken with caution, including monitoring of clinical effects and, if possible, plasma drug concentrations.
<b>Phenytoin</b>	Phenytoin AUC ↓	Co-treatment with phenytoin and [TB398 trade name] should be avoided.

Drugs by Therapeutic Area	Interaction	Recommendations concerning co-administration
<b>Valproic acid</b>	Interaction studies are lacking. Since valproic acid is eliminated through hepatic metabolism, including glucuronidation, reduced plasma levels of valproic acid are likely with concomitant use.	Co-treatment should be avoided. If deemed necessary, efficacy and, if possible, plasma concentrations of valproic acid should be carefully monitored.
<b>IMMUNOSUPPRESSIVES</b>		
<b>Cyclosporine</b>	Substantially increased cyclosporine clearance when co-administered with rifapentine.	Co-administration should be avoided. If deemed necessary, plasma concentrations of cyclosporine should be monitored and doses adapted accordingly (3-5 fold increases in cyclosporine dose have been required).
<b>Everolimus</b> <b>Sirolimus</b> <b>Tacrolimus</b>	Everolimus AUC ↓ Sirolimus AUC ↓ Tacrolimus AUC i.v. ↓ AUC p.o ↓	Co-administration of [TB398 trade name] and mTOR inhibitors should be avoided. If deemed necessary, plasma drug concentrations should be monitored, and the dose increased as appropriate.
<b>CARDIOVASCULAR MEDICINES</b>		
<i>Antiarrhythmics</i> <b>Diltiazem</b> <b>Disopyramide</b> <b>Mexiletine</b> <b>Propafenone</b> <b>Quinidine</b> <b>Tocainide</b>	Interaction studies are mostly lacking but based on rifampicin, an effect on antiarrhythmic exposure might be expected.	Dosage of these drugs may require adjustment when starting or stopping concomitantly administered [TB398 trade name].
<b>Warfarin</b>	Warfarin AUC ↓	Monitor closely and adjust warfarin dose as needed and reduce dose after withdrawing rifapentine treatment.
<i>Other cardiovascular medicines</i> <b>Atenolol</b> <b>Propranolol</b>	Atenolol AUC ↓	Dose adjustment may be required.
<b>Amlodipine</b> <b>Nifedipine</b>	Amlodipine and nifedipine like other calcium channel blockers, are metabolised by CYP3A; lower exposure is expected when co-treating with rifapentine.	Efficacy should be monitored.
<b>Clofibrate</b>	Rifapentine may increase the metabolism of clofibrate, thus decreasing its activity.	Dosage of clofibrate may require adjustment when starting or stopping concomitantly administered [TB398 trade name].
<b>Clopidogrel</b>	Rifapentine may increase active clopidogrel metabolite exposure due to CYP2C19 induction. Increased level of clopidogrel active metabolite and platelet inhibition may potentiate the risk of bleeding.	Concomitant use of clopidogrel and rifapentine is discouraged.
<b>Digoxin</b> <b>Digitoxin</b>	AUC p.o.↓	When co-administering [TB398 trade name] with digoxin, the efficacy and plasma concentration of digoxin

Drugs by Therapeutic Area	Interaction	Recommendations concerning co-administration
		should be monitored. A dose increase may be required.
<b>Enalapril</b>	No interaction expected. Empirical data are not available but based on data on rifampicin and enalapril, it is likely that enalapril active metabolite AUC ↓	Dosage of enalapril may require adjustment.
<b>Eplerenone</b>	Empirical data are not available but based on data on rifampicin and eplerenone, it is likely that: eplerenone AUC ↓	Dosage of eplerenone may require adjustment when starting or stopping concomitantly administered [TB398 trade name].
<b>Lidocaine</b>	Lidocaine CL i.v. ↑	Dose adjustment may be required.
<i>Statins</i> <b>Atorvastatin</b> <b>Simvastatin</b>	Atorvastatin AUC ↓ Simvastatin AUC ↓ Simvastatin acid AUC ↓	Co-administration is not recommended.
<b>Verapamil</b>	S-verapamil p.o CL/F ↑. With i.v. S-verapamil, CL ↑	[TB398 trade name] and verapamil per-orally should not be co-administered. If i.v. verapamil is given, the therapeutic effect should be carefully monitored; dose adjustment may be required.
<b>GASTROINTESTINAL MEDICINES</b>		
<b>Antacids</b>	Antacids may reduce the bioavailability of rifapentine.	The clinical importance is unknown.
<b>Ranitidine</b>	Ranitidine AUC ↓	Efficacy should be monitored, and ranitidine dose increased if necessary.
<b>PSYCHOTHERAPEUTIC MEDICINES</b>		
<i>Benzodiazepines</i> <b>Alprazolam</b> <b>Diazepam</b> <b>Midazolam</b> <b>Nitrazepam</b> <b>Triazolam</b>	Diazepam AUC ↓ Midazolam AUC ↓ Triazolam AUC ↓ Alprazolam AUC ↓ Reduced nitrazepam through concentrations, increased clearance.	Co-treatment is not recommended. Benzodiazepine withdrawal may occur in dependent individuals.
<i>Non-benzodiazepine sedative-hypnotics</i> <b>Zolpidem</b> <b>Zopiclone</b>	Zolpidem AUC ↓ Zopiclone AUC ↓	Co-administration should be avoided.
<i>Antipsychotics</i> <b>Chlorpromazine</b>	Rifapentine may reduce chlorpromazine exposure.	Co-administration should be avoided.
<b>Aripiprazole</b> <b>Clozapine</b> <b>Haloperidol</b>	Haloperidol clearance is substantially increased by rifapentine, theoretical considerations imply that same applies to aripiprazole and clozapine.	If co-treatment of [TB398 trade name] with aripiprazole, haloperidol or clozapine is deemed necessary, monitor clinical efficacy. A dose increase may be required.
<i>Tricyclic antidepressants</i> <b>Amitriptyline</b> <b>Nortriptyline</b>	Case reports (supported by theoretical considerations) suggest that rifapentine considerably increases clearance of tricyclic antidepressants.	Co-treatment should be avoided. If necessary, monitor for clinical response, side effects, and, if possible, plasma concentrations.

Drugs by Therapeutic Area	Interaction	Recommendations concerning co-administration
<b>HORMONES; OTHER ENDOCRINE MEDICINES AND CONTRACEPTIVES</b>		
<i>Corticosteroids</i> <b>Prednisolone</b> <b>Other systemically administered corticosteroids</b>	Prednisolone AUC ↓  Also, for other corticosteroids, exposure is likely to be substantially decreased when co-treating with rifapentine.	Co-administration of [TB398 trade name] with corticosteroids should be avoided. If deemed necessary, the clinical status of the patient should be carefully monitored, and corticosteroid doses adjusted as needed.
<i>Oral hypoglycemics</i> <i>Sulfonylureas</i> <b>Glibenclamide</b> <b>Gliclazide</b> <b>Glimepiride</b> <b>Glipizide</b> <b>Glyburide, etc</b>  <i>Other oral antidiabetics</i> <b>Repaglinide</b>	Glibenclamide AUC ↓ Glimepiride AUC ↓ Repaglinide AUC ↓	Blood glucose levels should be closely monitored. A dose increase of diabetes medication may be required.
<b>Insulin</b>	No interaction expected.	No dose adjustment required.
<b>Levothyroxine</b>	Case reports indicate that rifapentine may decrease the effect of levothyroxine.	TSH levels should be monitored.
<i>Estrogens</i> <b>Ethinylestradiol</b>	Ethinylestradiol AUC ↓	Co-administration with [TB398 trade name] may be associated with decreased contraceptive efficacy. Barrier or other non-hormonal methods of contraception should be used.
<i>Progestogens</i> <b>Levonorgestrel</b> <b>Norethindrone</b>	The metabolism of progestogens may be increased by concomitant administration of rifapentine.	Co-administration with [TB398 trade name] may be associated with decreased contraceptive efficacy. Barrier or other non-hormonal methods of contraception should be used.
<b>CHEMOTHERAPEUTICS</b>		
<i>Cytotoxics</i> <b>Irinotecan</b> <b>Imatinib</b>		Dosage of these drugs may require adjustment when starting or stopping concomitantly administered [TB398 trade name].
<i>Hormone antagonist: antiestrogens</i> <b>Tamoxifen</b> <b>Toremifene</b> <b>Gestrinone</b>		Dosages of these drugs may require adjustment when starting or stopping concomitantly administered [TB398 trade name].
<b>OTHERS</b>		
<b>Theophylline</b>	Rifapentine may increase the clearance of theophylline.	Theophylline dose adjustment may be needed.
<i>5-HT<sub>3</sub> receptor antagonists</i>		Dosages of these drugs may require adjustment when starting or stopping concomitantly administered [TB398 trade name].
<b>Riluzole</b>	Rifapentine may increase the clearance of riluzole.	Dosages of riluzole may require adjustment when starting or stopping concomitantly administered [TB398 trade name].

Drugs by Therapeutic Area	Interaction	Recommendations concerning co-administration
<i>Phosphodiesterase-5 (PDE-5) Inhibitors</i>	Rifapentine may increase clearance of PDE-5 inhibitors such as sildenafil.	Dosage of PDE-5 inhibitor may require adjustment during concomitant administration with [TB398 trade name].

### ***Interactions with laboratory tests***

Therapeutic levels of rifampicin may inhibit standard microbiological assays for serum folate and Vitamin B12. Similar effects may occur with rifapentine. Transient elevation of BSP and serum bilirubin may also occur. Rifapentine may impair biliary excretion of contrast media used for visualization of the gallbladder, due to competition for biliary excretion. Therefore, these tests should be performed before the morning dose of [TB398 trade name].

## **4.6 Fertility, pregnancy and breastfeeding**

### ***Pregnancy***

In animal reproduction and developmental toxicity studies, rifapentine produced fetal harm and was teratogenic (see section 5.3). When administered during the last few weeks of pregnancy, rifampicin, another rifamycin, may increase the risk for maternal postpartum haemorrhage and bleeding in the exposed infant. Therefore, pregnant women and their infants, who are exposed to rifapentine during the last few weeks of pregnancy, should have appropriate monitoring of clotting parameters. Treatment with vitamin K may be indicated.

[TB398 trade name] should only be used in pregnant women or in women of child-bearing potential if the potential benefit justifies the potential risk to the fetus. Untreated tuberculosis is considered to represent a far greater hazard to a pregnant woman and her fetus than treatment of the disease.

### ***Breast-feeding***

It is not known whether rifapentine is excreted into human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in breast-fed infants, a decision should be made whether to discontinue breast-feeding or discontinue [TB398 trade name], taking into account the importance of [TB398 trade name] to the mother and the benefits of breast-feeding.

Since rifapentine may produce a red-orange discoloration of body fluids, there is a potential for discoloration of breast milk.

### ***Fertility***

There are no data on the effects [TB398 trade name] on human male or female fertility. Fertility and reproductive performance were not affected by oral administration of rifapentine to male and female rats (see section 5.3).

## **4.7 Effects on ability to drive and use machines**

No studies on the effects on the ability to drive and use machines have been performed. Nevertheless, the clinical status of the patient and the adverse reaction profile of [TB398 trade name], should be borne in mind when considering the patient's ability to drive or operate machinery.

## **4.8 Undesirable effects**

Below is a table showing adverse drug reactions that have occurred when rifapentine and isoniazid were used concomitantly. The same adverse effects may be expected with the use of [TB398 trade name].

<b>System Organ Class</b>	<b>Adverse effects with a frequency of <math>\geq 1\%</math></b>	<b>Adverse effects with a frequency of <math>&lt; 1\%</math></b>
<b>Blood and lymphatic system disorders</b>	Anaemia, lymphopenia, neutropenia, leukocytosis, thrombocytosis, thrombocytopenia, lymphadenopathy	lymphocytosis, haematoma, purpura, thrombosis, leukopenia
<b>Cardiovascular and vascular disorders</b>		syncope, tachycardia, palpitation, orthostatic hypotension, pericarditis
<b>Eye disorders</b>	conjunctivitis	
<b>Gastrointestinal disorders</b>	Dyspepsia, nausea, diarrhoea, vomiting, abdominal pain	gastritis, oesophagitis, pancreatitis, salivary gland enlargement, constipation, dry mouth, oesophageal irritation
<b>General disorders</b>	Fever	fatigue, asthenia, chest pain, chills, feeling jittery, facial oedema
<b>Hepatobiliary disorders</b>	Elevated ALT, elevated AST	bilirubinaemia, hepatomegaly, jaundice
<b>Immune system disorders</b>	Hypersensitivity disorders	
<b>Investigations</b>	Blood urea increased	
<b>Infections and infestations</b>		pharyngitis, viral infection, vulvovaginal candidiasis, other fungal infections
<b>Metabolism and nutrition disorders</b>	Decreased appetite	hyperglycaemia, gout, hyperkalaemia, hyperlipidaemia, alkaline phosphatase increased
<b>Musculoskeletal and connective tissue disorders</b>	Arthralgia, back pain	myalgia, myositis, rhabdomyolysis
<b>Nervous system disorders</b>	Headache, dizziness	somnolence, dysphonia, convulsion, paresthesia, neuropathy peripheral, syncope.
<b>Pregnancy and perinatal conditions</b>		abortion
<b>Psychiatric disorders</b>		confusion, depression, anxiety, disorientation, suicidal ideation.
<b>Renal and urinary disorders</b>		azotemia
<b>Reproductive disorders</b>		vaginitis, vaginal haemorrhage, leucorrhoea, vulvovaginal pruritus
<b>Respiratory, thoracic and mediastinal disorders</b>	cough, haemoptysis	dyspnoea, oropharyngeal pain, asthma, bronchial hyperactivity, epistaxis, pneumonitis, pulmonary fibrosis, asthma, bronchospasm, laryngeal oedema, laryngitis.
<b>Skin disorders</b>	Rash, hyperhidrosis, pruritus	urticaria, skin discoloration

The following serious and otherwise important adverse drug reactions are discussed in Section 4.4 ‘Warning and Precautions’. Their frequencies are unknown.

- Severe cutaneous adverse reactions such as Stevens-Johnson syndrome (SJS) and drug reaction with eosinophilia and systemic symptoms (DRESS)
- Discoloration of body fluids
- *Clostridioides difficile*–associated diarrhoea
- Porphyria

#### ***Reporting of suspected adverse reactions***

Health care providers are asked to report adverse reactions that may be linked to a medicine, to the marketing authorisation holder, or, if available, to the national reporting system. Reports of suspected adverse reactions to a medicine are important for the monitoring of the medicine’s benefits and risks.

### **4.9 Overdose**

#### ***Symptoms***

When overdosed, rifapentine may cause heartburn, headache and pruritus. There is no experience with the treatment of acute overdose with rifapentine at doses exceeding 1200 mg per dose.

#### ***Treatment***

There is no specific antidote. Treatment is symptomatic and supportive.

## **5. PHARMACOLOGICAL PROPERTIES**

### **5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: Antimycobacterials, ATC Code: J04AB05.

#### ***Mechanism of action***

In vitro, rifapentine is bactericidal against a wide range of organisms, including *Mycobacterium tuberculosis*. The mode of action is by inhibition of DNA-dependent RNA polymerase, inhibiting transcription. In tuberculosis, rifampicin is bactericidal for both intracellular and extracellular microorganisms. Both rifapentine and the 25-desacetyl metabolite accumulate in human monocyte-derived macrophages with intracellular/extracellular ratios of approximately 24:1 and 7:1, respectively.

Microbial resistance may occur and is a result of alterations in the target enzyme (RNA polymerase). Development of rifapentine resistance in *M. tuberculosis* strains is principally due to one of several single point mutations that occur in the *rpoB* portion of the gene coding for the beta subunit of the DNA-dependent RNA polymerase. The incidence of rifapentine-resistant mutants in an otherwise susceptible population of *M. tuberculosis* strains is approximately one in 10<sup>7</sup> to 10<sup>8</sup> bacilli.

*M. tuberculosis* organisms resistant to other rifamycins are likely to be resistant to rifapentine. A high level of cross-resistance between rifampicin and rifapentine has been demonstrated. Cross-resistance does not appear between rifapentine and non-rifamycin antimycobacterial agents.

### **5.2 Pharmacokinetic properties**

#### ***Absorption of [TB398 trade name]***

The absorption characteristics of [TB398 trade name] have been determined after administration of 300 mg tablets in healthy volunteers in the fed state as follows:

Pharmacokinetic variable	Mean value* $\pm$ standard deviation
Maximum concentration ( $C_{\max}$ )	10.8 $\pm$ 2.4 $\mu\text{g/mL}$
Area under the curve ( $\text{AUC}_{0-\infty}$ ), a measure of the extent of absorption	257 $\pm$ 68 $\mu\text{g}\cdot\text{h/mL}$
Time to attain maximum concentration ( $t_{\max}$ )	5.39 $\pm$ 0.60 h

### Pharmacokinetics of Rifapentine

<b>Absorption</b>	
Absolute bioavailability	NA*
Oral bioavailability	>32%
Food effect	High fat meal: AUC $\uparrow$ 43%, $C_{\max}$ $\uparrow$ 44%
<b>Distribution</b>	
Volume of distribution (mean)	70.2 $\pm$ 9.1 L
Plasma proteinbinding <i>in vitro</i>	Rifapentine 98% 25-desacetyl rifapentine 93%
Tissue distribution	NA*
	hydrolyzed by esterase enzymes and CYP3A4
Active metabolite(s)	25-desacetyl rifapentine
<b>Elimination</b>	
Elimination half life	Rifapentine: 13.2 – 14.1 hours 25-desacetyl rifapentine: 13.3 – 24.3 hours
Mean systemic clearance (Cl/F)	2.0 $\pm$ 0.6 L
% of dose excreted in urine	17%
% of dose excreted in faeces	70%
<b>Pharmacokinetic linearity</b>	Linear up to a 600 mg dose; at higher dose less than dose proportional increase
<b>Drug interactions (<i>in vitro</i>)</b>	Rifapentine is an inducer of CYP3A4, 2C8 and 2C9 and P-gp Rifapentine is an auto-inducer by CYP3A
Transporters	NA*
Metabolizing enzymes	Esterases and CYP3A4

\*Information not available

### Special populations

#### Gender

The estimated apparent oral clearance of rifapentine for males and females was 2.51  $\pm$  0.14 L/h and 1.69  $\pm$  0.41 L/h, respectively. The clinical significance of the difference in the estimated apparent oral clearance is not known.

#### Elderly

Pharmacokinetic profile in patient over 65 years is similar to that of male healthy volunteers.



### *Paediatric*

In a pharmacokinetic study in paediatric patients (age 2 to 12 years), a single oral dose of 150 mg rifapentine was administered to those weighing <30 kg (n=11) and a single oral dose of 300 mg was administered to those weighing >30 kg (n=12). The mean estimates of AUC and C<sub>max</sub> were approximately 30% to 50% lower in these paediatric patients than those observed in healthy adults administered single oral doses of 600 mg and 900 mg.

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 <45 kg (n=2). The pharmacokinetics of rifapentine were similar to those observed in healthy adults.

### *Renal Impaired Patients*

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

### *Hepatic Impaired Patients*

Following oral administration of a single 600 mg dose of rifapentine to patients with mild to severe hepatic impairment (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). Since the elimination of these agents are primarily via the liver, the clinical significance of impaired hepatic function on the disposition of rifapentine and its 25-desacetyl metabolite is not known.

## **5.3 Preclinical safety data**

### *Rifapentine*

Hepatocellular carcinomas were increased in male mice that were treated orally with rifapentine for two years at or above doses of 5 mg/kg/day (equivalent to a human dose of 0.4 mg/kg/day or 1/5 of the recommended human dose, in the intensive phase, based on body surface area conversions). In a two year rat study, there was an increase in nasal cavity adenomas in rats treated orally with rifapentine at 40 mg/kg/day (equivalent to a human dose of 6.5 mg/kg/day or 3 times the recommended human dose in the intensive phase, 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-guaninephosphoribosyl transferase (CHO/HGPRT) forward mutation assay; in vitro chromosomal aberration assay utilizing rat lymphocytes; and in vivo mouse bone marrow micronucleus assay.

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

Animal studies in rats and rabbits revealed embryofetal toxicity in both species. Pregnant rats given rifapentine during organogenesis at doses 0.6 times the human dose (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 to mated female rats late in gestation, at 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 foetal weights, increased numbers of stillborn pups, and slightly increased pup mortality during lactation were also noted. When pregnant rabbits received rifapentine at doses 0.3 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.

Fertility and reproductive performance were not affected by oral administration of rifapentine to male and female rats at doses of up to one-third of the human dose (based on body surface area conversions).

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

<i>Core tablet:</i>	Microcrystalline cellulose
	Pregelatinised starch
	Low-substituted hydroxypropyl cellulose
	Sodium starch glycolate
	Sodium lauryl sulfate
	Hydroxypropyl cellulose
	Disodium edetate
	Sodium ascorbate
	Colloidal silicon dioxide
	Calcium stearate
<i>Film coat:</i>	Polyvinyl alcohol-partially hydrolysed
	Macrogol/ polyethylene glycol
	Titanium dioxide
	Talc
	Iron oxide red

This medicine is essentially 'sodium-free'. It contains less than 1 mmol sodium (23 mg) per *tablet*.

### **6.2 Incompatibilities**

Not applicable.

### **6.3 Shelf life**

36 months

### **6.4 Special precautions for storage**

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

### **6.5 Nature and contents of container**

*Alu/Alu strip*

Each strip contains 10 tablets. Such 10 strips are packed in a carton. Pack size: 10 x 10 tablets.

### **6.6 Special precautions for disposal and other handling**

No special requirements.

Any unused product or waste material should be disposed of in accordance with local requirements.

## **7. SUPPLIER**

Macleods Pharmaceuticals Limited  
304, Atlanta Arcade  
Marol Church road  
Andheri (East)  
Mumbai – 400 059, India  
Tel: +91-22-66762800  
Fax: +91-22-28216599

## **8. WHO REFERENCE NUMBER (WHO Prequalification Programme)**

TB398

## **9. DATE OF PREQUALIFICATION**

2 September 2023

## **10. DATE OF REVISION OF THE TEXT**

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All links were accessed on 09 May 2024

*Detailed information on this medicine is available on the World Health Organization (WHO) website:*  
<https://extranet.who.int/prequal/medicines/prequalified/finished-pharmaceutical-products>