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.

[*]https://extranet.who.int/pqweb/sites/default/files/documents/75%20SRA%20clarification_Feb2017_newtempl.pdf

1. NAME OF THE MEDICINAL PRODUCT

[TB398 trade name]†

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

† 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 some cases, [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^3. 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.

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, rilpivirine, etravirine, doravirine, artemisinin and its derivatives or any direct-acting antiviral for chronic Hepatitis C is contraindicated (see section 4.5).

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.

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 three 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.

Hyperbilirubinemia

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 two 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.

[TB398 trade name] may interact with a very large number of other medicines, primarily by reducing the exposure to co-administered agents, reducing their efficacy and increasing the risk of therapeutic failure. For many important therapeutic agents, no interaction data with rifapentine are available. However, clinically significant reductions in drug exposure may occur. Whenever co-prescribing any drug together with [TB398 trade name], the possibility of a drug-drug interaction should be considered.

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
ANTI-INFECTIVES		
Antiretrovirals		
Nucleoside/nucleotide reverse transcriptase inhibitors **Stavudine** **Didanosine** **Lamivudine** **Emtricitabine** **Zidovudine**	No interaction expected.	No dose adjustment required.
Abacavir	Empirical data are lacking, but rifapentine may decrease abacavir exposure through induction of glucuronidation.	Efficacy of abacavir should be closely monitored in co-treatment.

Drugs by Therapeutic Area	Interaction	Recommendations concerning co-administration
Tenofovir alafenamide/ emtricitabine	Interaction not studied. Co-administration of rifapentine, a P-gp inducer, may decrease tenofovir alafenamide plasma concentrations, which may result in loss of therapeutic effect and development of resistance.	Co-administration is not recommended.
Non-nucleoside reverse transcriptase inhibitors **Efavirenz**	No clinically meaningful effect on efavirenz clearance or mid-interval concentrations. Viral suppression was maintained during TB treatment.	When co-treating with [TB398 trade name], it may be considered to increase the efavirenz dose to 800 mg q.d.
Nevirapine	Rifapentine will decrease the level or effect of nevirapine by altering drug metabolism	Co-administration has not been studied but may decrease nevirapine concentrations. Nevirapine is unlikely to significantly alter rifapentine pharmacokinetics. The magnitude of rifapentine-mediated CYP3A4 induction is predicted to be lower than rifampicin but higher than rifabutin. Perform therapeutic drug monitoring for nevirapine and adjust dosage if needed.
Etravirine	Rifapentine significantly reduces exposure to etravirine.	Co-treatment of [TB398 trade name] and etravirine is contraindicated.
Rilpivirine	Significant decrease in rilpivirine concentration	Co-treatment of [TB398 trade name] and rilpivirine is contraindicated.
Doravirine	Significant decrease in doravirine concentration	Co-treatment of [TB398 trade name] and doravirine is contraindicated.
Protease inhibitors **Fosamprenavir** **Saquinavir** **Indinavir** **Ritonavir** **Lopinavir** **Atazanavir** **Tipranavir** **Darunavir** **Boceprevir**	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.	[TB398 trade name] must not be co-administered with HIV or HCV protease inhibitors (see section 4.3).
Integrase inhibitors **Raltegravir**	Raltegravir AUC ↑ 71%	Once weekly rifapentine can be used with raltegravir without dose adjustment.
Dolutegravir	Dolutegravir AUC ↓29%	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.
Elvitegravir/cobicistat	Co-administration has not been studied.	Co-administration is contraindicated.

Drugs by Therapeutic Area	Interaction	Recommendations concerning co-administration
	Rifapentine is a potent inducer of CYP450 metabolism and may cause significant decrease in the plasma concentration of elvitegravir and cobicistat resulting in loss of therapeutic effect.	
CCR5 inhibitors **Maraviroc**	Maraviroc AUC ↓	Co-treatment should be avoided. If deemed necessary, the maraviroc dose should be increased to 600 mg b.i.d.
Antivirals Hepatitis C-infection		
Daclatasvir **Elbasvir/Grazoprevir** **Glecaprevir/Pibrentasvir** **Ledipasvir/Sofosbuvir** **Ombitasvir/paritaprevir/ritonavir (with or without dasabuvir)** **Simeprevir** **Sofosbuvir (with or without velpatasvir with or without voxilaprevir)/**	*Rifapentine*: 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 (for further details see Summary of product characteristics of the drugs for therapy of HCV).
Antifungals		
Ketoconazole	Ketoconazole AUC ↓	Co-administration should be avoided. If deemed necessary, a dose increase of ketoconazole may be required.
Fluconazole	Fluconazole AUC ↓	Monitor therapeutic effect. An increased dose of fluconazole may be required.
Itraconazole	Itraconazole AUC ↓	Co-administration should be avoided.
Voriconazole	Voriconazole AUC ↓	No dosage adjustment necessary.
Antibacterials/TB medicines		
Clarithromycin	Clarithromycin mean serum concentration ↓. 14-OH clarithromycin levels unchanged.	Co-administration should be avoided.
Chloramphenicol	Reduction of chloramphenicol exposure.	Co-administration should be avoided.
Ciprofloxacin	No significant interaction.	No dose adjustment required.
Doxycycline	Doxycycline AUC ↓	If co-treatment is considered necessary, the dose of doxycycline should be doubled.
Metronidazole	Metronidazole AUC i.v. ↓	The clinical relevance of the interaction is unknown. No dose adjustment is routinely recommended. Efficacy should be monitored.

Drugs by Therapeutic Area	Interaction	Recommendations concerning co-administration
Sulfamethoxazole	Sulfamethoxazole AUC ↓	Interaction probably not clinically significant. Efficacy of sulfamethoxazole should be monitored.
Trimethoprim	Trimethoprim AUC ↓	A dose increase of trimethoprim may be required. Efficacy should be monitored.
Ethionamide		Rifapentine and ethionamide should not be co-administered, due to an increased risk of hepatotoxicity.
***p*-Aminosalicylic acid**	Co-administration has not been studied, but based on experience with rifampicin *p*-aminosalicylic acid granules may reduce absorption of rifapentine if given concomitantly.	If *p*-aminosalicylic acid and rifapentine are both included in the treatment regimen, they should be given not less than eight hours apart to ensure satisfactory blood levels.
Telithromycin	Co-administration has not been studied, but based on experience with rifampicin, exposure to telithromycin may be reduced.	Dosage of telithromycin may require adjustment when starting or stopping concomitantly administered [TB398 trade name].
Dapsone	Co-administration has not been studied, but based on experience with rifampicin, exposure to dapsone may be reduced.	Dosage of dapsone may require adjustment when starting or stopping concomitantly administered [TB398 trade name].
Antimalarials		
Chloroquine	Empirical data are not available. Since chloroquine undergoes polymorphic hepatic metabolism, lower levels are likely during rifapentine co-therapy.	Co-administration should be avoided.
Atovaquone	Atovaquone AUC ↓ Rifapentine AUC ↑	Co-administration should be avoided.
Mefloquine	Mefloquine AUC ↓	Co-administration should be avoided.
Amodiaquine	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.
Quinine	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.
Lumefantrine	Lumefantrine AUC ↓	Co-administration should be avoided.
Artemisinin and its derivatives	Artemether AUC ↓ Dihydroarthemisinin AUC ↓	Co-administration is contraindicated.
Anthelmintics **Praziquantel**	Praziquantel AUC ↓	Co-treatment with [TB398 trade name] should be monitored closely.

Drugs by Therapeutic Area	Interaction	Recommendations concerning co-administration
ANALGESICS, ANTIPYRETICS, NON-STEROIDAL ANTI-INFLAMMATORY DRUGS		
Morphine	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.
Codeine	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.
Methadone	Methadone AUC ↓	Patients should be monitored for possible withdrawal effects, and methadone dose increased as appropriate (up to 2-3 fold).
Acetaminophen (paracetamol)	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.
ANTICONVULSANTS		
Carbamazepine	Rifapentine is expected to decrease the serum concentration of carbamazepine whereas isoniazid may increase them. Neurological side effects and the risk of hepatotoxicity increase when co-treating with carbamazepine.	Co-administration of [TB398 trade name] and carbamazepine should be avoided.
Phenobarbital	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.
Phenytoin	Phenytoin AUC i.v. ↓	Co-treatment with phenytoin and [TB398 trade name] should be avoided.
Valproic acid	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.
Lamotrigine	Lamotrigine AUC ↓	Co-treatment should be avoided. If deemed necessary, lamotrigine dose should be increased as appropriate.
IMMUNOSUPPRESSIVES		
Cyclosporine	Substantially increased cyclosporine clearance when co-administered with	Co-administration should be avoided. If deemed necessary, plasma concentrations of cyclosporine should

Drugs by Therapeutic Area	Interaction	Recommendations concerning co-administration
	rifapentine.	be monitored and doses adapted accordingly (3-5 fold increases in cyclosporine dose have been required).
Tacrolimus **Sirolimus** **Everolimus**	Tacrolimus AUC i.v. ↓ AUC p.o ↓ Sirolimus AUC ↓ Everolimus AUC ↓	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.
CARDIOVASCULAR MEDICINES		
Antiarrhythmics **Disopyramide** **Mexiletine** **Quinidine** **Propafenone** **Tocainide**	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].
Warfarin	Warfarin AUC ↓	Monitor closely and adjust warfarin dose as needed and reduce dose after withdrawing rifapentine treatment.
Clopidogrel	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.
Atenolol	Atenolol AUC ↓	No dose adjustment required.
Verapamil	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.
Digoxin **Digitoxin**	AUC p.o ↓	When co-administering [TB398 trade name] with digoxin, the efficacy and plasma concentration of digoxin should be monitored. A dose increase may be required.
Lidocaine	Lidocaine CL i.v. ↑	No dose adjustment required.
Amlodipine **Nifedipine**	Amlodipine and nifedipine like other calcium channel blockers, is metabolised by CYP3A; lower exposure is expected when co-treating with rifapentine.	Efficacy should be monitored.
Enalapril	No interaction expected.	No dose adjustment required.
Simvastatin	Simvastatin AUC ↓ Simvastatin acid AUC ↓	Co-administration is not recommended.
Atorvastatin	Atorvastatin AUC ↓	Co-administration is not recommended.
Clofibrate		Dosage of clofibrate may require adjustment when starting or stopping concomitantly administered [TB398 trade name].
Eplerenone		Dosage of eplerenone may require

Drugs by Therapeutic Area	Interaction	Recommendations concerning co-administration
		adjustment when starting or stopping concomitantly administered [TB398 trade name].
GASTROINTESTINAL MEDICINES		
Ranitidine	Ranitidine AUC ↓	Efficacy should be monitored, and ranitidine dose increased if necessary.
Antacids	Antacids may reduce the bioavailability of rifapentine by up to one third.	The clinical importance is unknown. Acid-suppressing drugs or antacids that do not contain aluminium hydroxide should be used if co-treatment with [TB398 trade name] is necessary. Furthermore, the dose of [TB398 trade name] should be given at least 1 hour before the ingestion of antacids.
PSYCHOTHERAPEUTIC MEDICINES		
Diazepam **Midazolam** **Triazolam** **Alprazolam** **Nitrazepam**	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.
Zolpidem **Zopiclone**	Zolpidem AUC ↓ Zopiclone AUC ↓	Co-administration should be avoided.
Chlorpromazine	Rifapentine may reduce chlorpromazine exposure.	Co-administration should be avoided. If considered necessary, patients should be carefully monitored for isoniazid toxicity.
Haloperidol **Clozapine** **Aripiprazole**	Haloperidol clearance is substantially increased by rifapentine, theoretical considerations imply that same applies to clozapine.	If co-treatment of [TB398 trade name] with haloperidol or clozapine is deemed necessary, monitor clinical efficacy. A dose increase may be required.
Amitriptyline **Nortriptyline**	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.
HORMONES; OTHER ENDOCRINE MEDICINES AND CONTRACEPTIVES		
Prednisolone **Other systemically administered corticosteroids**	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.
Glibenclamide **Glimepiride** **Repaglinide** **Rosiglitazine**	Glibenclamide AUC ↓ Glimepiride AUC ↓ Repaglinide AUC ↓	Blood glucose levels should be closely monitored. A dose increase of diabetes medication may be required.
Insulin	No interaction expected.	No dose adjustment required.
Levothyroxine	Case reports indicate that rifapentine may decrease the effect of levothyroxine.	TSH levels should be monitored.

Drugs by Therapeutic Area	Interaction	Recommendations concerning co-administration
Estrogens **Ethinylestradiol**	Ethinylestradiol AUC ↓	Co-adminstration with [TB398 trade name] may be associated with decreased contraceptive efficacy. Barrier- or other non-hormonal methods of contraception should be used.
Progestogens **Norethindrone**	Norethindrone 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.
CHEMOTHERAPEUTICS		
Cytotoxics **Irinotecan** **Imatinib**		Dosage of these drugs may require adjustment when starting or stopping concomitantly administered [TB398 trade name].
Hormone antagonist: antiestrogens **Tamoxifen** **Toremifene** **Gestrinone**		Dosages of these drugs may require adjustment when starting or stopping concomitantly administered [TB398 trade name].
OTHERS		
Theophylline	. Rifapentine may increase the clearance of theophylline.	Theophylline dose adjustment may be needed.
5-HT3 receptor antagonists		Dosages of these drugs may require adjustment when starting or stopping concomitantly administered [TB398 trade name].
Riluzole		Dosages of riluzole may require adjustment when starting or stopping concomitantly administered [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

Tabulated list of adverse reactions

In the table below, ADRs are listed under system organ class (SOC) with two columns showing those that are common and very common (seen in at least 1% of patients) and those that are uncommon, rare and very rare (less than 1%).

Frequency of ADRs that may be expected in adult patients taking [TB398 trade name]:

SOC	1% occurrence or more	Less than 1% occurrence
Infections and infestations	Influenza, herpes zoster	Fungal infections, parasitic infections, protozoal infection
Neoplasms		pulmonary carcinoma, carcinoma, lipoma
Blood and lymphatic system disorders	Anaemia, lymphopenia, neutropenia, leukopenia, leukocytosis, neutrophilia, thrombocytosis, thrombocytopenia, polycythaemia, lymphadenopathy	Lymphocytosis, haematoma, purpura, hypochromic anaemia, normocytic,anaemia thrombosis
Metabolism and nutrition disorders	Hyperuricaemia, hyperkalaemia, hypoglycaemia, increased non-protein nitrogen, hyperglycaemia, increased LDH, hyperphosphataemia	Weight decrease, increased BUN, diabetes mellitus, increased alkaline phosphatase, hypophosphataemia, hypercalcaemia, hypovolaemia, weight increase
Psychiatric disorders	Anorexia, insomnia	Anxiety, confusion, drug abuse, aggressive reaction, agitation
Nervous system disorders	Headache, dizziness, tremor	Somnolence, seizures, dysphonia, hypoesthesia, torticollis, hypertonia, hyporeflexia, meningitis, migraine headache, stupor
Eye disorders	Conjunctivitis	eye pain, eye abnormality
Ear and labyrinth disorders		Ear disorder not specified, otitis media, earache, otitis externa, tympanic membrane perforation.
Cardiovascular and vascular disorders	Hypertension	Syncope, tachycardia, palpitation, hypotension orthostatic, pericarditis, deep thrombophlebitis, vascular disorder,

		vasodilation
Respiratory, thoracic and mediastinal disorders	Haemoptysis, coughing, upper respiratory tract infection, bronchitis, pharyngitis, epistaxis, pleuritis	Abnormal breath sounds, pneumothorax, pneumonia, pleural effusion, rhinitis, dyspnoea, pneumonitis, sinusitis, increased sputum, pulmonary fibrosis, upper respiratory congestion, asthma, abnormal chest x-ray, bronchospasm, laryngeal oedema, laryngitis, respiratory disorder
Gastrointestinal disorders	Dyspepsia, vomiting, nausea, constipation, diarrhoea, haemorrhoids	Tooth disorder, gastroenteritis, gastritis, oesophagitis, cheilitis, dry mouth, pancreatitis, proctitis, salivary gland enlargement, tenesmus, gastrointestinal disorder not specified, ageusia
Hepatobiliary disorders	Increased ALT, increased AST	Bilirubinaemia, hepatomegaly, jaundice
Skin and subcutaneous tissue disorders	Rash, sweating, pruritis, acne, skin disorder, maculopapular rash, eczema	Skin ulceration, urticaria, dry skin, furunculosis, skin discoloration, fungal dermatitis, nail disorder, alopecia, erythematous rash
Musculoskeletal and connective tissue disorders	Arthralgia, arthritis, arthrosis, gout	Myalgia, myositis, bone fracture, muscle weakness, muscle spasm
Renal and urinary disorders	Pyuria, proteinuria, haematuria, urinary tract infections, urinary casts, cystitis	Urethral disorder, dysuria, pyelonephritis, urinary incontinence, urination disorder.
Reproductive system and breast disorders		Abortion, penis disorder, vaginitis, vaginal haemorrhage, positive cervical smear test, leucorrhoea, male mastitis, prostatic disorder
General disorders	Red-orange discoloration of body tissues and/or fluids (eg, skin, teeth, tongue, urine, faeces, saliva, sputum, tears, sweat, and cerebrospinal fluid). Contact lenses or dentures may become permanently stained. Back Pain, chest pain, abdominal pain, fever, fatigue	Laboratory test abnormal, oedema of legs, asthenia, oedema of face, abscess, peripheral oedema, malaise

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 *rpo*B 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 10^7 to 10^8 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* ± standard deviation**
Maximum concentration (C_{max})	10.8 ± 2.4 µg/mL
Area under the curve ($AUC_{0-\infty}$), a measure of the extent of absorption	257 ± 68 µg·h/mL
Time to attain maximum concentration (t_{max})	5.39 ± 0.60 h

Pharmacokinetics of rifapentine

Absorption	
Absolute bioavailability	NA*
Oral bioavailability	>32%
Food effect	High fat meal: AUC ↑ 43%, Cmax ↑ 44%
Distribution	
Volume of distribution (mean)	70.2 ± 9.1 L
Plasma proteinbinding *in vitro*	Rifapentine 98% 25-desacetyl rifapentine 93%
Tissue distribution	NA*
	hydrolyzed by esterase enzymes and CYP3A4
Active metabolite(s)	25-desacetyl rifapentine
Elimination	
Elimination half life	Rifapentine: 13.2 – 14.1 hours 25-desacetyl rifapentine: 13.3 – 24.3 hours
Mean systemic clearance (Cl/F)	2.0 ± 0.6 L
% of dose excreted in urine	17%

% of dose excreted in faeces	70%
Pharmacokinetic linearity	Linear up to a 600 mg dose; at higher dose less than dose proportional increase
Drug interactions *(in vitro)*	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 ± 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

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_{max} 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 25desacetyl 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 (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/hypoxanthineguaninephosphoribosyl 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

Core tablet: 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

Film coat: 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) tablet.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

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

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

October 2023

References

WHO operational handbook on tuberculosis: module 4: treatment: drug-susceptible tuberculosis treatment. WHO, Geneva, 2022. Available at https://www.who.int/publications/i/item/9789240050761 [accessed 12 October 2023]

WHO consolidated guidelines on tuberculosis. Module 4: treatment - drug-susceptible tuberculosis treatment. WHO, Geneva; 2022. Available at: https://www.who.int/publications/i/item/9789240048126 [accessed 12 October 2023].

WHO consolidated guidelines on tuberculosis: tuberculosis preventive treatment. WHO, Geneva; 2020. Available at: https://www.who.int/publications/i/item/9789240001503 [accessed 12 October 2023]

WHO operational handbook on tuberculosis: module 1: prevention: tuberculosis preventive treatment. WHO, Geneva, 2020. Available at https://www.who.int/publications/i/item/9789240002906 [accessed 12 October 2023].

US FDA Priftin® (rifapentine) tablets highlights of prescribing information. U.S. Food and Drug Administration; May 2010 (https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/021024s009lbl.pdf, accessed 12 October 2023).

Detailed information on this medicine is available on the World Health Organization (WHO) website: https://extranet.who.int/pqweb/medicines