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/prequal/sites/default/files/document_files/75%20SRA%20clarification_Feb2017_newtempl.pdf

1. NAME OF THE MEDICINAL PRODUCT

[TB369 trade name][†]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 300 mg isoniazid and 300 mg rifapentine.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

[TB369 trade name] are reddish-brown, capsule-shaped, film-coated tablets. They are biconvex, (rounded on top and bottom) with a bevelled edge. The tablets are debossed with "J" and "21" on either side of the break-line on one side and plain on the other side. The tablets can be divided into equal doses.

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4. CLINICAL PARTICULARS

4.1 Therapeutic indications

[TB369 trade name] is indicated for the prevention of tuberculosis caused by *Mycobacterium tuberculosis* in persons at risk.

Prophylactic regimens should follow the most recent WHO treatment guidelines, supplemented by other authoritative guidelines.

4.2 Posology and method of administration

Posology

[TB369 trade name] should be administered once weekly for a period of 3 months (12 doses). Doses are based on body weight and age as shown below:

Age > 14 years

For patients aged over 14 years, the dose is 900 mg isoniazid and 900 mg rifapentine (3 tablets of [TB369 trade name]) once a week for 3 months (12 doses).

Age 2–14 years

For patients aged between 2 and 14 years, the following weekly dose should be taken for 3 months (12 doses):

Body weight	Number of tablets
10–15 kg	1
16–23 kg	1½
24–30 kg	2
31 kg or more	2½

[†] Trade names are not prequalified by WHO. This is the national medicines regulatory agency's responsibility.

Special populations

Elderly

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

Hepatic and renal impairment

Use should be carefully monitored in patients with chronic liver disease or severe renal dysfunction.

Missed doses and vomiting after a dose

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

If a dose is missed but it is remembered within the next 2 days, the person 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 [TB369 trade name], the dose should be repeated.

Method of administration

[TB369 trade name] should be taken orally with a meal.

4.3 Contraindications

- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.
- Acute liver disease, icterus or severe liver impairment.
- History of drug-induced liver disease with isoniazid, rifapentine or any other medicine.
- Previous experience of severe side effects with isoniazid or rifapentine, such as drug fever or chills.
- Co-administration of [TB369 trade name] with HIV protease inhibitors, elvitegravir/cobicistat, nevirapine, rilpivirine, etravirine, doravirine, artemisinin & its derivatives, or direct-acting antivirals for chronic Hepatitis C (see section 4.4).

4.4 Special warnings and precautions for use

Hepatotoxicity

Rifapentine and isoniazid may cause hepatotoxicity (see section 4.8). Therefore, patients' symptoms should be carefully monitored at monthly intervals.

Severe and sometimes fatal hepatitis associated with isoniazid therapy may occur and may develop even after many months of treatment. Patient groups especially at risk of developing hepatitis include:

- older patients (hepatotoxicity is rare in those below 20 years of age and commonest in those aged over 50)
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- daily users of alcohol (patients should be strongly advised to restrict intake of alcoholic beverages, see section 4.5)
- patients with active chronic liver disease ([TB369 trade name] is contraindicated in those with a history of acute liver disease, see section 4.3)
- individuals with a history of drug misuse by injection.

Careful monitoring is also advised in malnourished or HIV-infected patients, those known to be slow acetylators (see section 5.2) and those taking other long-term therapy with potentially hepatotoxic medicines (see also section 4.5).

Patients should be instructed to immediately report signs or symptoms consistent with liver damage or other adverse effects. These include any of the following: unexplained anorexia, nausea, vomiting, dark urine, icterus, rash, persistent paresthesia of the hands and feet, persistent fatigue, weakness for more than 3 consecutive days and abdominal tenderness, especially of the right upper quadrant. If these symptoms appear or if signs suggestive of hepatic damage are detected, [TB369 trade name] should be discontinued promptly. Continued use in these cases may cause a more severe form of liver damage.

In addition to monthly symptom reviews, hepatic enzymes (specifically AST and ALT) should be measured prior to starting therapy with [TB369 trade name] and periodically throughout treatment.

Increased liver enzyme values are common during therapy with [TB369 trade name]. A cholestatic pattern is usually caused by rifapentine, whereas elevated transaminases may be caused by rifapentine or isoniazid. These effects on liver function tests are usually mild to moderate, and will most commonly normalise spontaneously within 3 months, even with continued therapy. However, if the concentration of liver enzymes exceeds 3 to 5 times the upper limit of normal, discontinuation of [TB369 trade name] should be strongly considered.

Rechallenge with component drugs after intercurrent hepatotoxicity, if deemed appropriate, should not be performed until after symptoms and laboratory abnormalities have subsided. In case of rechallenge, [TB369 trade name] should not be used, as the component drugs should be given one by one and at gradually increasing doses, or alternative agents should be used.

Hypersensitivity

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 [TB369 trade name] should immediately be discontinued. Such patients should not be rechallenged with rifapentine. If rifapentine therapy is temporarily discontinued, rifapentine should be restarted carefully at a reduced dose, and with close monitoring. In this situation, [TB369 trade name] should not be used.

Cross-sensitivity

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

Peripheral neuropathy

This is the most common toxic effect of isoniazid (see section 4.8). The frequency depends on the dose and on predisposing conditions such as malnutrition, chronic alcohol dependence, HIV infection, renal failure or diabetes, infancy, adolescence, pregnancy or breastfeeding. [TB369 trade name] should therefore be used with careful monitoring in patients with pre-existing neuropathy or conditions that may predispose to it, and concomitant pyridoxine administration is advised in such cases.

Epilepsy and psychotic disorders

[TB369 trade name] should be used with caution in patients with seizure disorders or a history of psychosis.

Haematological toxicity

Rifapentine may be associated with haemolytic anaemia, leucopenia and thrombocytopenia; full blood count should be monitored regularly throughout therapy with [TB369 trade name]. In case of severe haematological disturbances [TB369 trade name] must be discontinued.

Renal impairment

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

Nephrotoxicity

[TB369 trade name] should be discontinued in case of clinical signs of nephrotoxicity.

Diabetes mellitus

Patients with diabetes should be carefully monitored since blood glucose control may be affected by isoniazid. Such individuals may also be at greater risk of peripheral neuropathy, see above.

Drug interactions

Rifapentine is a strong inducer of hepatic drug metabolism. Therefore [TB369 trade name] may reduce exposure and efficacy of many therapeutic drugs, including antiretroviral agents, antiepileptic drugs, immunosuppressants and coumarin derivatives (see section 4.5).

Contraception

Oral contraceptives do not provide adequate protection against conception when co-administered with [TB369 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.

Treatment with corticosteroids

[TB369 trade name] may reduce the efficacy of corticosteroids in Addison's disease and induce an Addisonian crisis (see section 4.5).

Porphyria

[TB369 trade name] should be used with caution in patients with porphyria, since the enzyme induction by rifapentine may cause symptoms.

Discolouration of body fluids

[TB369 trade name] may cause a reddish-orange discolouration of body fluids such as urine, sputum and tears. 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

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**.** Administration of rifapentine with drugs that undergo biotransformation through these metabolic pathways is likely to accelerate elimination of co-administered drugs, 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 [TB369 trade name], the possibility of a drug-drug interaction should be considered.

In vitro, isoniazid acts as an inhibitor of CYP2C19 and CYP3A4. Thus, it may increase exposure to drugs mainly eliminated through either of these pathways. However, when co-treating with rifapentine, as when using [TB369 trade name], these effects are likely to be outweighed by the hepatic enzyme induction due to rifapentine. Insofar as it has been investigated, the net effect of rifapentine and isoniazid on drug clearance will be an increase due to rifapentine rather than a decrease due to isoniazid.

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

The following list of drug interactions with [TB369 trade name] 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
INFECTION		
Antiretrovirals		
Stavudine **Didanosine** **Lamivudine** **Emtricitabine** **Zidovudine/** rifapentine	No interaction expected.	No dose adjustment required.
Tenofovir alafenamide/ **emtricitabine/** rifapentine	Interaction not studied. Co-administration of rifapentine, a P-gp inducer, may decrease tenofovir alafenamide plasma concentrations.	Co-administration is not recommended.
Abacavir / rifapentine	Empirical data are lacking, but rifapentine may decrease abacavir exposure through induction of glucuronidation.	No dose adjustment required.
Non-nucleoside analogues **Efavirenz** / rifapentine	No clinically meaningful effect on efavirenz clearance or mid-interval concentrations. Viral suppression was maintained during TB treatment.	No dose adjustment required.
Nevirapine / rifapentine	Rifapentine will decrease the level or effect of nevirapine by altering drug metabolism	Co-treatment of [TB369 trade name] and nevirapine is contraindicated.
Etravirine / rifapentine	Rifapentine significantly reduces exposure to etravirine.	Co-treatment of [TB369 trade name] and etravirine iscontraindicated.
Rilpivirine/ rifapentine	Significant decrease in rilpivirine concentration.	Co-treatment of [TB369 trade name]and rilpivirine is contraindicated.
Doravirine/ rifapentine	Significant decrease in doravirine concentration.	Co-treatment of [TB369 trade name]and doravirine is contraindicated.
Protease inhibitors **Fosamprenavir /** rifapentine **Ritonavir** **Lopinavir** **Atazanavir** **Tipranavir** **Darunavir**	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.	[TB369 trade name] must not be co-administered with HIV or HCV protease inhibitors.
Others		
Raltegravir / rifapentine	Raltegravir AUC ↑ 71%	Once weekly rifapentine can be used with raltegravir without dose adjustment.
Dolutegravir / rifapentine	Dolutegravir AUC ↓29%	No dose adjustment required.

Drugs by Therapeutic Area	Interaction	Recommendations concerning co-administration
Elvitegravir/cobicistat/rifapentine	Co-administration has not been studied. 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.	Co-administration is contraindicated.
Maraviroc / rifapentine	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)** **Sofosbuvir (with or without velpatasvir with or without voxilaprevir)/** Rifapentine Isoniazid	*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. *Isoniazid:* Co-administration has not been studied.	Co-administration of [TB369 trade name] with these antivirals is contraindicated.
Antifungals		
Ketoconazole / rifapentine	Ketoconazole AUC ↓	Co-administration should be avoided. If deemed necessary, a dose increase of ketoconazole may be required.
Fluconazole / rifapentine	Fluconazole AUC ↓	Monitor therapeutic effect. An increased dose of fluconazole may be required.
Itraconazole / rifapentine	Itraconazole AUC ↓	Co-administration should be avoided.
Voriconazole / rifapentine	Voriconazole AUC ↓	No dosage adjustment necessary
Antibacterials/Antituberculotics		
Clarithromycin / rifapentine	Clarithromycin mean serum concentration ↓. 14-OH clarithromycin levels unchanged.	Co-administration should be avoided.
Chloramphenicol / rifapentine	Reduction of chloramphenicol exposure.	Co-administration should be avoided.
Ciprofloxacin / rifapentine	No significant interaction.	No dose adjustment required.
Doxycycline / rifapentine	Doxycycline AUC ↓	If co-treatment is considered necessary, the dose of doxycycline should be doubled.
Metronidazole / rifapentine	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 / rifapentine	Sulfamethoxazole AUC ↓	Interaction probably not clinically significant. Efficacy of sulfamethoxazole should be monitored.
Trimethoprim / rifapentine	Trimethoprim AUC ↓	A dose increase of trimethoprim may be required. Efficacy should be monitored.
Ethionamide / rifapentine		Rifapentine and ethionamide should not be co-administered, due to an increased risk of hepatotoxicity.
Para-aminosalicylic acid / isoniazid		Para-aminosalicylic acid may increase the plasma concentration and elimination half-life of isoniazid by competing for acetylating enzymes.
Antimalarials		
Chloroquine / rifapentine	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 / rifapentine	Atovaquone AUC ↓ Rifapentine AUC ↑	Co-administration should be avoided.
Mefloquine / rifapentine	Mefloquine AUC ↓	Co-administration should be avoided.
Amodiaquine / rifapentine	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 / rifapentine	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 / rifapentine	Lumefantrine AUC ↓	Co-administration should be avoided.
Artemisinin and its derivatives / rifapentine	Artemether AUC ↓ Dihydroarthemisinin AUC ↓	Co-administration is contra-indicated.
ANALGESICS, ANTIPYRETICS, NON-STEROIDAL ANTI-INFLAMMATORY DRUGS		
Morphine / rifapentine	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 / rifapentine	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.

Drugs by Therapeutic Area	Interaction	Recommendations concerning co-administration
Methadone / rifapentine	Methadone AUC ↓	Patients should be monitored for possible withdrawal effects, and methadone dose increased as appropriate (up to 2-3 fold).
Acetaminophen (paracetamol) / rifapentine / isoniazid	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. Concurrent use with isoniazid may increase hepatotoxicity.	Co-administration of [TB369 trade name] and acetaminophen (paracetamol) should be avoided.
ANTICONVULSANTS		
Carbamazepine / rifapentine / isoniazid	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 [TB369 trade name] and carbamazepine should be avoided.
Phenobarbital / rifapentine / isoniazid	Phenobarbital and rifapentine are both strong hepatic enzyme inducers, and each drug may lower the plasma concentrations of the other. Also, co-treatment with phenobarbital and isoniazid may increase the risk of hepatotoxicity.	Co-administration of [TB369 trade name] and phenobarbital should be undertaken with caution, including monitoring of clinical effects and, if possible, plasma drug concentrations.
Phenytoin / rifapentine isoniazid	Phenytoin AUC i.v. ↓ Co-treatment with phenytoin and isoniazid may result in an increased risk of hepatotoxicity.	Co-treatment with phenytoin and [TB369 trade name] should be avoided.
Valproic acid / rifapentine	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 / rifapentine	Lamotrigine AUC ↓	Co-treatment should be avoided. If deemed necessary, lamotrigine dose should be increased as appropriate.
IMMUNOSUPPRESSIVES		
Cyclosporine / rifapentine	Substantially increased cyclosporine clearance	Co-administration should be avoided. If deemed necessary, plasma concentrations of cyclosporine should

Drugs by Therapeutic Area	Interaction	Recommendations concerning co-administration
	when co-administered with rifapentine.	be monitored and doses adapted accordingly (3-5 fold increases in cyclosporine dose have been required).
Tacrolimus / rifapentine **Sirolimus** **Everolimus**	Tacrolimus AUC i.v. ↓ AUC p.o ↓ Sirolimus AUC ↓ Everolimus AUC ↓	Co-administration of [TB369 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		
Warfarin / rifapentine /isoniazid	Warfarin AUC ↓ Isoniazid may inhibit hepatic metabolism of warfarin.	Monitor closely and adjust warfarin dose as needed. Reduce dose after withdrawing rifapentine treatment.
Atenolol / rifapentine	Atenolol AUC ↓	No dose adjustment required.
Verapamil / rifapentine	S-verapamil p.o CL/F ↑. With i.v. S-verapamil, CL ↑	[TB369 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 / rifapentine	AUC p.o ↓	When co-administering [TB369 trade name] with digoxin, the efficacy and plasma concentration of digoxin should be monitored. A dose increase may be required.
Lidocaine / rifapentine	Lidocaine CL i.v. ↑	No dose adjustment required.
Amlodipine / rifapentine **Nifedipine** /rifapentine	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 / rifapentine	No interaction expected.	No dose adjustment required.
Simvastatin / rifapentine	Simvastatin AUC ↓ Simvastatin acid AUC ↓	Co-administration is not recommended.
Atorvastatin / rifapentine	Atorvastatin AUC ↓	Co-administration is not recommended.
GASTROINTESTINAL MEDICINES		
Ranitidine / rifapentine	Ranitidine AUC ↓	Efficacy should be monitored, and ranitidine dose increased if necessary.
Antacids / isoniazid / rifapentine	Antacids may reduce the bioavailability of rifapentine by up to one third. Aluminium hydroxide impairs the absorption of isoniazid.	The clinical importance is unknown. Acid-suppressing drugs or antacids that do not contain aluminium hydroxide should be used if co-treatment with [TB369 trade name] is necessary.
PSYCHOTHERAPEUTIC MEDICINES		
Diazepam / rifapentine / isoniazid **Midazolam** **Triazolam** **Alprazolam** **Nitrazepam**	Diazepam AUC ↓ Midazolam AUC ↓ Triazolam AUC ↓ Alprazolam AUC ↓	Co-treatment is not recommended. Benzodiazepine withdrawal may occur in dependent individuals.

Drugs by Therapeutic Area	Interaction	Recommendations concerning co-administration
	Reduced nitrazepam through concentrations, increased clearance.	
Zolpidem / rifapentine **Zopiclone** /rifapentine	Zolpidem AUC ↓ Zopiclone AUC ↓	Co-administration should be avoided.
Chlorpromazine / rifapentine / isoniazid	Rifapentine may reduce chlorpromazine exposure. Also, concomitant use of chlorpromazine with isoniazid may impair the metabolism of isoniazid.	Co-administration should be avoided. If considered necessary, patients should be carefully monitored for isoniazid toxicity.
Haloperidol / rifapentine **Clozapine**	Haloperidol clearance is substantially increased by rifapentine, theoretical considerations imply that same applies to clozapine.	If co-treatment of [TB369 trade name] with haloperidol or clozapine is deemed necessary, monitor clinical efficacy. A dose increase may be required.
Amitriptyline / rifapentine **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 / rifapentine **And 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 [TB369 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 / rifapentine **Glimepiride** **Repaglinide**	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 / rifapentine	Case reports indicate that rifapentine may decrease the effect of levothyroxine.	TSH levels should be monitored.
Ethinylestradiol / rifapentine	Ethinylestradiol AUC ↓	Co-adminstration with [TB369 trade name] may be associated with decreased contraceptive efficacy. Barrier- or other non-hormonal methods of contraception should be used.
Norethindrone / rifapentine	Norethindrone AUC ↓	Co-administration with [TB369 trade name] may be associated with decreased contraceptive efficacy. Barrier- or other non-hormonal methods of contraception should be used.
OTHERS		
Praziquantel / rifapentine	Praziquantel AUC ↓	Co-treatment with [TB369 trade name] should be monitored closely.
Disulfiram / isoniazid	Concurrent use of disulfiram together with isoniazid may result in increased incidence of	Dose reduction or discontinuation of disulfiram may be necessary during therapy with [TB369 trade name].

Drugs by Therapeutic Area	Interaction	Recommendations concerning co-administration
	adverse effects on the central nervous system.	
Theophylline / Isoniazid / Rifapentine	Isoniazid may increase the serum concentration of theophylline and rifapentine may decrease it. The effects of combination are unknown.	Theophylline dose adjustment may be needed.
Enflurane / Isoniazid	Isoniazid may increase the formation of the potentially nephrotoxic inorganic fluoride metabolite of enflurane.	Coadministration of [TB369 trade name] with enflurane should be avoided.
Sildenafil / Rifapentine	Sildenafil AUC ↓	Co-treatment with [TB369 trade name] should be monitored closely.

Interactions with food and drinks

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

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

Interactions with laboratory tests

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

4.6 Fertility, pregnancy and breastfeeding

Pregnancy

Isoniazid crosses the placenta but is not expected to pose any additional risks to the patient or fetus.

In animal reproduction and developmental toxicity studies, rifapentine produced fetal harm and was teratogenic (see section 5.3). However, data from clinical trials, case reports, epidemiology studies and post-marketing experience with rifapentine use in pregnant women are insufficient to establish a drug-associated risk of major birth defects, adverse maternal or fetal outcomes. When administered during the last few weeks of pregnancy, rifampin, 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.

[TB369 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.

Breastfeeding

Isoniazid passes into breast milk. In breast-fed infants whose mothers are taking isoniazid, there is a theoretical risk of convulsions and neuropathy (associated with vitamin B6 deficiency), therefore they should be monitored for early signs of these effects and consideration should be given to treating both mother and infant prophylactically with pyridoxine.

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 [TB369 trade name], taking into account the importance of [TB369 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 [TB369 trade name] on human male or female fertility. Studies in rats with isoniazid have shown slight reductions in fertility (see section 5.3). 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 [TB369 trade name], especially the potential neurotoxicity of isoniazid, 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) and ranked by headings of frequency. Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness, using the following convention: ≥ 1% occurrence (common and very common) and < 1% occurrence (uncommon, rare and very rare).

Frequency of ADRs which may be expected in adult patients taking [TB369 trade name]:

SOC	≥ 1% occurrence	< 1% occurrence
Metabolic & nutritional		Alkaline phosphatase increased, metabolic acidosis, pellagra, hyperglycaemia, pyridoxine deficiency, nicotinic acid deficiency may be related to an isoniazid-induced pyridoxine deficiency which affects the conversion of tryptophan to nicotinic acid.
Haematologic	Anaemia, lymphopenia, neutropenia, leucocytosis, thrombocytosis, thrombocytopenia, lymphadenopathy	Lymphocytosis, haematoma, purpura, anaemia (hypochromic, normocytic, haemolytic, sideroblastic or aplastic) thrombosis, leucopenia (allergic), neutropenia with eosinophilia, agranulocytosis
Dermatologic	Rash, increased sweating, pruritis, maculopapular rash	Urticaria, skin discoloration, toxic epidermal necrolysis, eosinophilia systemic symptoms (DRESS), erythema multiforme, Stevens-Johnson syndrome, exfoliative dermatitis, pemphigus, rash, acne
Immune system		Anaphylactic reactions
Respiratory	Haemoptysis, coughing,	Dyspnoea, pneumonitis, pulmonary fibrosis, asthma, bronchospasm, laryngeal oedema, laryngitis.

Gastrointestinal	Dyspepsia, vomiting, nausea, diarrhoea	Gastritis, esophagitis, pancreatitis, salivary gland enlargement, anorexia, epigastric distress, acute pancreatitis
Infections		Fungal infections
Hepatic & biliary	Increased ALT, Increased AST	Bilirubinaemia, hepatomegaly, jaundice, hepatitis, acute hepatic failure, liver injury, jaundice
Neurologic	Headache, dizziness	Somnolence, dysphonia
Nervous system disorders	Peripheral neuropathy, usually preceded by paraesthesia of the feet and hands. The frequency depends on the dose and on predisposing conditions such as malnutrition, alcoholism or diabetes. It has been reported in as many as 3.5 to 17% of patients treated with isoniazid. Concomitant pyridoxine administration largely reduces this risk (see sections 4.2 and 4.4).	Seizures, toxic encephalopathy, polyneuritis, presenting as muscle weakness, loss of tendon reflexes Hyperreflexia may be troublesome with isoniazid doses of 10mg per kg body weight
Psychiatric	Anorexia, insomnia	Anxiety, confusion, memory impairment, toxic psychosis, elevated mood, psychotic disorder Although isoniazid usually has a mood elevating effect, mental disturbances, ranging from minor personality changes to major mental derangement have been reported; these are usually reversed on withdrawal of the drug.
Musculoskeletal	Arthralgia	Myalgia, myositis, arthritis, systemic lupus erythematosus, lupus-like syndrome, rheumatic syndrome
Cardiovascular		Syncope, tachycardia, palpitation, orthostatic hypotension, pericarditis
Ophthalmologic	Conjunctivitis	Optic atrophy or neuritis
Vascular		Vasculitis
Renal and urinary disorders		Dysuria
Hearing & Vestibular		Deafness, tinnitus, vertigo These have been reported in patients with end stage renal impairment
Reproductive		Abortion, vaginitis, vaginal haemorrhage, leucorrhoea, gynaecomastia
General	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, abdominal pain, fever, fatigue., anorexia	Abnormal laboratory test results, asthenia, facial oedema, anti-nuclear antibodies
Miscellaneous		Withdrawal symptoms, which may occur on cessation of treatment, include headache, insomnia, excessive dreaming, irritability and nervousness.

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

Anorexia, nausea, vomiting, gastrointestinal disturbances, fever, headache, dizziness, slurred speech, hallucinations or visual disturbances have occurred within 30 minutes to 3 hours after ingestion of isoniazid. Periorbital myoclonus, tinnitus, tremor, hyperreflexia, tachycardia, arrhythmias, and rhabdomyolysis have been reported. With marked isoniazid overdoses (≥ 80 mg/kg body weight) respiratory distress and CNS depression, progressing rapidly from stupor to profound coma, along with severe intractable seizures are to be expected. Typical laboratory findings are severe metabolic acidosis, acetonuria, and hyperglycaemia. The toxicity is potentiated by alcohol. Lethal doses have been reported to range between 80 and 150 mg/kg.

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 with special attention to monitoring/support of ventilation and correction of metabolic acidosis.

Emesis, gastric lavage and activated charcoal may be of value if instituted within a few hours of ingestion. Subsequently, pyridoxine (intravenous bolus on a gram per gram basis, equal to the isoniazid dose, if latter dose is unknown an initial dose of 5 g in adults or 80 mg/kg in children should be considered), intravenous diazepam (in case of seizures not responding to pyridoxine) and haemodialysis may be of value.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antimycobacterials, combinations of drugs for treatment of tuberculosis, ATC Code: J04AM02.

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. Microbial resistance may occur, and is a result of alterations in the target enzyme (RNA polymerase).

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

5.2 Pharmacokinetic properties

The absorption characteristics of [TB369 trade name] have been determined after administration of single tablets (containing 300 mg isoniazid and 300 mg rifapentine) in healthy volunteers in the fed state as follows:

Pharmacokinetic variable	**Mean value* (± standard deviation)**	
	Isoniazid	**Rifapentine**
Maximum concentration (C_{max})	3737 ± 1205 ng/ml	8.85 ± 1.84 µg/ml

Area under the curve (AUC_{0-72h}), a measure of the extent of absorption	22941 ± 11549 ng·h/ml	217 ± 49 µg·h/ml
Time to attain maximum concentration (t_{max})	2.51 ± 0.83 h	5.42 ± 0.87 h

* Arithmetic mean

Pharmacokinetics of Rifapentine and Isoniazid

	Rifapentine	**Isoniazid**
Absorption		
Absolute bioavailability	NA*	NA*
Oral bioavailability	>32%	>80%
Food effect	High fat meal: AUC ↑ 43%, C_{max} ↑ 44%	Reduced.
Distribution		
Volume of distribution (mean)	70.2 ± 9.1 L	43 L
Plasma proteinbinding *in vitro*	Rifapentine 98% 25-desacetyl rifapentine 93%	< 10%
Tissue distribution	NA*	It diffuses readily into all body fluids (cerebrospinal, pleural and ascitic fluids), tissues, organs and excreta (saliva, sputum and faeces). It crosses the placenta and is secreted in the milk.
Metabolism		
		Extensive metabolism in the mucosal cells of the small intestine and in the liver. Firstly, isoniazid is inactivated through acetylation. Subsequently, acetylisoniazid is further hydrolysed. Isoniazid acetylation is dependent on the genetically determined metabolic rate of the individual patients, who are termed fast or slow acetylators (this is due to a genetic polymorphism in the metabolizing enzyme N-acetyl transferase). Different ethnic groups contain differing proportions of acetylator phenotypes. Acetylator status is the main determinant of isoniazid exposure at a given dose. At recommended doses, exposure in fast acetylators is about half that seen in slow acetylators.
	Hydrolyzed by esterase enzymes and CYP3A4	Hepatic; primarily acetylated by N-acetyltransferase to N-acetylisoniazid

Active metabolite(s)	25-desacetyl rifapentine	Nicotinoyl-NAD adduct
Elimination		
Elimination half life	Rifapentine: 13.2 – 14.1 hours 25-desacetyl rifapentine: 13.3 – 24.3 hours	1.2 hours: rapid acetylators 3.5 hours: slow acetylators
Mean systemic clearance (Cl/F)	2.0 ± 0.6 L	15.5 L/hour: slow NAT2 genotype 26.1 L/hour: rapid/intermediate NAT2 genotype
% of dose excreted in urine	17%	75 − 95%
% of dose excreted in faeces	70%	<10%
Pharmacokinetic linearity	Linear up to a 600 mg dose; at higher dose less than dose proportional increase	NA*
Drug interactions *(in vitro*)	Rifapentine is an inducer of CYP3A4, 2C8 and 2C9 and P-gp Rifapentine is an auto-inducer by CYP3A	Isoniazid is CYP450 inducer and inhibitor. Isoniazid is an arylamine n-acetyltransferase 2 substrate and inhibitor
Transporters	NA*	NA*
Metabolizing enzymes	esterases and CYP3A4	CYP450: 2C19, 3A4

*Information not available

Special populations

Rifapentine

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 patients 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 mild to severe hepatic impaired patients (n=15), the pharmacokinetics of rifapentine and 25-desacetyl metabolite were similar in patients with various degrees of hepatic impairment and to that observed in another study for healthy volunteers (n=12). 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.

Isoniazid

In slow acetylators with severely impaired renal function, accumulation of isoniazid may occur.

An impaired liver function prolongs the elimination half-life of isoniazid.

5.3 Preclinical safety data

Isoniazid

Non-clinical data reveal no special hazard for humans at recommended doses based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenic potential.

Treatment of pregnant rats with isoniazid at high dose resulted in reduced litter sizes and decreased postnatal growth, development, and cognitive ability in the offspring. Spermatogenesis impairment was observed in treated rats.

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
Croscarmellose
sodium Iron oxide
red Povidone
Low-substituted hydroxypropyl cellulose
Sodium starch glycolate
Sodium ascorbate
EDTA disodium
Sodium lauryl sulfate
Hydroxypropyl cellulose
Calcium stearate

Seal coating: Hypromellose

Film coat: Hypromellose
Macrogol/ polyethylene glycol
Titanium dioxide
Iron oxide red
Talc

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.

6.5 Nature and contents of container

Aluminium on aluminium (Alu/Alu) strip. Each strip contains 6 tablets. Such 7 strips are packed in a carton along with a patient information leaflet. Pack size: 7 x 6 tablets.

Aluminium on aluminium (Alu/Alu) strip. Each strip contains 12 tablets. Such 3 strips are packed in a carton along with a patient information leaflet. Pack size: 3 x 12 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

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