SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the medicinal product
Isoniazid/rifapentine 300 mg/300 mg tablets

2. Qualitative and quantitative composition
Each tablet contains 300 mg of isoniazid and 300 mg of rifapentine.

For the full list of excipients, see section 6.1.

3. Pharmaceutical form
Tablet.

Reddish brown-coloured, biconvex, capsule-shaped, film-coated tablets debossed with "J" and "21" on either side of the breakline on one side and plain on the other side. The tablets can be divided into equal doses.

Clinical particulars

4.1 Therapeutic indications
Isoniazid/rifapentine is indicated for the prevention of tuberculosis caused by *Mycobacterium tuberculosis* in patients above 2 years of age and weighing more than 10 kg.

Consideration should be given to current official treatment guidelines for tuberculosis including those of WHO.

4.2 Posology and method of administration

Posology
Isoniazid/rifapentine should be administered once weekly for a period of 3 months (12 doses). Dosing should be 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) 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	1.5
24–30kg	2
> 30 kg	2.5

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
The patient must take 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 isoniazid/rifapentine, the dose should be repeated.

Method of administration
Isoniazid/rifapentine should be taken orally with a light meal.

4.3 Contraindications

- Hypersensitivity to the active substances or any of the excipients listed in section 6.1.
  Acute liver disease, icterus or severe liver impairment.
- Drug-induced liver disease.
- Previous liver damage linked to isoniazid or rifapentine.
- Previous experience of severe side effects with isoniazid or rifapentine, such as drug fever or chills.
- Co-administration of isoniazid/rifapentine with HIV protease inhibitors, elvitegravir/cobicistat, rilpivirine, etravirine, doravirine, artemisinin and its derivatives or any direct-acting antiviral for chronic Hepatitis Cis contraindicated (see section 4.5).

4.4 Special warnings and precautions for use

Hepatotoxicity
Rifapentine and isoniazid may cause hepatotoxicity (see section 4.8). Therefore, patients should be carefully monitored at monthly intervals. The use of isoniazid should be carefully monitored in patients with current chronic liver disease. Severe and sometimes fatal hepatitis associated with isoniazid therapy may occur and may develop even after many months of treatment.

Whenever possible, the use of isoniazid/rifapentine should be avoided in patients with preexisting hepatic impairment (ALT> 3 x ULN) due to the risk of liver toxicity. Patients should be strongly advised to restrict intake of alcoholic beverages while being treated with isoniazid/rifapentine.

Patient groups especially at risk for developing hepatitis include:

- age > 35 years,

- daily users of alcohol (see section 4.5),
- patients with active chronic liver disease
- intravenous drug users.

Furthermore, the following patients should be carefully monitored:

- patients with concurrent use of any chronically administered medication (see section 4.5),
- existence of peripheral neuropathy or conditions predisposing to neuropathy,
- pregnant patients
- HIV-positive patients.

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 paraesthesiae of the hands and feet, persistent fatigue and/or weakness of greater than 3 days duration and/or abdominal tenderness, especially of the right upper quadrant. If these symptoms appear or if signs suggestive of hepatic damage are detected, isoniazid/rifapentine should be discontinued promptly, since 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 isoniazid/rifapentine and periodically throughout treatment.

Increased liver function tests are common during therapy with isoniazid/rifapentine. 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 three months, even with continued therapy.

If abnormalities of liver function exceed three to five times the upper limit of normal, discontinuation of isoniazid/rifapentine should be strongly considered.

Rechallenge with component drugs after intercurrent hepatotoxicity, if deemed appropriate, should not be performed until symptoms and laboratory abnormalities have subsided. In case of rechallenge, isoniazid/rifapentine 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, isoniazid/rifapentine 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, isoniazid/rifapentine 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 predisposing conditions such as malnutrition,

alcoholism or diabetes. Concomitant pyridoxine administration largely reduces the risk of developing neuropathy. Therefore, pyridoxine should be co-administered routinely with isoniazid/rifapentine at doses of 10 mg per day to prevent and at doses of 300 - 300 mg daily to treat peripheral neuropathy.

Epilepsy and psychotic disorders: Isoniazid/rifapentine should be used with caution in patients with pre-existing 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 isoniazid/rifapentine. In case of severe haematological disturbances isoniazid/rifapentine must be discontinued.

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

Nephrotoxicity: Isoniazid/rifapentine 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.

Drug interactions: Rifapentine is a strong inducer of hepatic drug metabolism. Therefore, isoniazid/rifapentine 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 isoniazid/rifapentine. 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: Isoniazid/rifapentine may reduce the efficacy of corticosteroids in Addison's disease and induce an Addisonian crisis (see section 4.5).

Porphyria: Isoniazid/rifapentine should be used with caution in patients with porphyria, since the enzyme induction by rifapentine may cause symptoms.

Discolouration of body fluids: Isoniazid/rifapentine 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.

4.5 Interaction with other medicinal products and other forms of interaction

Rifapentine is a very potent inducer of the hepatic and intestinal cytochrome P-450 enzyme system, as well as glucuronidation and the P-glycoprotein transport system. Administration of rifapentine with drugs that undergo biotransformation through these metabolic pathways is likely to accelerate the elimination of co-administered drugs. These effects approach their maximum after about 10 days of treatment and gradually return to normal within 2 or more

weeks after discontinuation. This must be taken into account when co-treating with other drugs. To maintain optimum therapeutic blood levels, dosages of drugs metabolized by these enzymes may require adjustment when starting or stopping the administration of isoniazid/rifapentine. In addition, the magnitude of enzyme induction by rifapentine was dose and dosing frequency-dependent; less enzyme induction occurred when 600 mg oral doses of rifapentine were given once every 72 hours versus daily. *In vitro* and *in vivo* enzyme induction studies have suggested rifapentine induction potential may be less than rifampin but more potent than rifabutin.

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 isoniazid/rifapentine, 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.

Mainly due to rifapentine, isoniazid/rifapentine may interact with a very large number of other drugs, primarily by reducing the exposure to coadministered 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 isoniazid/rifapentine, the possibility of a drug-drug interaction should be considered. The following list of drug interactions with isoniazid/rifapentine 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**	No interaction is expected.	No dose adjustment is required.
Tenofovir alafenamide/ emtricitabine/ rifapentine	Interaction not studied. Co-administration of rifapentine, a P-gp inducer may decrease tenofovir alafenamide plasma concentrations, which may result in a loss of therapeutic effect and development of resistance.	Co-administration is not recommended.

Abacavir / rifapentine	Empirical data are lacking, but rifapentine may decrease abacavir exposure through induction of glucuronidation.	The efficacy of abacavir should be closely monitored in co-treatment.
Non-nucleoside analogues **Efavirenz** / rifapentine	No clinically meaningful effect on efavirenz clearance or mid-interval concentrations. Viral suppression was maintained during TB treatment.	When co-treating with isoniazid/rifapentine it may be considered to increase the efavirenz dose to 800 mg q.d.
Nevirapine / rifapentine	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 rifapentine but higher than rifabutin. Perform therapeutic drug monitoring for nevirapine and adjust dosage if needed.
Etravirine / rifapentine	Rifapentine significantly reduces exposure to etravirine.	Co-treatment of isoniazid/rifapentine and etravirine is contraindicated.
Rilpivirine/ rifapentine	Significant decrease in rilpivirine concentration	Co-treatment of isoniazid/rifapentine and rilpivirine is contraindicated.
Doravirine/ rifapentine	Significant decrease in doravirine concentration	Co-treatment of isoniazid/rifapentine and doravirine is contraindicated.
Protease inhibitors **Fosamprenavir /** rifapentine **Saquinavir** **Indinavir** **Ritonavir** **Lopinavir** **Atazanavir** **Tipranavir** **Darunavir** **Boceprevir**	Protease inhibitor exposure will be reduced to a 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.	Isoniazid/rifapentine must not be co-administered with HIV or HCV protease inhibitors (see section 4.3).
Others		
Raltegravir / rifapentine	Raltegravir AUC ↑ 71%	Once weekly rifapentine can be used with raltegravir without dose adjustment.
Dolutegravir / rifapentine	Dolutegravir AUC ↓29%	A dose adjustment of dolutegravir to 300 mg twice daily is recommended when co-administered with isoniazid/rifapentine in the absence of

		integrase class resistance. In the presence of integrase class resistance, this combination should be avoided.
Elvitegravir/cobicistat/rifapentine	Co-administration has not been studied. Rifapentine is a potent inducer of CYP4300 metabolism and may cause a 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)** **Simeprevir** **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.* *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)* *Isoniazid:* *Co-administration has not been studied.* *Patients with current chronic liver disease should be carefully monitored. Severe and sometimes fatal hepatitis associated with isoniazid therapy may develop even after many months of treatment.*	Co-administration of isoniazid/rifapentine with these antivirals is contraindicated (for further details see Summary of product characteristics of the drugs for therapy of HCV).
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 is necessary
Antibacterials/Antitubeculotics		
Clarithromycin / rifapentine	*Clarithromycin mean serum concentration* ↓. *14-OH clarithromycin levels are 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 is 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.
Sulfamethoxazole / rifapentine	*Sulfamethoxazole AUC* ↓	Interaction is 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.
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, clearance is likely 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 contradicted.
ANALGESICS, ANTIPYRETICS, NON-STEROIDAL ANTI-INFLAMMATORY DRUGS		
Morphine / rifapentine	Morphine AUC decreased with a 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.
Methadone / rifapentine	Methadone AUC ↓	Patients should be monitored for possible withdrawal effects, and the 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 isoniaid/rifapentine and acetaminophen (paracetamol) should be avoided.
ANTICONVULSANTS		
Carbamazepine / rifapentine / isoniazid	Rifapentine is expected to decrease the serum concentration of carbamazepine whereas isoniazid may increase	Co-administration of isoniaid/rifapentine and carbamazepine should be avoided.

	them. Neurological side effects and the risk of hepatotoxicity increase when co-treating with carbamazepine.	
Phenobarbital / rifapentine / isoniazid	Phenobarbital and rifapentine is 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 isoniazid/rifapentine 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 isoniazid/rifapentine 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, the lamotrigine dose should be increased as appropriate.
IMMUNOSUPPRESSIVES		
Cyclosporine / rifapentine	Substantially increased cyclosporine clearance when co-administered with rifapentine.	Co-administration should be avoided. If deemed necessary, plasma concentrations of cyclosporine should be monitored and doses adapted accordingly (3-5 fold increases in cyclosporine dose have been required).
Tacrolimus / rifapentine **Sirolimus** **Everolimus**	Tacrolimus AUC i.v. ↓ AUC p.o ↓ Sirolimus AUC ↓ Everolimus AUC ↓	Co-administration of isoniazid/rifapentine 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 and reduce dose after withdrawing rifapentine treatment.
Atenolol / rifapentine	Atenolol AUC ↓	No dose adjustment is required.
Verapamil / rifapentine	S-verapamil p.o CL/F ↑. With i.v. S-verapamil, CL ↑	Isoniazid/rifapentine 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 isoniazid/rifapentine with digoxin, the
Drugs by Therapeutic Area	**Interaction**	**Recommendations concerning co-administration**
		efficacy and plasma concentration of digoxin should be monitored. A dose increase may be required.
Lidocaine / rifapentine	Lidocaine CL i.v. ↑	No dose adjustment is 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 is expected.	No dose adjustment is 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 isoniazid/rifapentine is necessary.
PSYCHOTHERAPEUTIC MEDICINES		
Diazepam / rifapentine / isoniazid	Diazepam AUC ↓ Midazolam AUC↓	Co-treatment is not recommended. Benzodiazepine withdrawal may

Midazolam **Triazolam** **Alprazolam** **Nitrazepam**	Triazolam AUC ↓ Alprazolam AUC ↓ Reduced nitrazepam through concentrations, increased clearance.	occur in dependent individuals.
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.
Drugs by Therapeutic Area	**Interaction**	**Recommendations concerning co-administration**
Haloperidol / rifapentine **Clozapine**	Haloperidol clearance is substantially increased by rifapentine, theoretical considerations imply that same applies to clozapine.	If co-treatment of isoniazid/rifapentine 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 the 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 isoniazid/rifapentine with corticosteroids should be avoided. If deemed necessary, the clinical status of the patient should be carefully monitored, and corticosteroid doses are 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 is expected.	No dose adjustment is required.
Levothyroxine / rifapentine	Case reports indicate that rifapentine may decrease the effect of levothyroxine.	TSH levels should be monitored.

Ethinylestradiol / rifapentine	Ethinylestradiol AUC ↓	Co-administration with isoniazid/rifapentine 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 isoniazid/rifapentine 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 isoniazid/rifapentine should be monitored closely.
Drugs by Therapeutic Area	**Interaction**	**Recommendations concerning co-administration**
Disulfiram / isoniazid	Concurrent use of disulfiram together with isoniazid may result in an increased incidence of adverse effects on the central nervous system.	Dose reduction or discontinuation of disulfiram may be necessary during therapy with isoniazid/rifapentine.
Theophylline / Isoniazid / Rifapentine	Isoniazid may increase the serum concentration of theophylline and rifapentine may increase it. The effects of the 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 isoniazid/rifapentine with enflurane should be avoided.
Sildenafil / Rifapentine	Sildenafil AUC ↓	Co-treatment with isoniazid/rifapentine 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 the 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. There are no adequate and well-controlled studies of rifapentine use during pregnancy. In animal reproduction and developmental toxicity studies, rifapentine produced foetal harm and was teratogenic (see section 5.3). 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.

Isoniazid/rifapentine should only be used in pregnant women or women of childbearing potential if the potential benefit justifies the potential risk to the foetus.
It is considered that untreated tuberculosis represents a far greater hazard to a pregnant woman and her foetus than does treatment of the disease. Pyridoxine supplementation is recommended.

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 isoniazid/rifapentine, taking into account the importance of isoniazid/rifapentine to the mother and the benefits of breastfeeding.

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

Fertility
There is no data on the effects of isoniazid/rifapentine 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 the 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

isoniazid/rifapentine, 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 isoniazid/rifapentine:

SOC	≥ 1% occurrence	< 1% occurrence
Renal and Urinary	Pyuria, proteinuria, haematuria, urinary tract infections, urinary casts, cystitis	Urethral disorder, dysuria, pyelonephritis, urinary incontinence, urination disorder.
Metabolic & nutritional	Hyperuricaemia, hyperkalaemia, hypoglycaemia, increased non-protein nitrogen, hyperglycaemia, increased LDH, hyperphosphataemia	Weight decrease, BUN increased, diabetes mellitus, alkaline phosphatase increased, hypophosphataemia, hypercalcaemia, hypovolaemia, weight increase
Haematologic	Anaemia, lymphopenia, neutropenia, leukopenia, leukocytosis, neutrophilia, thrombocytosis, thrombocytopenia, polycythaemia, lymphadenopathy	Lymphocytosis, haematoma, purpura, anaemia hypochromic, anaemia normocytic, thrombosis
Dermatologic	Rash, sweating, pruritis, acne, skin disorder, maculopapular rash, eczema	Skin ulceration, urticaria, dry skin, furunculosis, skin discolouration, dermatitis fungal, nail disorder, alopecia, rash erythematous
Respiratory	Haemoptysis, coughing, upper respiratory tract infection, bronchitis, pharyngitis, epistaxis, pleuritis	Abnormal breath sounds, pneumothorax, pneumonia, pleural effusion, rhinitis, dyspnoea, pneumonitis, sinusitis, sputum
		increased, pulmonary fibrosis, upper respiratory congestion, asthma, chest x-ray abnormal, bronchospasm, laryngeal

		oedema, laryngitis, respiratory disorder
Gastrointestinal	Dyspepsia, vomiting, nausea, constipation, diarrhoea, haemorrhoids	Tooth disorder, gastroenteritis, gastritis, esophagitis, cheilitis, dry mouth, pancreatitis, proctitis, salivary gland enlargement, tenesmus, gastrointestinal disorder not specified
Infections	Influenza, herpes zoster	Fungal infections, parasitic infections, protozoa infection
Hepatic & biliary	Increased ALT, Increased AST	Bilirubinaemia, hepatomegaly, jaundice
Neurologic	Headache, dizziness, tremor	Somnolence, seizure not specified, dysphonia, hypoesthesia, torticollis, hypertonia, hyporeflexia, meningitis, migraine headache, stupor
Psychiatric	Anorexia, insomnia	Anxiety, confusion, drug abuse, aggressive reaction, agitation
Musculoskeletal	Arthralgia, arthritis, arthrosis, gout	Myalgia, myositis, bone fracture, muscle weakness, muscle spasm
Cardiovascular	Hypertension	Syncope, tachycardia, palpitation, hypotension orthostatic, pericarditis
Ophthalmologic	Conjunctivitis	eye pain, eye abnormality
Neoplasm		pulmonary carcinoma, carcinoma, lipoma
Vascular		Thrombophlebitis deep, vascular disorder, vasodilation
Special senses		Taste loss
Hearing & Vestibular		Ear disorder not specified, otitis media, earache, otitis externa, tympanic membrane perforation.
Reproductive		Abortion, penis disorder, vaginitis, vaginal haemorrhage, cervical smear test positive, leucorrhoea, male mastitis, prostatic disorder
General	Red-orange discolouration 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 tests abnormal, oedema legs, asthenia, oedema face, abscess, oedema peripheral, malaise

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Adverse Drug Reaction (ADR)/ Serious Adverse Event (SAE) electronic form linked to the MCAZ database using the following link: https://primaryreporting.who-umc.org/ZW.

4.9 Overdose

Symptoms
Anorexia, nausea, vomiting, gastrointestinal disturbances, fever, headache, dizziness, slurred speech, hallucinations and/or visual disturbances have occurred within 30 minutes to 3 hours after ingestion of isoniazid. 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.

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
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 the 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. There is no specific antidote. Treatment is symptomatic and supportive with special attention to monitoring/support of ventilation and correction of metabolic acidosis.

5. Pharmacological properties

5.1 Pharmacodynamic properties
Pharmacological classification: 7.3 Antituberculars.

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, rifapentine 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 isoniazid/rifapentine 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 (Cmax)	3737 ± 1205 ng/ml	8.85 ± 1.84 µg/ml
The 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 (Tmax) in hours	2.51 ± 0.83 h	5.42 ± 0.87 h

Pharmacokinetic properties of rifapentine and isoniazid

	Rifapentine	**Isoniazid**
Absorption		
Absolute bioavailability	90 − 95%	NA*
Oral bioavailability	> 90%	>80%
Food effect	No effect on the extent of absorption. Rate of absorption is reduced.	Reduced.
Distribution		
Volume of distribution (mean)	55 L	43 L
Plasma protein binding *in vitro*	60 − 90%	< 10%
Tissue distribution	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		
	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 the dose excreted in urine	17%	75 − 95%
% of dose excreted in faeces	70%	<10%
Pharmacokinetic linearity	Linear up to a 600 mg dose; at a higher dose less than a 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 a 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

*NA 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
The 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 Cmax were approximately 30% to 50% lower in these paediatric patients than those observed in healthy adults administered single oral doses of 600 mg and 900 mg.

In another pharmacokinetics study of rifapentine in healthy adolescents (age 12 to 15 years), 600 mg rifapentine was administered to those weighing ≥45 kg (n=10) and 450 mg was administered to those weighing <45 kg (n=2). The pharmacokinetics of rifapentine were similar to those observed in healthy adults.

Renal Impaired Patients
The pharmacokinetics of rifapentine have not been evaluated in renal-impaired patients. Although only about 17% of an administered dose is excreted via the kidneys, the clinical

significance of impaired renal function on the disposition of rifapentine and its 25 desacetyl metabolite is not known.

Hepatic Impaired Patients
Following oral administration of a single 600 mg dose of rifapentine to 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 is 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

Rifapentine
Hepatocellular carcinomas were increased in male mice that were treated orally with rifapentine for two years at or above doses of 5 mg/kg/day (equivalent to a human dose of 0.4 mg/kg/day or 1/5 of the recommended human dose, in the intensive phase, based on body surface area conversions). In a two-year rat study, there was an increase in nasal cavity adenomas in rats treated orally with rifapentine at 40 mg/kg/day (equivalent to a human dose of 6.5 mg/kg/day or 3 times the recommended human dose in the intensive phase, based on body surface area conversions).

Rifapentine was negative in the following genotoxicity tests: *in vitro* gene mutation assay in bacteria (Ames test); *in vitro* point mutation test in Aspergillus nidulans; *in vitro* gene conversion assay in Saccharomyces cerevisiae; host-mediated (mouse) gene conversion assay with Saccharomyces cerevisiae; *in vitro* Chinese hamster ovary cell/hypoxanthine-guanine phosphoribosyl 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-guanine phosphoribosyl 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).

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 resulted in reduced litter sizes and decreased postnatal growth, development, and cognitive ability in the offspring. Spermatogenesis impairment was observed in treated rats.

6. Pharmaceutical particulars

6.1 List of excipients
Tablet core
Microcrystalline cellulose
Croscarmellose sodium
Povidone
Sodium ascorbate
Hypromellose
Pregelatinized starch
Sodium starch glycolate
Calcium stearate
Iron oxide red
Isopropyl alcohol
Low-substituted hydroxypropyl cellulose

Tablet coat
Opadry brown 03F565224
Purified water

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
24 months.

6.4 Special precautions for storage
Store below 30°C.

6.5 Nature and contents of the container
Blister packs: The tablets are packed in Opa-Alu-PVC packs.
Pack sizes: 3 x 12 tablets.

Strip packs: The tablets are packed in an aluminium foil laminated with a 150g polyethylene film pack.
Pack sizes: 3 x 12 tablets.

Not all pack sizes may be marketed.

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. APPLICANT

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9. REGISTRATION DETAILS

Zimbabwe registration number: 2023/7.3/6528
Zimbabwe category for distribution: Prescription Preparations (P.P.)

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