SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the medicinal product
Rifampicin/isoniazid 75 mg/50 mg tablets

2. Qualitative and quantitative composition
Each tablet contains 75 mg of rifampicin and 50 mg of isoniazid.

Excipient with known effect
Each tablet also contains 0.15 mg of colour ponceau 4R (cochineal red A) and 2 mg of aspartame (see section 4.4).

For the full list of excipients, see section 6.1.

3. Pharmaceutical form
Tablet.

Brick red, flat-faced, bevelled-edged, mottled, circular, uncoated dispersible tablet, plain on both sides with a characteristic flavour.

Clinical particulars

4.1 Therapeutic indications
Rifampicin/isoniazid is indicated in children weighing less than 25 kg, for the prevention and treatment of tuberculosis caused by the bacterium *Mycobacterium tuberculosis*.

This product is intended for use in children. Safety information on use in adults is also provided.

4.2 Posology and method of administration
For oral use.

Posology
Rifampicin/isoniazid is taken once daily.

Children weighing less than 25 kg
The dose of isoniazid/rifampicin for prevention or treatment of tuberculosis (TB) is as follows:

Patient's weight	**Dose (isoniazid/rifampicin)**	**Number of rifampicin/isoniazid tablets**
4-7 kg	50mg / 75mg	1
8-11 kg	100mg / 150mg	2
12-15 kg	150mg / 225mg	3
16-24 kg	200mg / 300mg	4
> 25 kg	--*	--*

*For these patients, formulations containing more isoniazid/rifampicin should be used.

Rifampicin/isoniazid should not be used for intermittent treatment regimens.

For situations where discontinuation of therapy with one of the active agents of this medicine, or dose reduction is necessary, separate preparations of rifampicin and/or isoniazid should be used.

Children with a body weight of less than 4 kg
Rifampicin/isoniazid is not recommended for patients with a body weight below 4 kg, since appropriate dose adjustments cannot be made.

For these patients, other formulations containing less isoniazid/rifampicin should be used.

Renal impairment:
No dose adjustment in patients with renal impairment is generally recommended. However, patients should be closely monitored for signs of isoniazid toxicity, especially peripheral neuropathy. A dose reduction to 2/3 of the normal daily dose may be considered in slow acetylators with severe renal failure (ClCr <25 mL/min) or in those with signs of isoniazid toxicity. If so, separate preparations of rifampicin and isoniazid should be administered (see section 4.4).

Hepatic impairment:
Limited data indicate that the pharmacokinetics of rifampicin and isoniazid are altered in patients with hepatic impairment. Therefore, patients with hepatic impairment should be closely observed for signs of toxicity. Rifampicin/isoniazid must not be used in patients with severe liver disease (see section 4.3).

Advice on missed doses
In case of missing a dose, this dose should be taken as soon as possible, unless the next regular dose is scheduled within 6 hours. Otherwise, the missed dose should be skipped.

Method of administration
Rifampicin/isoniazid is administered orally and should be taken on an empty stomach (at least one hour prior to or two hours after a meal). If taken with food to improve gastrointestinal tolerance bioavailability may be impaired.

The tablets should be dispersed in drinking water before administration of the dose. Each tablet should be dispersed in a minimum of 10 mL water; the maximum volume of water recommended for dispersion of a dose is 50 mL (see section 6.6).

Renal impairment:
No dose adjustment in patients with renal impairment is generally recommended. However, patients should be closely monitored for signs of isoniazid toxicity, especially peripheral neuropathy. A dose reduction to 2/3 of the normal daily dose may be considered in slow acetylators with severe renal failure (ClCr <25 ml/min) or in those with signs of isoniazid toxicity. If so, separate preparations of rifampicin and isoniazid should be administered (see section 4.4).

Hepatic impairment:
Limited data indicate that the pharmacokinetics of rifampicin and isoniazid are altered in patients with hepatic impairment. Therefore, patients with hepatic impairment should be closely observed for signs of toxicity. Rifampicin/isoniazid must not be used in patients with severe liver disease (see section 4.3).

Missed doses
It is important that the patient takes the medicine regularly as prescribed. Missing doses can increase the risk of resistance to rifampicin/isoniazid and reduce its effectiveness.
In case a dose is missed, this dose should be taken as soon as possible. However, if the next regular dose is due within 6 hours, the missed dose should be omitted.

Method of administration
Rifampicin/isoniazid is administered orally and should be taken on an empty stomach (at least 1 hour prior to or 2 hours after a meal). Bioavailability may be impaired if rifampicin/isoniazid is taken with food to improve gastrointestinal tolerance.

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.

Co-administration of rifampicin/isoniazid with voriconazole, any HIV protease inhibitor, elvitegravir/cobicistat or any direct-acting antiviral for chronic Hepatitis C is contraindicated (see section 4.5).

4.4 Special warnings and precautions for use

Liver toxicity: Rifampicin and isoniazid may cause hepatotoxicity (see section 4.8).

Whenever possible, the use of rifampicin/isoniazid 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 their intake of alcoholic beverages while being treated with rifampicin/isoniazid. 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, rifampicin/isoniazid 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 rifampicin/isoniazid and periodically throughout treatment.

Increased liver function tests are common during therapy with rifampicin/isoniazid. A cholestatic pattern is usually caused by rifampicin, whereas elevated transaminases may be caused by rifampicin 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 rifampicin/isoniazid 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, rifampicin/isoniazid 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: Rifampicin 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 rifampicin hypersensitivity do appear (e.g., thrombocytopenia, purpura, haemolytic anaemia, dyspnoea, shock or acute renal failure). Then, rifampicin/isoniazid should immediately be discontinued. Such patients should not be rechallenged with rifampicin. If rifampicin therapy is temporarily discontinued, rifampicin should be restarted carefully at a reduced dose, and with close monitoring. In this situation, rifampicin/isoniazid 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 rifampicin/isoniazid at doses of 10 mg per day to prevent and at doses of 50 - 75 mg daily to treat peripheral neuropathy.

Epilepsy and psychotic disorders: Rifampicin/isoniazid should be used with caution in patients with pre-existing seizure disorders or a history of psychosis.

Haematological toxicity: Since rifampicin treatment has been associated with haemolytic anaemia, leucopenia and thrombocytopenia, full blood count should be monitored regularly throughout therapy with rifampicin/isoniazid. In case of severe haematological disturbances rifampicin/isoniazid 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: Rifampicin/isoniazid 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: Rifampicin is a strong inducer of hepatic drug metabolism. Therefore rifampicin/isoniazid 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 rifampicin/isoniazid. 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: Rifampicin/isoniazid may reduce the efficacy of corticosteroids in Addison's disease and induce an Addisonian crisis (see section 4.5).

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

Discolouration of body fluids: Rifampicin/isoniazid may cause a reddish-orange discolouration of body fluids such as urine, sputum and tears. This is due to rifampicin and does not require medical attention.

Laboratory monitoring: Full blood count and liver function should be monitored prior to and at regular intervals during treatment with rifampicin/isoniazid.

Excipients
This medicine contains **the colour ponceau 4R** (**cochineal red A**) which may cause allergic reactions.

This medicine also contains **aspartame**. Aspartame is a source of phenylalanine. Neither non-clinical nor clinical data are available to assess aspartame use in infants below 12 weeks of age.

It is important to consider the contribution of excipients from all the medicines that the patient is taking.

4.5 Interaction with other medicinal products and other forms of interaction

Rifampicin 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 rifampicin 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 cotreating with other drugs. To maintain optimum therapeutic blood levels, dosages of drugs metabolized by these enzymes may require adjustment when starting or stopping the concomitant administration of rifampicin/isoniazid.

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 rifampicin, as when using rifampicin/isoniazid, these effects are likely to be outweighed by the hepatic enzyme induction due to rifampicin. Insofar as it has been investigated, the net effect of rifampicin and isoniazid on drug clearance will be an increase due to rifampicin 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 rifampicin, rifampicin/isoniazid 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 rifampicin are available. However, clinically significant reductions in drug exposure may occur. Whenever co-prescribing any drug together with rifampicin/isoniazid, the possibility of a drug-drug interaction should be considered. The following list of drug interactions with rifampicin/isoniazid 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.

Use of isoniazid should be carefully monitored with 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.

Drugs by Therapeutic Area	**Interaction**	**Recommendations concerning co-administration**
INFECTION *Antiretrovirals*		
Nucleoside analogues **Zidovudine** / rifampicin	Zidovudine AUC □ 47%	The clinical significance of the lowered zidovudine exposure is unknown. Dose modifications of zidovudine in this situation have not been formally evaluated.
Stavudine **Didanosine** **Lamivudine** **Emtricitabine**	No interaction expected	No dose adjustment is required.
Tenofovir alafenamide/ emtricitabine/ rifampicin	Interaction not studied. Co-administration of rifampicin, a P-gp inducer, may decrease	Coadministration is not recommended.
Drugs by Therapeutic Area	**Interaction**	**Recommendations concerning co-administration**
	tenofovir alafenamide plasma concentrations, which may result in loss of therapeutic effect and development of resistance.	
Tenofovir disoproxil / rifampicin	Tenofovir AUC □ 13%	No dose adjustment is required.

Abacavir / rifampicin	Empirical data are lacking, but rifampicin may decrease abacavir exposure through induction of glucuronidation.	The efficacy of abacavir should be closely monitored in co-treatment.
Non-nucleoside analogues **Efavirenz** / rifampicin	Efavirenz AUC □ 26%	When co-treating with rifampicin/isoniazid, it may be considered to increase the efavirenz dose to 800 mg q.d.
Nevirapine / rifampicin	nevirapine: AUC □ 58%	Since neither appropriate doses of nevirapine, when given concomitantly with rifampicin, nor the safety of this combination have been established, concomitant use of rifampicin/isoniazid and nevirapine is not recommended.
Etravirine / rifampicin	Rifampicin is likely to significantly reduce exposure to etravirine.	Co-treatment of [TB360 trade name]and etravirine should be avoided.
Protease inhibitors **Fosamprenavir**/rifampicin **Saquinavir** **Indinavir** **Ritonavir** **Lopinavir** **Atazanavir** **Tipranavir** **Darunavir** **Boceprevir**	Protease inhibitor exposure will be reduced to a subtherapeutic level due to interaction with rifampicin. 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.	Rifampicin/isoniazid must not be co-administered with HIV or HCV protease inhibitors (see section 4.3).
Others		
Raltegravir / rifampicin	Raltegravir AUC ↓ 40%	Co-treatment should be avoided. If deemed necessary, consider an increase of the raltegravir dose to 600 mg b.i.d.
Dolutegravir / rifampicin	Dolutegravir AUC ↓ 54%	A dose adjustment of dolutegravir to 50 mg twice daily is recommended when coadministered with rifampicin/isoniazid in the absence of integrase class resistance. In the presence of
Drugs by Therapeutic Area	Interaction	Recommendations concerning co-administration

		integrase class resistance this combination should be avoided.
Elvitegravir/cobicistat/rifampicin	Coadministration has not been studied. Rifampicin is a potent inducer of CYP450 metabolism and may cause a significant decrease in the plasma concentration of elvitegravir and cobicistat resulting in a loss of therapeutic effect.	Coadministration is contraindicated.
Maraviroc / rifampicin	Maraviroc AUC ↓ 63%	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)/** Rifampicin Isoniazid	Rifampicin: Coadministration has not been studied but is expected to decrease concentrations of these HCV-antivirals due to induction of CYP3A4 by rifampicin and hence to reduce their therapeutic effect. Isoniazid: Coadministration 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.	Coadministration of rifampicin/isoniazid with these antivirals is contraindicated (for further details see Summary of product characteristics of the drugs for therapy of HCV).
Antifungals		
Ketoconazole / rifampicin	Ketoconazole AUC □ 80%	Co-administration should be avoided. If deemed necessary, a dose increase of ketoconazole may be required.

Fluconazole / rifampicin	Fluconazole AUC ↓ 23%	Monitor therapeutic effect. An increased dose of fluconazole may be required.
Drugs by Therapeutic Area	Interaction	Recommendations concerning co-administration
Itraconazole / rifampicin	Itraconazole AUC ↓ >64-88%	Co-administration should be avoided.
Voriconazole / rifampicin	Voriconazole AUC ↓ 96%	Co-administration is contraindicated. If necessary, rifabutin should be substituted for rifampicin.
Antibacterials/Antituberculotics		
Clarithromycin/rifampicin	Clarithromycin means a serum concentration ↓ of 85%. 14-OH clarithromycin levels are unchanged.	Co-administration should be avoided.
Chloramphenicol/rifampicin	Case reports indicate >60-80% reduction of chloramphenicol exposure.	Co-administration should be avoided.
Ciprofloxacin / rifampicin	No significant interaction	No dose adjustment is required.
Doxycyclin/rifampicin	Doxycyclin AUC ↓ 50-60%	If co-treatment is considered necessary, the dose of doxycycline should be doubled.
Metronidazole / rifampicin	Metronidazole AUC i.v.↓ 33%	The clinical relevance of the interaction is unknown. No dose adjustment is routinely recommended. Efficacy should be monitored.
Sulfamethoxazole/rifampicin	Sulfamethoxazole AUC ↓ 23%	Interaction is probably not clinically significant. Efficacy of sulfamethoxazole should be monitored.
Trimethoprim/rifampicin	Trimethoprim AUC ↓ 47%	A dose increase of trimethoprim may be required. Efficacy should be monitored.
Ethionamide/rifampicin		Rifampicin and ethionamide should not be co-administered, due to an increased risk of hepatotoxicity.
Antimalarials		
Chloroquine / rifampicin		Empirical data are not available. Since chloroquine undergoes polymorphic hepatic metabolism, lower levels are likely during

		rifampicin co-therapy. Co-administration should be avoided.
Atovaquone / rifampicin	Atovaquone AUC ↓ 50% Rifampicin AUC ↑ 30%	Co-administration should be avoided.
Mefloquine / rifampicin	Mefloquine AUC ↓ 68%	Co-administration should be avoided.
Amodiaquine / rifampicin	Empirical data are not available. Since amodiaquine undergoes hepatic metabolism, it is	Co-administration should be avoided.
Drugs by Therapeutic Area	Interaction	Recommendations concerning co-administration
	likely that clearance is increased when co-treating with rifampicin.	
Quinine/rifampicin	Quinine AUC ↓ □ 80%. 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 / rifampicin	Lumefantrine AUC ↓ 68%	Co-administration should be avoided.
Artemisinin and its derivatives / rifampicin	Artemether AUC ↓ 89% Dihydroarthemisinin AUC ↓ 85%	Co-administration should be avoided.
ANALGESICS, ANTIPYRETICS, NON- STEROIDAL ANTI-INFLAMMATORY DRUGS		
Morphine/rifampicin	Morphine AUC p.o ↓ 30%, loss of analgesic effect.	Co-treatment should be avoided. If deemed necessary, efficacy should be monitored and the dose may need to be increased.
Codeine/rifampicin	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/rifampicin	Methadone AUC ↓ 33-66%	Patients should be monitored for possible withdrawal effects, and the methadone dose increased as appropriate (up to 2-3 fold).
Acetaminophen (paracetamol) / rifampicin **/ isoniazid**	Rifampicin may increase the glucuronidation of paracetamol and decrease the efficacy. There may be an increased risk of	Co-administration of rifampicin/isoniazid and acetaminophen (paracetamol) should be avoided.

	hepatotoxicity on co-administration, but data are inconclusive. Concurrent use with isoniazid may increase hepatotoxicity.	
ANTICONVULSANTS		
Carbamazepine / rifampicin / isoniazid	Rifampicin is expected to decrease the serum concentration of	Co-administration of [TB360 trade name]and carbamazepine should be avoided.
Drugs by Therapeutic Area	Interaction	Recommendations concerning co-administration
	carbamazepine whereas isoniazid may increase them. Neurological side effects and the. risk of hepatotoxicity increases when co-treating with carbamazepine.	
Phenobarbital / rifampicin / isoniazid	Phenobarbital and rifampicin 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 rifampicin/isoniazid and phenobarbital should be undertaken with caution, including monitoring of clinical effects and, if possible, plasma drug concentrations.
Phenytoin / rifampicin isoniazid	Phenytoin AUC i.v. ↓ 42% Co-treatment with phenytoin and isoniazid may result in an increased risk of hepatotoxicity.	Co-treatment with phenytoin and rifampicin/isoniazid should be avoided.
Valproic acid / rifampicin	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, also plasma concentrations of valproic acid, should be carefully monitored.
Lamotrigine / rifampicin	Lamotrigine AUC ↓ 45%	Co-treatment should be avoided. If deemed necessary, the lamotrigine dose should be increased as

		appropriate.
IMMUNOSUPPRESSIVES		
Cyclosporine / rifampicin	Several studies and case reports have shown substantially increased cyclosporine clearance when co-administered with rifampicin.	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 / rifampicin **Sirolimus Everolimus**	Tacrolimus AUC i.v. ↓ 35%; AUC p.o ↓ 6870% Sirolimus AUC ↓ 82%	Co-administration of rifampicin/isoniazid and mTOR inhibitors should be avoided. If deemed necessary, plasma drug concentrations should be monitored, and the dose increased as appropriate.
Drugs by Therapeutic Area	Interaction	Recommendations concerning co-administration
	Everolimus AUC ↓ 63%	
CARDIOVASCULAR MEDICINES		
Warfarin/rifampicin /isoniazid	Warfarin AUC ↓ 85% Isoniazid may inhibit the hepatic metabolism of warfarin.	Monitor closely and adjust warfarin dose as needed and reduce dose after withdrawing rifampicin treatment.
Atenolol / rifampicin	Atenolol AUC ↓ 19%	No dose adjustment is required.
Verapamil / rifampicin	S-verapamil p.o CL/F ↑ 32-fold. With i.v. S-verapamil, CL ↑ 1.3-fold	rifampicin/isoniazid 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/rifampicin	AUC p.o ↓ 30%	When co-administering rifampicin/isoniazid with digoxin, the efficacy and plasma concentration of digoxin should be monitored. A dose increase may be required.
Lidocaine. / rifampicin	Lidocaine CLi.v. ↑ 15%	No dose adjustment required

Amlodipine / rifampicin	Amlodipine, like other calcium channel blockers, is metabolised by CYP3A; lower exposure is expected when co-treating with rifampicin.	Efficacy should be monitored.
Enalapril / rifampicin	No interaction expected	No dose adjustment is required.
Simvastatin / rifampicin	Simvastatin AUC ↓ 87% Simvastatin acid AUC ↓ 93%	Co-administration is not recommended.
Atorvastatin / rifampicin	Atorvastatin AUC ↓ 80%	Co-administration is not recommended
GASTROINTESTINAL MEDICINES		
Ranitidine / rifampicin	Ranitidine AUC ↓ 52%	Efficacy should be monitored, and ranitidine dose increased if necessary.
Antacids/isoniazid / rifampicin	Antacids may reduce the bioavailability of rifampicin 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 rifampicin/isoniazidis necessary.
PSYCHOTHERAPEUTIC MEDICINES		
Drugs by Therapeutic Area	Interaction	Recommendations concerning co-administration
Diazepam / rifampicin / isoniazid Midazolam Triazolam Alprazolam Nitrazepam	Diazepam AUC ↓ >70% Midazolam AUC ↓ 98% Triazolam AUC ↓ 95% Alprazolam AUC ↓ 88% Reduced nitrazepam through concentrations, increased clearance.	Co-treatment is not recommended. Benzodiazepine withdrawal may occur in independent individuals.
Zolpidem / rifampicin **Zopiclone /rifampicin**	Zolpidem AUC ↓73% Zopiclone AUC ↓82%	Co-administration should be avoided.
Chlorpromazine / rifampicin / isoniazid	Rifampicin 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 / rifampicin **Clozapine**	Haloperidol clearance is substantially increased by rifampicin, theoretical considerations imply that same applies to clozapine.	If co-treatment of rifampicin/isoniazid with haloperidol or clozapine is deemed necessary, monitor clinical efficacy. A dose increase may be required.
Amitriptyline / rifampicin **Nortriptyline**	Case reports (supported by theoretical considerations) suggest that rifampicin 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/rifampicin And other systemically administered corticosteroids	Prednisolone AUC ↓ 66% Also for other corticosteroids, exposure is likely to be substantially decreased when co-treating with rifampicin.	Co-administration of rifampicin/isoniazid 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 / rifampicin **Glimepiride Repaglinide**	Glibenclamide AUC ↓ 39% Glimepiride AUC ↓ 34% Repaglinide AUC ↓ 57%	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/rifampicin	Case reports indicate that rifampicin may decrease the effect of levothyroxine.	TSH levels should be monitored.
Drugs by Therapeutic Area	Interaction	Recommendations concerning co-administration
Ethinylestradiol / rifampicin	Ethinylestradiol AUC ↓ 66%	Co-administration with rifampicin/isoniazid may be associated with decreased contraceptive efficacy. Barrier- or other non-hormonal methods of contraception should be used.
Norethindrone/rifampicin	Norethindrone AUC ↓ 51%	Co-administration with rifampicin/isoniazid may be associated with decreased contraceptive efficacy. Barrier- or other non-hormonal methods of contraception should be

		used.
OTHERS		
Praziquantel / rifampicin	Praziquantel AUC ↓ 80-99%	Co-treatment with rifampicin/isoniazid should be avoided.
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 rifampicin/isoniazid.
Theophylline / Isoniazid / Rifampicin	Isoniazid may increase the serum concentration of theophylline and rifampicin may increase it. The effects of the combination is 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 rifampicin/isoniazid with enflurane should be avoided.

Interactions with food and drink:
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
At very high doses in animals, rifampicin has been shown to have teratogenic effects. There are no well-controlled studies with rifampicin in pregnant women. Although rifampicin has been reported to cross the placental barrier and appear in cord blood, the effect of rifampicin, alone or in combination with other antituberculosis drugs, on the human fetus is not known. Therefore, rifampicin/isoniazid should be used in pregnant women or women of childbearing potential only if the potential benefit justifies the potential risk to the foetus. When

rifampicin/isoniazid is administered during the last few weeks of pregnancy it may cause post-natal haemorrhages in the mother and infant for which treatment with Vitamin K1 may be indicated.
Breastfeeding
Rifampicin and isoniazid are excreted into the breast milk of lactating mothers. However, concentrations in breast milk are so low, that breast-feeding cannot be relied upon for adequate tuberculosis prophylaxis or therapy for nursing infants. No adverse effects on the baby have been reported.

Fertility
There is no data on the effects of rifampicin/isoniazid on human male or female fertility. Studies in rats with isoniazid have shown slight reductions in fertility. Animal studies indicate no effects of rifampicin on fertility (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 rifampicin/isoniazid, 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
The most important adverse reactions of rifampicin are hepatotoxicity, particularly cholestatic reactions, and skin reactions. Rifampicin may cause subclinical, unconjugated hyperbilirubinaemia or jaundice without hepatocellular damage, but occasionally causes hepatocellular injury. It can also potentiate the hepatotoxicity of the other anti-tuberculosis medications.

The most important adverse reactions of isoniazid are peripheral and central neurotoxic effects and hepatotoxicity. Severe and sometimes fatal hepatitis due to isoniazid therapy has been reported. The majority of cases have occurred within the first three months of therapy, but hepatotoxicity may also develop after a longer duration of treatment.

Adverse events considered at least possibly related to treatment are listed below by body system, organ class and frequency. They are not based on adequately sized randomized controlled trials but on published literature data, generated mostly during post-approval use. Therefore, often no frequency data can be given. Frequencies are defined as very common (≥1/10), common (≥1/100, <1/10), uncommon (≥1/1000, <1/100), rare (≥1/10,000, <1/1000), very rare (≤1/10,000), 'not known'.

Nervous system disorders
Very common: Peripheral neuropathy, usually preceded by paraesthesias of the feet and hands. The frequency depends on the dose and predisposing conditions such as malnutrition, alcoholism or diabetes. It has been reported in 3.5 to 17% of patients treated with isoniazid. Concomitant pyridoxine administration largely reduces this risk (see section 4.4),
Uncommon: headache, lethargy, ataxia, difficulties concentrating, dizziness, seizures, toxic encephalopathy,
Not known: tremor, vertigo, insomnia, hyperreflexia.

Psychiatric disorders
Uncommon: memory impairment, toxic psychosis,

Not known: confusion, disorientation, hallucination.

Gastrointestinal disorders
Common: Diarrhoea, abdominal pain, nausea, anorexia, vomiting, Rare: Erosive gastritis, pseudomembranous colitis,
Not known: dry mouth, flatulence, constipation.

Hepatobiliary disorders
Very common: Transient increases of serum transaminases,
Uncommon: Increases of serum bilirubin and alkaline phosphatases, hepatitis.

Renal and urinary disorders
Rare: acute renal failure, interstitial nephritis, Not known: urinary retention.

Metabolic and nutrition disorders
Very rare: aggravated porphyria,
Not known: hyperglycaemia, metabolic acidosis, pellagra, decreased appetite.

General disorders
Very common: Flushing,
Common: Reddish discolouration of body fluids and –secretions, such as urine, sputum, tears, saliva and sweat,
Not known: allergic reactions with skin manifestations, pruritus, fever, leucopenia, anaphylaxis, allergic pneumonitis, neutropenia, eosinophilia, vasculitis, lymphadenopathy, rheumatic syndrome, lupus–like syndrome, hypotension, shock.

Blood and lymphatic systems disorders
Not known: anaemia (haemolytic, sideroblastic, or aplastic), thrombocytopenia, leucopenia, neutropenia with eosinophilia, agranulocytosis.
Musculoskeletal disorders
Not known: Arthralgia, myalgia.

Skin and subcutaneous tissue disorders
Common: Erythema, exanthema, pruritus with or without rash, urticaria.
Rare: photosensitivity reaction, exfoliative dermatitis, pemphigoid reactions, purpura.
Not known: Lyell's Syndrome, Stevens-Johnson Syndrome, sweat discolouration.

Eye disorders
Common: Ocular redness, permanent discolouration of soft contact lenses,
Rare: Exudative conjunctivitis,
Not known: Optic atrophy or neuritis, tear discolouration.

Reproductive system and breast disorders
Common: Disturbances of the menstrual cycle.
Not known: Gynaecomastia

Vascular disorders
Not known: Shock, flushing, vasculitis

Investigations

Common: Blood bilirubin increased, aspartate aminotransferase increased, alanine aminotransferase increased
Not known: Blood pressure decreased, blood creatinine increased, hepatic enzyme increased

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 e-PV desktop applications (https://drive.google.com/file/d/16hwTz0587ZWtSWadbBAMwQPOD_KSExZP/view) or search for e-PV Mobile applications on the Google Play or Apple App Store.

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, rifampicin may cause a reddish-orange discolouration of the skin ('red man syndrome'). Further symptoms include facial oedema, pruritus, nausea, vomiting and abdominal tenderness. In adults, a total dose of 14 g has caused cardiopulmonary arrest.

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, rifampicin 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 rifampicin/isoniazid have been determined in healthy volunteers for isoniazid and rifampicin that are summarised in the following table:

	ISONIAZID	**RIFAMPICIN**
Characteristic	Test formulation (T) arithmetic mean ± SD (*)	Test formulation (T) arithmetic mean ± SD (*)
Maximum concentration (Cmax)	3070 ± 1154 (2821)	3139 ± 1210 (2929)
Area under the curve ($AUC_{0-\infty}$), a measure of the extent of absorption	8289 ± 4299	14835 ± 5285
Time to attain maximum concentration (Tmax) in hours	0.67 ± 0.57	1.52 ± 1.01

Pharmacokinetic properties of rifampicin and isoniazid

	Rifampicin	**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	CSF concentrations are in the same order of magnitude as the unbound concentrations in plasma. Concentrations in the liver, spleen, kidneys and lung tissue are higher than serum concentrations. Penetrates vaginal and cervical tissue and into cervicovaginal fluid. Passes the placenta; serum concentration in fetes is about 1/3 of that in the mother.	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		
General	Primarily hepatic, rapidly deacetylated.	Hepatic; primarily acetylated by N-acetyltransferase to N-acetylisoniazid
Active metabolite(s)	25-o-diacetyl rifampicin	Nicotinoyl-NAD adduct
Elimination		
Elimination half-life	3 − 5 hours Decreases to 2 −3 hours after repeated administration	1.2 hours: rapid acetylators 3.5 hours: Slow acetylators
Mean systemic clearance (Cl/F)	5.7 − 9 .0 L/hour	15.5 L/hour: slow NAT2 genotype 26.1 L/hour: rapid/intermediate NAT2 genotype
% of the dose excreted in urine	30%	75 − 95%
% of dose excreted in faeces	60 − 65%	<10%
Pharmacokinetic linearity	Non-linear	NA*
Drug interactions *(in vitro*)	Rifampicin induces hepatic enzymes	Isoniazid is a CYP450 inducer and inhibitor. Isoniazid is an arylamine n-n-acetyltransferase 2 substrate and inhibitor
Transporters	Solute carrier transporters (SLC) ATP Binding Cassette transporters (ABC) P-glycoprotein 1	NA*
Metabolizing enzymes	CYP450	CYP450: 2C19, 3A4

*NA information not available

Special populations

Rifampicin
The half-life of rifampicin has been reported to be longer in patients with liver impairment or biliary obstruction.

The half-life does not differ in patients with renal failure at doses not exceeding 600 mg daily, and consequently, no dosage adjustment is required. The half-life of rifampin at a dose of 720 mg daily has not been established in patients with renal failure. Following a single 900 mg oral dose of rifampin in patients with varying degrees of renal insufficiency, the mean half-life increased from 3.6 hours in healthy adults to 5.0, 7.3, and 11.0 hours in patients with glomerular filtration rates of 30 to 50 mL/min, less than 30 mL/min, and anuric patients, respectively.

In one study, paediatric patients 6 to 58 months old were given rifampin suspended in simple syrup or as dry powder mixed with applesauce at a dose of 10 mg/kg body weight. Peak serum concentrations of 10.7 ± 3.7 and 11.5 ± 5.1 mcg/mL were obtained 1 hour after preprandial ingestion of the drug suspension and the applesauce mixture, respectively. After the administration of either preparation, the t1/2 of rifampin averaged 2.9 hours. It should be noted that in other studies in paediatric populations, at doses of 10 mg/kg body weight, mean peak serum concentrations of 3.5 mcg/mL to 15 mcg/mL have been reported.

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

Rifampicin
After oral administration of 100 mg/kg body weight (bw) rifampicin for 6 months in rats no toxic effects were observed. After chronic administration of 200 mg/kg bw swelling and hydropic degeneration of the liver were observed. In monkeys, vomiting, anorexia and weight loss were observed at chronic doses of 105 mg/kg bw/day.

Because of only limited evidence available for the carcinogenicity of rifampicin in mice and the absence of epidemiological studies, no evaluation of the carcinogenicity of rifampicin in humans can be made. The available studies on mutagenicity indicate an absence of a mutagenic effect. Rifampicin concentrations in cord blood reach 12-33% of maternal blood concentrations.

Teratogenic effects were noted in rodents treated with high doses. 100 to 150 mg/kg bw daily in rodents have been reported to cause cleft palate and spina bifida. In rats, neither fertility nor peri- or postnatal development was impaired. Malformation and death in infants born to mothers exposed to rifampicin were reported at the same frequency as in the general population.

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
Microcrystalline cellulose
Crospovidone
Colloidal silicon dioxide
Pregelatinized starch
Ascorbic acid
Magnesium stearate
Colour ponceau 4R (Cochineal red A)
Saccharin sodium
Raspberry flavour
Strawberry flavour
Aspartame

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
24 months.

6.4 Special precautions for storage
Store below 30°C. Protect from light and moisture.

6.5 Nature and contents of the container
Strip packs: The tablets are packed in aluminium strip packs.
Pack sizes: 3 strips of 28's and 14 strips of 6's.

Blister packs: The tablets are packed in alu-alu blister packs.
Pack sizes: 3 x 28 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
Lupin Limited
Kalpataru Inspire
3rd Floor, Off Western Express Highway
Santacruz (East)
Mumbai - 400055
India

8. MANUFACTURER

Lupin Limited
A-28/1. MIDC area, Chikalthana
Aurangabad - 431210
India

9. REGISTRATION DETAILS

Zimbabwe registration number: 2023/7.3/6462
Zimbabwe category for distribution: Prescription Preparations (P.P.)

10. DATE OF REVISION OF THE TEXT

November 2023