SUMMARY OF PRODUCT CHARACTERISTICS

Rifampicin 75mg and Isoniazid 50 mg

1. NAME OF THE MEDICINAL PRODUCT

Rifampin and Isoniazid dispersible Tablets 75/50 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Rifampin and Isoniazid dispersible Tablets 75/50 mg
Each uncoated tablet contains:
Rifampin USP 75mg
Isoniazid USP.....50 mg

For the full list of excipients, refer to Section 6.1.

3. PHARMACEUTICAL FORM

Dispersible Tablets

Visual appearance: Brick red colored, flat faced beveled edged, mottled, circular uncoated tablet plain on both sides with characteristic flavor.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Rifampicin 75mg and Isoniazid 50 mg is indicated for the treatment of tuberculosis in children, caused by Mycobacterium tuberculosis.

4.2 Posology and method of administration

Oral use.

The following dosing table provides information on the number of daily tablets needed to reach the proper dosing, based on the child's weight:

Weight band	Numbers of tablets	
	nsive phase: RHZ 75/50/150*	Continuation phase: RH 75/50
4-7 kg	1	1

8-11 kg	2	2
12-15 kg	3	3
16-24 kg	4	4
25+ kg	Adult dosages recommended	

*Ethambutol should be added in the intensive phase for children with extensive disease or living in settings where the prevalence of HIV or of isoniazid resistance is high.

The following dosages of first-line anti-TB medicines should be used daily for the treatment of TB in children:

Isoniazid (H)	10 mg/kg (range 7–15 mg/kg)
Rifampicin (R)	15 mg/kg (range 10–20 mg/kg)
Pyrazinamide (Z)	35 mg/kg (range 30–40 mg/kg)
Ethambutol (E)	20 mg/kg (range 15–25 mg/kg)
As children approach a body weight of 25 kg, adult dosages can be used	

- First line treatment of drug-sensitive TB consists of a two-month intensive phase with isoniazid, rifampicin, pyrazinamide (and, depending on the setting and type of disease, ethambutol), followed by a continuation phase with isoniazid and rifampicin for at least four months.
- HIV-infected children with TB require antiretroviral therapy (ART) and co-trimoxazole preventive therapy (CPT) in addition to TB treatment.
- Isoniazid in the same dosage is recommended as preventive therapy over six months for children under the age of five as well as HIV-positive children of any age.

Rifampicin 75mg and Isoniazid 50 mg tablets should be taken on an empty stomach (at least one hour before or two hours after a meal). Taking with food (e.g. to improve gastrointestinal tolerance) reduces absorption.

If it is necessary to discontinue or reduce the dose of either isoniazid or rifampicin then single-component preparations should be used instead of Rifampicin 75mg and Isoniazid 50 mg tablets.

Renal impairment

Dose adjustment is generally not necessary in patients with renal impairment. However, patients should be closely monitored for signs of isoniazid toxicity, especially peripheral neuropathy. A dose reduction to two-thirds of the normal daily dose may be considered in slow acetylators with severe renal failure (creatinine clearance < 25 ml/minute) or in those with signs of isoniazid toxicity. If such cases, separate preparations of rifampicin and isoniazid tablets 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 75mg and Isoniazid 50 mg tablets must not be used in patients with severe liver disease (see section 4.3).

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients. Acute liver disease, icterus or severe liver impairment, Porphyria.

Co-administration of Rifampicin 75mg and Isoniazid 50 mg tablets with voriconazole or any HIV protease inhibitor is contraindicated (see section 4.5).

4.4 Special warnings and special precautions for use

Liver toxicity

Isoniazid and Rifampicin may cause hepatotoxicity (see section 4.8).

Whenever possible, the use of Rifampicin 75mg and Isoniazid 50 mg tablets should be avoided in patients with hepatic impairment (ALT greater than 3 times upper limit of normal) due to the risk of liver toxicity. Patients should be strongly advised to restrict intake of alcoholic beverages while being treated with rifampicin and isoniazid. Patient groups especially at risk for developing hepatitis include:

- patients with active chronic liver disease;

Furthermore, the following patients should be carefully monitored:

- patients taking long-term 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: unexplained anorexia, nausea, vomiting, dark urine, icterus, rash, persistent paraesthesia of the hands and feet, persistent fatigue or weakness lasting longer than 3 days, and abdominal tenderness especially of the right upper quadrant. If these symptoms appear or if signs suggestive of hepatic damage are detected, Rifampicin 75mg and Isoniazid 50 mg tablets should be discontinued promptly, because continued use may cause severe liver damage.

In addition to monthly symptom reviews, hepatic enzymes (specifically AST and ALT) should be measured before starting therapy with Rifampicin 75mg and Isoniazid 50 mg tablets and periodically throughout treatment.

Raised liver enzymes are common during therapy with rifampicin and

isoniazid. A cholestatic pattern is usually caused by rifampicin, whereas elevated transaminases are associated with rifampicin or isoniazid. These effects on liver enzymes are usually mild to moderate and will most commonly return to normal spontaneously within three months, even with continued therapy.

If the concentration of liver enzymes exceeds three to five times the upper limit of normal, discontinuation of Rifampicin 75mg and Isoniazid 50 mg tablets should be strongly considered.

If deemed appropriate, component drugs can be reintroduced after intercurrent hepatotoxicity but only after symptoms and laboratory abnormalities have subsided. In such cases of rechallenge, the component drugs should be given one by one and at gradually increasing doses or alternative drugs should be used; Rifampicin 75mg and Isoniazid 50 mg tablets should not 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 case of severe acute signs of rifampicin hypersensitivity (e.g. thrombocytopenia, purpura, haemolytic anaemia, dyspnoea, shock, or acute renal failure), Rifampicin 75mg and Isoniazid 50 mg tablets should immediately be discontinued. Such patients should not be treated with rifampicin again. If rifampicin is temporarily discontinued, rifampicin should be reintroduced carefully at a reduced dose and with close monitoring. In this situation, Rifampicin 75mg and Isoniazid 50 mg tablets 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

Peripheral neuropathy is the most common toxic effect of isoniazid (see section 4.8). The frequency depends on the dose and on predisposing conditions such as malnutrition, alcoholism or diabetes. Concomitant pyridoxine administration largely reduces the risk of developing neuropathy. Therefore, pyridoxine 10 mg daily should be given routinely with Rifampicin 75mg and Isoniazid 50 mg tablets.

Epilepsy and psychotic disorders

Rifampicin 75mg and Isoniazid 50 mg tablets should be used with caution in patients with seizure disorders or a history of psychosis.

Haematological toxicity

Since rifampicin is associated with haemolytic anaemia, leucopenia and thrombocytopenia, full blood count should be monitored regularly throughout therapy with Rifampicin 75mg and Isoniazid 50 mg tablets. In case of severe haematological disturbances Rifampicin 75mg and Isoniazid

50 mg tablets 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, pyridoxine (see above), in an adequate dose, should be given to avoid neurotoxicity.

Nephrotoxicity

Rifampicin 75mg and Isoniazid 50 mg tablets 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 75mg and Isoniazid 50 mg tablets may reduce efficacy of many therapeutic drugs, including antiretroviral agents, antiepileptic drugs, immunosuppressants and coumarin derivatives (see section 4.5).

Treatment with corticosteroids

Rifampicin 75mg and Isoniazid 50 mg tablets may reduce the efficacy of corticosteroids in Addison's disease and induce an Addisonian crisis (see section 4.5).

Discoloration of body fluids

Rifampicin in Rifampicin 75mg and Isoniazid 50 mg tablets may cause a reddish-orange discoloration of body fluids such as urine, sputum and tears. This does not require medical attention.

Laboratory monitoring

Full blood count and liver function testing is required before treatment with Rifampicin 75mg and Isoniazid 50 mg tablets and at regular intervals during treatment.

Excipients

Rifampicin 75mg and Isoniazid 50 mg tablets contains aspartame, which is a source of phenylalanine and may be harmful for people with phenylketonuria.

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 of glucuronidation and the P-glycoprotein transport system. Giving rifampicin with drugs that are biotransformed

through these metabolic pathways is likely to accelerate 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 metabolised by these enzymes may require adjustment when starting or stopping the concomitant administration of Rifampicin 75mg and Isoniazid 50 mg tablets.

In vitro, Isoniazid acts as an inhibitor of CYP2C19 and CYP3A4. Thus it may increase exposure to drugs eliminated mainly through either of these pathways. However, when co-treating with rifampicin, as when using Rifampicin 75mg and Isoniazid 50 mg tablets, these effects are likely to be outweighed by 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 75mg and Isoniazid 50 mg tablets may interact with a very large number of other drugs, primarily by reducing the exposure to co-administered agents, reducing their efficacy and increasing the risk of therapeutic failure. For many important therapeutic agents, no interaction data with Rifampicin are available. However, clinically significant reduction in drug exposure may occur. Whenever prescribing any drug with Rifampicin 75mg and Isoniazid 50 mg tablets, the possibility of a drug–drug interaction should be considered. The following list of drug interactions with Rifampicin 75mg and Isoniazid 50 mg tablets is not exhaustive, but is a selection of interactions of putative importance. Data on drug interactions is mainly derived from studies in adults. The scope of the table is largely based on the WHO Model List of Essential Medicines.

Drugs by Therapeutic Area	**Interaction**	**Recommendations on co-administration**
INFECTION *Antiretrovirals: nucleoside analogues*		
Zidovudine + rifampicin	Zidovudine AUC □ 47%	The clinical significance of the lowered zidovudine exposure is unknown. Dose modification of zidovudine in this situation has not been formally evaluated.

idanosine Emtricitabine Lamivudine Stavudine	No interaction expected	No dose adjustment required
Tenofovir disoproxil + rifampicin	Tenofovir AUC □ 13%	No dose adjustment required
Abacavir + rifampicin	Empirical data are lacking, but rifampicin may decrease abacavir exposure by inducing glucuronidation.	Efficacy of abacavir should be closely monitored in co-treatment
Antiretrovirals: non-nucleoside analogues		
Efavirenz + rifampicin	Efavirenz AUC □ 26%	When co-treating with Rifampicin 75mg and Isoniazid 50 mg tablets, consideration may be given to increasing the efavirenz dose (to 800 mg once daily in adults)
Drugs by Therapeutic Area	**Interaction**	**Recommendations on co-administration**
Nevirapine + rifampicin	Nevirapine: AUC □ 58%	Since neither the appropriate nevirapine dose when given with rifampicin, nor the safety of the combination has been established, concomitant use of Rifampicin 75mg and Isoniazid 50 mg tablets and nevirapine is not recommended
Etravirine + rifampicin	Rifampicin is likely to significantly reduce exposure to etravirine	Concomitant treatment of Rifampicin 75mg and Isoniazid 50 mg tablets with etravirine should be avoided
Antiretrovirals: protease inhibitors		
Fosamprenavir + rifampicin **Saquinavir Indinavir Ritonavir Nelfinavir Lopinavir Atazanavir Tipranavir Darunavir**	Protease inhibitor exposure will be reduced to sub-therapeutic level due to interaction with rifampicin. Attempts to compensate for this by increasing doses of the protease inhibitors, or an increase in ritonavir-boosting, have been ill-tolerated with a high rate of hepatotoxicity.	Rifampicin 75mg and Isoniazid 50 mg tablets must not be co-administered with protease inhibitors (see section 4.3).

Other antiretrovirals		
Raltegravir + rifampicin	Raltegravir AUC ↓ 40%	If co-treatment deemed necessary, increasing the raltegravir dose (to 600 mg twice daily in adults) should be considered
Maraviroc + rifampicin	Maraviroc AUC ↓ 63%	Co-treatment should be avoided. If deemed necessary, the maraviroc dose should be increased (to 600 mg twice daily in adults)
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%	Efficacy should be monitored. An increased dose of fluconazole may be required
Itraconazole + rifampicin	Itraconazole AUC ↓ > 64–88%	Co-administration should be avoided
Drugs by Therapeutic Area	**Interaction**	**Recommendations on co-administration**
Voriconazole + rifampicin	Voriconazole AUC ↓ 96%	Co-administration is contraindicated. If necessary, rifabutin should be substituted for rifampicin.
Antibacterials including antituberculosis antibacterials		
Clarithromycin + rifampicin	Clarithromycin mean serum concentration ↓ 85%. 14-OH clarithromycin levels 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 required
Doxycycline + rifampicin	Doxycycline 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 recommended. Efficacy should be monitored

Sulfamethoxazole + rifampicin	Sulfamethoxazole AUC □ 23%	Interaction 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 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
Drugs by Therapeutic Area	**Interaction**	**Recommendations on co-administration**
Amodiaquine + rifampicin	Empirical data are not available. Since amodiaquine undergoes hepatic metabolism, it is likely that clearance is increased when co-treating with rifampicin.	Co-administration should be avoided
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	Empirical data are not available. Since lumefantrine is metabolised by CYP3A, lower levels are expected with rifampicin co-treatment.	Co-administration should be avoided

Artemisinin and derivatives + rifampicin	Empirical data are not available. During co-treatment with rifampicin, lower levels of artemisinin and its derivatives may be expected.	Co-administration should be avoided
ANALGESICS, ANTIPYRETICS, NON-STEROIDAL ANTI-INFLAMMATORY DRUGS		
Morphine + rifampicin	Morphine AUC p.o □ 30%	If deemed necessary, efficacy should be monitored and the dose may need to be increased
Codeine + rifampicin	Plasma level of morphine, an active metabolite of codeine, is 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 methadone dose increased as appropriate
Paracetamol (acetaminophen) + rifampicin + isoniazid	Rifampicin may increase the glucuronidation of paracetamol and decrease its 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 Rifampicin 75mg and Isoniazid 50 mg tablets and paracetamol should be avoided
ANTICONVULSANTS		
Carbamazepine + rifampicin + isoniazid	Rifampicin is expected to decrease the serum concentration of carbamazepine. Isoniazid appears to have an increased risk of hepatotoxicity when co-treating with carbamazepine.	Co-administration of Rifampicin 75mg and Isoniazid 50 mg tablets and carbamazepine should be avoided
Drugs by Therapeutic Area	**Interaction**	**Recommendations on co-administration**
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 75mg and Isoniazid 50 mg tablets 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 increase risk of hepatotoxicity	Co-treatment with phenytoin and Rifampicin 75mg and Isoniazid 50 mg tablets should be avoided
Valproic acid + rifampicin	Interaction studies are lacking. Since valproic acid is eliminated through hepatic metabolism, including glucuronidation, reduced plasma level of valproic acid is 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, lamotrigine dose should be increased as appropriate.
IMMUNOSUPPRESSIVES		
Ciclosporin + rifampicin	Several studies and case reports have shown substantially increased ciclosporin clearance when co-administered with rifampicin	Co-administration should be avoided. If deemed necessary, plasma concentration of ciclosporin should be monitored and doses adapted accordingly (3–5 fold increases in ciclosporin dose have been required).
Tacrolimus + rifampicin	Tacrolimus AUC i.v. ↓ 35%; AUC p.o ↓ 70%	Co-administration of Rifampicin 75mg and Isoniazid 50 mg tablets and tacrolimus should be avoided. If deemed necessary, plasma drug concentrations of tacrolimus should be monitored, and the dose increased as appropriate
CARDIOVASCULAR MEDICINES		
Warfarin + rifampicin	Warfarin AUC ↓ 85%	Co-administration should be avoided
Atenolol + rifampicin	Atenolol AUC ↓ 19%	No dose adjustment required
Drugs by Therapeutic Area	**Interaction**	**Recommendations on co-administration**

Verapamil + rifampicin	S-verapamil p.o CL/F ↑ 32-fold. With i.v. S-verapamil, CL ↑ 1.3-fold	Rifampicin 75mg and Isoniazid 50 mg tablets and oral verapamil 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 75mg and Isoniazid 50 mg tablets 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 required
Simvastatin + rifampicin	Simvastatin AUC ↓ 87% Simvastatin acid AUC ↓ 93%	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 75mg and Isoniazid 50 mg tablets is necessary
PSYCHOTHERAPEUTIC MEDICINES		
Diazepam + rifampicin	Diazepam AUC □ > 70%	Co-treatment is not recommended. If deemed necessary, diazepam doses may need to be increased

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
Drugs by Therapeutic Area	**Interaction**	**Recommendations on co-administration**
Haloperidol + rifampicin	Haloperidol clearance is substantially increased by rifampicin	If co-treatment of Rifampicin 75mg and Isoniazid 50 mg tablets with haloperidol is deemed necessary, efficacy of haloperidol should be monitored. A dose increase may be required
Amitriptyline + rifampicin	Case reports (supported by theoretical considerations) suggest that rifampicin considerably increases amitriptyline clearance	Co-treatment should be avoided. If necessary, efficacy and, if possible, also plasma concentrations of amitriptyline should be monitored.
HORMONES; OTHER ENDOCRINE MEDICINES AND CONTRACEPTIVES		
Prednisolone and other systemically administered corticosteroids + rifampicin	Prednisolone AUC ↓ 66% Also for other corticosteroids, exposure is likely to be substantially decreased when co-treating with rifampicin.	Co-administration of Rifampicin 75mg and Isoniazid 50 mg tablets 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	Glibenclamide AUC ↓ 34%	Blood glucose levels should be closely monitored. A dose increase of glibenclamide may be required
Insulin		No interaction expected
Levothyroxine + rifampicin	Case reports indicate that rifampicin may decrease the effect of levothyroxine.	TSH levels should be monitored
Ethinylestradiol + rifampicin	Ethinylestradiol AUC ↓ 66%	Co-adminstration with Rifampicin 75mg and Isoniazid 50 mg tablets may be associated with decreased contraceptive efficacy. Barrier- or other non-hormonal methods of contraception should be used

Norethisterone + rifampicin	Norethisterone AUC ↓ 51%	Co-administration with Rifampicin 75mg and Isoniazid 50 mg tablets may be associated with decreased contraceptive efficacy. Barrier- or other non-hormonal methods of contraception should be used
OTHERS		

Drugs by Therapeutic Area	Interaction	Recommendations on co-administration
Praziquantel + rifampicin	Praziquantel AUC □ 80–99%	Co-treatment with Rifampicin 75mg and Isoniazid 50 mg tablets should be avoided
Disulfiram + isoniazid	Concurrent use of disulfiram together with isoniazid may result in increased adverse effects on the central nervous system	Dose reduction or discontinuation of disulfiram may be necessary during therapy with Rifampicin 75mg and Isoniazid 50 mg tablets
Enflurane + isoniazid	Isoniazid may increase the formation of the potentially nephrotoxic inorganic fluoride metabolite of enflurane	Coadministration of Rifampicin 75mg and Isoniazid 50 mg tablets with enflurane should be avoided.

Interactions with food and drink:

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

Cheese and fish (histamine- or tyramine-rich food): concurrent ingestion with isoniazid may lead to inhibition of mono- or diamine-oxidases by isoniazid, interfering with the metabolism of histamine and tyramine. 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:

Therapeutic levels of rifampicin have been shown to inhibit standard microbiological assays for serum folate and Vitamin B12. Thus alternative assay methods should be considered. Transient elevation of BSP and serum bilirubin has been reported. Rifampicin may impair biliary excretion of contrast media used for visualization of the gallbladder, due to competition for biliary excretion. Therefore, these tests should be performed before the morning dose of rifampicin.

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

4.6 Pregnancy and lactation

Pregnancy

As per the information reported in literature, no adverse effects of isoniazid on the human fetus has been reported. At very high doses in animals rifampicin has teratogenic effects. 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. Use of rifampicin in the third trimester has

been associated with postnatal haemorrhage in the mother and infant. Rifampicin 75mg and Isoniazid 50 mg tablets should be used in pregnancy only if the benefits are considered to outweigh the risks. If Rifampicin 75mg and Isoniazid 50 mg tablets is used in the last weeks of pregnancy, the mother and neonate should receive vitamin K supplements.

Breastfeeding

Isoniazid and rifampicin appear in breast milk. Hence, patients receiving rifampicin and isoniazid should not breast feed unless in the physician's judgement the potential benefit to the patient outweighs the potential risk to the infant. Also, breast-fed infants should be

monitored for possible signs of isoniazid and rifampicin toxicity. Administration of pyridoxine to the breast-feeding mother and infant may be considered.

4.7 Effects on ability to drive and use machines

Isoniazid is associated with vertigo, visual disorders and psychotic reactions (see section 4.8). Patients should be informed of these, and advised that if affected, they should not drive, operate machinery or take part in any activities where these symptoms may put either the patients or others at risk.

4.8 Undesirable effects

Rifampicin is well tolerated by most patients at currently recommended doses, although gastrointestinal intolerance can be unacceptably severe. Other adverse effects (skin rashes, fever, influenza-like syndrome and thrombocytopenia) are more likely to occur with intermittent administration. Temporary oliguria, dyspnoea and haemolytic anaemia have also been reported in patients taking the drug three times weekly. These reactions usually subside if the regimen is changed to one with daily dosage.

Moderate rises in serum concentrations of bilirubin and transaminases, which are common at the outset of treatment, are often transient and without clinical significance. However, dose-related hepatitis can occur, which is potentially fatal. It is consequently important not to exceed the maximum recommended daily dose of 10 mg/kg (600 mg).

Isoniazid is generally well tolerated at recommended doses. Systemic or cutaneous hypersensitivity reactions occasionally occur during the first weeks of treatment.

The risk of peripheral neuropathy is excluded if vulnerable patients receive daily supplements of pyridoxine. Other less common forms of neurological disturbance, including optic neuritis, toxic psychosis and generalized convulsions, can develop in susceptible individuals, particularly in the later stages of treatment, and occasionally necessitate the withdrawal of isoniazid.

Hepatitis is an uncommon but potentially serious reaction that can usually be averted by prompt withdrawal of treatment. More often, however, a sharp rise in serum concentrations of hepatic transaminases at the outset

of treatment is not of clinical significance. If the enzyme levels drop rapidly when dosage is suspended, they are unlikely to rise sharply again when treatment is resumed.

Rifampicin

The following CIOMS frequency rating is used, when applicable:

Very common ≥ 10 %; Common ≥ 1 and <10%; Uncommon ≥ 0.1 and <1%;

Rare ≥ 0.01 and <0.1%; Very rare <0.01%, Unknown (cannot be estimated from available data). Reactions occurring with either daily or intermittent dosage regimens include:

Infections and infestations

Unknown: Pseudomembranous colitis, influenza consisting of episodes of pyrexia, chills, headache, dizziness

Blood and lymphatic system disorders

Common: Thrombocytopenia with or without purpura, usually associated with intermittent therapy, but is reversible if drug is discontinued as soon as purpura occurs.

Uncommon: leukopenia

Unknown: Disseminated intravascular coagulation,eosinophilia, agranulocytosis, hemolytic anemia

Immune system disorders

Unknown: anaphylactic reaction

Endocrine disorders

Unknown: adrenal insufficiency in patients with compromised adrenal function have been observed.

Metabolism and nutritional disorders

Unknown: decreased appetite

Psychiatric disorders

Unknown: Psychotic disorder

Nervous system disorders

Unknown: Cerebral hemorrhage and fatalities have been reported when rifampicin administration has been continued or resumed after the appearance of purpura.

Eye disorders

Unknown: Tear discoloration

Vascular disorders

Unknown: Shock, flushing, vasculitis

Respiratory, thoracic and mediastinal disorders

Unknown: Dyspnoea, wheezing, sputum discoloured

Gastrointestinal disorders Common: Nausea, vomiting Uncommon: Diarrhea

Unknown: Gastrointestinal disorder, abdominal discomfort

Hepatobiliary disorders

Unknown: Hepatitis, hyperbilirubinaemia

Skin and subcutaneous tissue disorders

Unknown: Erythema multiforme including Stevens-Johnson syndrome and toxic epidermal necrolysis, Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) syndrome (See section 4.4), skin reaction, pruritus, rash pruritic, urticaria, dermatitis allergic, pemphigoid, sweat discoloration.

Musculoskeletal and connective tissue disorders

Unknown: Muscle weakness, myopathy, bone pain

Renal and urinary disorders

Unknown: acute kidney injury usually due to renal tubular necrosis or tubulointerstitial nephritis, chromaturia

Pregnancy, puerperium and perinatal conditions

Unknown: Post-partum haemorrhage, fetal-maternal haemorrhage

Reproductive system and breast disorders

Unknown: Menstrual disorder

Congenital, familial and genetic disorders

Unknown: Porphyria

General disorders and administration site conditions

Unknown: Edema

Investigations

Common: Blood bilirubin increased, aspartate aminotransferase increased, alanine aminotransferase increased

Unknown: Blood pressure decreased, blood creatinine increased, hepatic enzyme increased.

Isoniazid

Undesirable effects are listed by MedDRA System Organ Classes.

Assessment of undesirable effects is based on the following frequency groupings: Very common: ≥1/10

Common: ≥1/100 to <1/10 Uncommon: ≥1/1,000 to <1/100 Rare: ≥1/10,000 to <1/1,000 Very rare: <1/10,000

Frequency not known: cannot be estimated from the available data

The frequency of the reactions described below cannot be determined from the data available.

Blood and lymphatic system disorders

Frequency not known: Agranulocytosis, Aplastic anaemia, Haemolytic anaemia

Immune system disorders

Frequency unknown: Hypersensitivity reactions including various types of skin eruptions, fever, lymphadenopathy

Metabolism & Nutrition disorders

Frequency Unknown: Hyperglycaemia, metabolic acidosis, pellagra (nicotinic acid deficiency). Nicotinic acid deficiency may be related to an isoniazid-induced pyridoxine deficiency which affects the conversion of tryptophan to nicotinic acid.

Psychiatric disorders

Frequency Unknown: Psychotic disorder; euphoria. Although isoniazid usually has a mood elevating effect, mental disturbances, ranging from minor personality changes to major mental derangement have been reported; these are usually reversed on withdrawal of the drug.

Nervous system disorders

Frequency unknown: Peripheral neuropathy; seizure; Hyperreflexia may be troublesome with doses of 10mg per kg body weight, Optic neuritis

Eye disorders

Rare: Optic atrophy

Musculoskeletal and connective tissue disorders

Frequency unknown: Systemic lupus erythematosus, lupus-like syndrome

General disorders and administration site conditions

Frequency unknown: Pyrexia

Ear & labyrinth disorders

Frequency unknown: Deafness; tinnitus; vertigo. These have been reported in patients with end stage renal impairment

Vertigo may be troublesome with doses of 10mg per kg body weight

Respiratory, thoracic & mediastinal disorders

Frequency unknown: Interstitial lung disease

Gastrointestinal disorders

Frequency unknown: Nausea, vomiting, constipation, dry mouth, pancreatitis

Hepatobiliary disorders

Frequency unknown: Acute hepatic failure, Liver injury, Jaundice

The risk of these undesirable effects increases with age, especially over the age of 35; it may be serious and sometimes fatal with the development of necrosis.

Uncommon: Hepatitis

Skin and subcutaneous tissue disorders

Frequency unknown: Erythema multiforme, Stevens-Johnson syndrome.

Rare: Toxic epidermal necrolysis, eosinophilia systemic symptoms

Renal & urinary disorders

Frequency unknown: Dysuria

Reproductive system & breast disorders

Frequency unknown: Gynaecomastia

Vascular disorders

Frequency Unknown: Vasculitis

Investigations

Frequency unknown: Hepatic enzyme increased

Withdrawal symptoms, which may occur on the cessation of the treatment, include headache, insomnia, excessive dreaming, irritability and nervousness.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions: Healthcare professionals are asked to report any suspected adverse reactions via pharmacy and poisons board, Pharmacovigilance Electronic Reporting System (PvERS) https://pv.pharmacyboardkenya.org.

4.9 Overdose

Symptoms

Anorexia, nausea, vomiting, gastrointestinal disturbances, fever, headache, dizziness, slurred speech, hallucinations and 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 discoloration 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 injection on a gram-per-gram basis, equal to the isoniazid dose, if latter dose is unknown an initial dose of 5 g in adults or 80 mg/kg in children should be considered), intravenous diazepam (in case of seizures not responding to pyridoxine) and haemodialysis may be of value. There is no specific antidote. Treatment is symptomatic and supportive with special attention to monitoring and support of ventilation and correction of metabolic acidosis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action

In vitro, rifampicin is bactericidal against a wide range of organisms, including *Mycobacterium tuberculosis*. It inhibits 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 mycobacterial infection.

5.2 Pharmacokinetic Properties

Rifampicin

As per the information reported in literature, Rifampicin is readily absorbed from the gastrointestinal tract. Peak serum concentrations of the order of 10 µg /ml may occur about 2-4 hours after a dose of 10 mg/kg body weight on an empty stomach.

The pharmacokinetics (oral and intravenous) in children are similar to adults.

In normal subjects the biological half-life of rifampicin in serum averages about 3 hours after a 600 mg dose and increases to 5.1 hours after a 900 mg dose. With repeated administration, the half-life decreases and reaches average values of approximately 2-3 hours. At a dose of up to 600 mg/day, it does not differ in patients with renal failure and consequently, no dosage adjustment is required.

Rifampicin is rapidly eliminated in the bile and an enterophepatic circulation ensues. During this process, rifampicin undergoes progressive deacetylation, so that nearly all the drug in the bile is in this form in about 6 hours. This metabolite retains essentially complete antibacterial activity. Intestinal reabsorption is reduced by deacetylation and elimination is facilitated. Up to 30 % of a dose is excreted in the urine, with about half of this being unchanged drug. Absorption of rifampicin is reduced when the drug is ingested with food.

Rifampicin is widely distributed throughout the body. It is present in effective concentrations in many organs and body fluids, including cerebrospinal fluid. Rifampicin is about 80 % protein bound. Most of the unbound fraction is not ionized and therefore is diffused freely in tissues.

Isoniazid

As per the information reported in literature, Isoniazid (INH) is readily absorbed from the gastrointestinal tract. Peak concentrations are attained within 1-2 hours following oral administration. Protein binding is low.

It is widely distributed to all body fluids and tissues including cerebrospinal fluid, pleural and ascitic fluids and caseous tissues. Isoniazid crosses the placenta and appears in foetal blood when administered during pregnancy.

It also appears in the milk of nursing mothers.

The primary metabolic route is the acetylation of isoniazid to acetylisoniazid by N-acetyl transferase found in the liver and small intestine. Acetylisoniazid is then hydrolysed to isonicotinic acid and monoacetylhydrazine. Isonicotinic acid is conjugated with glycine to isonicotinyl glycine (isonicotinic acid) and monoacetylhydrazine is further acetylated to diacetyihydrazine. Some unacetylated isoniazid is also conjugated to hydrazones. The metabolites of isoniazid have no tuberculostatic activity and apart possibly from monoacetyihydrazine they are also less toxic.

The rate of acetylation of INH and monoacetylhydrazine is genetically determined and there is bimodal distribution of persons who acetylate them either slowly or rapidly. Rapid acetylators have been reported to acetylate LNH about 5 times more rapidly than slow acetylators. The half-life of isoniazid has been reported to be 0.5-1.5 hours in rapid acetylators and 2 or more hours in slow acetylators.

Elimination of isoniazid depends on the rate of acetylation. In patients with normal renal function approximately 70% of a dose appears in urine in 24 hours mostly as inactive metabolites; of this amount 93% of INH as excreted in urine may occur as the acetylated form in fast acetylators and 63% is slow acetylators, 7% of the 11411 excreted in the urine may occur as the free or conjugated form in fast acetylators and 37% in slow acetylators.

It is also excreted in the breast milk. Small quantities are excreted in saliva, sputum and faeces.

5.3 Preclinical safety data

Rifampicin

As per the information reported in literature, after oral administration of 100 mg/kg bodyweight rifampicin for 6 months in rats no toxic effects were observed. After chronic administration of 200 mg/kg 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/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 to 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. 100–150 mg/kg daily in rodents have been reported to cause cleft palate and spina bifida.

In rats neither fertility nor perinatal 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

As per the information reported in literature, non-clinical data reveal no special hazard for humans at recommended doses based on conventional studies of safety pharmacology, repeated-dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline Cellulose(Avicel PH101), Pregelatinized Starch (Starch 1500), Colloidal Silicon Dioxide (Aerosil 200), Saccharin Sodium, Crospovidone (Polyplasdone XL), Ascorbic Acid, Magnesium Stearate, Aspartame,Colour Ponceau 4R Supra LD, Dry Flavour Trusil Raspberry Special and Dry Flavour Trusil Strawberry select.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 months

6.4 Special precautions for storage

Do not store above 30°C. Protected from moisture.

6.5 Nature and contents of container Pack I: Aluminium Strip Pack

Description: 10 Tablets shall be packed per strip using Plain Strip

Aluminium foil 0.03 mm as a base material and Plain Strip 0.03 mm

Aluminium foil as a lidding material.

Pack II: Aluminium Blister Pack

Description: 5 Tablets shall be packed per Blister using Plain Aluminium foil 25 micron as a lidding material and Cold forming Alu-Alu base material.

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. Marketing authorization holder

Lupin Ltd

Kalpataru Inspire 3rd Floor,

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Mumbai 400055 India

8. Marketing authorization number
H2025/CTD9390/18070

9. Date of first authorization/renewal of the authorization
27/July/2025

10. Date of Revision of the Text

27/July/2025