1. Name of the Medicinal Product

Rifampicin 150 mg/ Isoniazid 75 mg Tablets

2. Qualitative and Quantitative Composition

Each film coated tablet contains:
Rifampicin BP ..... 150 mg
Isoniazid BP ..... 75 mg

3. Pharmaceutical Form

Film Coated Tablet

Brownish red coloured, circular, biconvex, film coated tablet having a breakline on one side.

4. Clinical Particulars

4.1 Therapeutic Indications

Rifampicin 150 mg/Isoniazid 75 mg Tablets is indicated for the continuation treatment phase of tuberculosis caused by Mycobacterium tuberculosis

4.2 Posology and Method of Administration

Oral use.

This product is not suitable for pediatric dosing.

Patient's body weight	**Dose**
30–39 kg	2 tablets as a single daily dose
40–54 kg	3 tablets as a single daily dose
55–70 kg	4 tablets as a single daily dose

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 dose should be skipped.

Rifampicin 150 mg/Isoniazid 75 mg Tablets should not be used for intermittent treatment regimens.

Rifampicin 150 mg/Isoniazid 75 mg Tablets 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.

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.

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.

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 150 mg/Isoniazid 75 mg Tablets must not be used in patients with severe liver disease.

Children and adolescents / patients with a body weight < 30 kg
Rifampicin 150 mg/Isoniazid 75 mg Tablets is not recommended for children, adolescents and adult patients with a body weight below 30 kg, since appropriate dose adjustments cannot be made.

For these patients other formulations are available.

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients.

Acute liver disease, icterus or severe liver impairment.

Co-administration of Rifampicin 150 mg/Isoniazid 75 mg Tablets with voriconazole or any HIV or HCV protease inhibitor is contraindicated

4.4 Special Warnings and Precautions for Use

Liver toxicity: Rifampicin and/or isoniazid may cause hepatotoxicity.

Whenever possible, the use of Rifampicin 150 mg/Isoniazid 75 mg Tablets should be avoided in patients with preexisting hepatic impairment (ALT> 3 x ULN) due to the risk of liver toxicity. Patients should be strongly advised to restrict intake of alcoholic beverages while being treated with Rifampicin 150 mg/Isoniazid 75 mg Tablets.

Patient groups especially at risk for developing hepatitis include:
- age > 35 years,
- daily users of alcohol (patients should be strongly advised to restrict intake of alcoholic beverages),
- 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,
- existence of peripheral neuropathy or conditions predisposing to neuropathy,
- pregnant patients
- HIV positive patients.

All 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 paraesthesias 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 150 mg/Isoniazid 75 mg Tablets 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 150 mg/Isoniazid 75 mg Tablets and periodically throughout treatment.

Increased liver function tests are common during therapy with Rifampicin 150 mg/Isoniazid 75 mg Tablets. 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 in the presence of continued therapy.

If abnormalities of liver function exceed three to five times the upper limit of normal, discontinuation of Rifampicin 150 mg/Isoniazid 75 mg Tablets 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 150 mg/Isoniazid 75 mg Tablets should not be used, as the component drugs should be given one by one and at gradually increasing doses, or alternative agents used.

Hypersensitivity:
Rifampicin may cause a hypersensitivity syndrome including 'flu-like' symptoms and/or organ manifestations. The risk is higher in intermittent therapy or if treatment is resumed after discontinuation. If severe, acute signs of rifampicin hypersensitivity should appear (e.g. thrombocytopenia, purpura, haemolytic anemia, dyspnoea, shock or acute renal failure), Rifampicin 150 mg/Isoniazid 75 mg Tablets 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 150 mg/Isoniazid 75 mg Tablets should not be used.

Cross-sensitivity:
Patients hypersensitive to ethionamide, 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. 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 should be co-administered routinely with Rifampicin 150 mg/Isoniazid 75 mg Tablets, at doses of 10 mg per day.

Epilepsy and psychotic disorders: Rifampicin 150 mg/Isoniazid 75 mg Tablets 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, leukopenia and thrombocytopenia, full blood count should be monitored regularly throughout therapy with Rifampicin 150 mg/Isoniazid 75 mg Tablets. In case of severe haematological disturbances Rifampicin 150 mg/Isoniazid 75 mg Tablets must be discontinued.

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

Nephrotoxicity:
Rifampicin 150 mg/Isoniazid 75 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 150 mg/Isoniazid 75 mg Tablets may reduce exposure and efficacy of many therapeutic drugs, including antiretroviral agents, antiepileptic drugs, immunosuppressants and coumarin derivatives.

Contraception:
Oral contraceptives do not provide adequate protection against conception when co-administered with Rifampicin 150 mg/Isoniazid 75 mg Tablets. This probably also pertains to other formulations of hormonal contraceptives (e.g. patches, transdermal implants). Barrier- or other non-hormonal methods of contraception should be used.

Treatment with corticosteroids: Rifampicin 150 mg/Isoniazid 75 mg Tablets may reduce the efficacy of corticosteroids in Addison's disease and induce an Addisonian crisis.

Porphyria:
Rifampicin 150 mg/Isoniazid 75 mg Tablets should be used with caution in patients with porphyria, since the enzyme induction by rifampicin may cause symptoms.

Discoloration of body fluids:
Rifampicin 150 mg/Isoniazid 75 mg Tablets may cause a reddish-orange discoloration 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, liver function and serum uric acid should be monitored prior to and at regular intervals during treatment with Rifampicin 150 mg/Isoniazid 75 mg Tablets.

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. Administration of rifampicin with drugs that undergo biotransformation through these metabolic pathways is likely to accelerate elimination of coadministered 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 150 mg/Isoniazid 75 mg Tablets.

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 150 mg/Isoniazid 75 mg Tablets, 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 150 mg/Isoniazid 75 mg Tablets 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 150 mg/Isoniazid 75 mg Tablets, the possibility of a drug-drug interaction should be considered. The following list of drug interactions with Rifampicin 150 mg/Isoniazid 75 mg Tablets is not exhaustive, but is a selection of interactions of putative importance. The scope of the table is largely based on the WHO Essential Medicines List.

Drugs by Therapeutic Area	**Interaction**	**Recommendations on 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
Tenofovir disoproxil fumarate + Rifampicin	Tenofovir AUC ↓ 13%	No dose adjustment required.

Abacavir + Rifampicin	Empirical data are lacking, but rifampicin may decrease abacavir exposure through induction of 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 150 mg/Isoniazid 75 mg Tablets, consider increase of the efavirenz dose to 800 mg daily.
Nevirapine + Rifampicin	Nevirapine AUC ↓ 58%	Concomitant use of Rifampicin 150 mg/Isoniazid 75 mg Tablets and nevirapine is not recommended because neither appropriate doses of nevirapine nor the safety of this combination have been established.
Etravirine + Rifampicin	Rifampicin is likely to significantly reduce exposure to etravirine.	Co-treatment of Rifampicin 150 mg/Isoniazid 75 mg Tablets and etravirine should be avoided.
Antiretrovirals: protease inhibitors		
Fosamprenavir + Rifampicin Saquinavir Indinavir Ritonavir Nelfinavir Lopinavir Atanzanavir Tipranavir Darunavir	Protease inhibitor exposure will be reduced to subtherapeutic level, due to interaction with rifampicin. Attempts to increase doses or to increase ritonavir-boosting are ill-tolerated with a high rate of hepatotoxicity.	Rifampicin 150 mg/Isoniazid 75 mg Tablets should not be co-administered with HIV protease inhibitors.
Antiretrovirals: others		
Raltegravir + Rifampicin	Raltegravir AUC ↓ 40%	Avoid co-treatment. If deemed necessary, consider an increase of the raltegravir dose to 800 mg twice daily
Maraviroc + Rifampicin	Maraviroc AUC ↓ 63%	Avoid co-treatment. If deemed necessary, the maraviroc dose should be increased to 600 mg twice daily.
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.
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 and antituberculotics		
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 intravenous AUC ↓ 33%	The clinical relevance of the interaction is unknown. No dose adjustment is recommended. Monitor efficacy.
Sulfamethoxazole + Rifampicin	Sulfamethoxazole AUC ↓ 23%	Interaction probably not clinically significant. Monitor efficacy.
Trimethoprim + Rifampicin	Trimethoprim AUC ↓ 47%	Monitor efficacy. A dose increase of trimethoprim may be required.
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.	Avoid co-administration.
Atovaquone + Rifampicin	Atovaquone AUC ↓ 50% Rifampicin AUC ↑ 30%	Avoid co-administration.

Mefloquine + Rifampicin	Mefloquine AUC ↓ 68%	Avoid 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.	Avoid co-administration.
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.	Avoid co-administration.
Artemisinin and derivatives + Rifampicin	Empirical data are not available. During co-treatment with rifampicin, lower levels of arteminisin and its derivatives may be expected.	Avoid co-administration.
ANALGESICS, ANTIPYRETICS, NON-STEROIDAL ANTI-INFLAMMATORY DRUGS		
Morphine + Rifampicin	Morphine oral AUC ↓ 30%	Co-treatment should be avoided. If necessary, monitor clinical effects and increase dose if necessary.
Codeine + Rifampicin	Plasma levels of morphine, the active moiety of codeine, are likely to be substantially reduced.	Monitor clinical effect and increase codeine dose if necessary.
Methadone + Rifampicin	Methadone AUC ↓ 33–66%	Monitor for possible withdrawal effects, and increase methadone dose as appropriate.
Paracetamol + Rifampicin	Rifampicin may increase paracetamol glucuronidation and decrease its effect. Co-administration may increase the risk of hepatotoxicity, but data are inconclusive.	Co-administration of Rifampicin 150 mg/Isoniazid 75 mg Tablets and paracetamol should be avoided.

Paracetamol + Isoniazid		Concurrent use with isoniazid may increase hepatotoxicity
ANTICONVULSANTS		
Carbamazepine + Rifampicin	Rifampicin is expected to decrease the serum concentration of carbamazepine.	Co-administration of Rifampicin 150 mg/Isoniazid 75 mg Tablets and carbamazepine should be avoided.
Carbamazepine + Isoniazid		The risk of hepatotoxicity with isoniazid appears to be increased when co-treating with carbamazepine.
Phenobarbital + Rifampicin	Phenobarbital and rifampicin are both strong hepatic enzyme inducers, and each drug may lower the plasma concentrations of the other.	Co-administration of Rifampicin 150 mg/Isoniazid 75 mg Tablets and phenobarbital should be undertaken with caution, including monitoring of clinical effects and, if possible, plasma drug concentrations.
Phenobarbital + Isoniazid		Co-treatment with phenobarbital and isoniazid may increase the risk of hepatotoxicity.
Phenytoin + Rifampicin	Phenytoin intravenous AUC ↓ 42%	Co-treatment with Rifampicin 150 mg/Isoniazid 75 mg Tablets USP and phenytoin should be avoided.
Phenytoin + Isoniazid	Co-treatment with phenytoin and isoniazid may result in an increased risk of hepatotoxicity.	
Valproic acid + Rifampicin	Though interaction studies are lacking, 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 necessary, therapeutic efficacy and, if possible, plasma concentrations of valproic acid, should be carefully monitored.
Lamotrigine + Rifampicin	Lamotrigine AUC ↓ 45%	Co-treatment should be avoided. If deemed necessary, increase lamotrigine dose as appropriate.

IMMUNOSUPPRESSANTS		
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 drug concentrations of ciclosporin should be monitored and doses adapted accordingly (3–5 fold increases in ciclosporin dose have been required).
Tacrolimus + Rifampicin	Tacrolimus intravenous AUC ↓ 35%; oral ↓ 70%	Co-administration of Rifampicin 150 mg/Isoniazid 75 mg Tablets and tacrolimus should be avoided. If deemed necessary, plasma drug concentration of tacrolimus should be monitored, and the dose increased as appropriate.
CARDIOVASCULAR MEDICINES		
Warfarin + Rifampicin + Isoniazid	Warfarin AUC ↓ 85% Increased anticoagulant response to warfarin has been reported when co-administered with isoniazid	Co-administration should be avoided.
Atenolol + Rifampicin	Atenolol AUC ↓ 19%	No dose adjustment required.
Verapamil + Rifampicin	S-verapamil oral CL/F ↑ 32-fold. With intreavenous S-verapamil, CL ↑ 1.3-fold	Rifampicin 150 mg/Isoniazid 75 mg Tablets should not be co-administered with verapamil given by mouth. If verapamil is given intravenously, the therapeutic effect should be monitored carefully; dose adjustment may be required.
Digoxin + Rifampicin	Digoxin oral AUC ↓ 30%	When co-administering Rifampicin 150 mg/Isoniazid 75 mg Tablets with digoxin, the clinical efficacy and plasma concentration of digoxin should be monitored. A dose increase may be required.
Lidocaine + Rifampicin	Lidocaine intravenous CL ↑ 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	Monitor efficacy.
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%	Monitor for ranitidine efficacy, and increase dose 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 of this is unknown. Acid-suppressing drugs or antacids that do not contain aluminium hydroxide should be used if co- treatment with Rifampicin 150 mg/Isoniazid 75 mg Tablets is necessary.
PSYCHOTHERAPEUTIC MEDICINES		
Diazepam + Rifampicin 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. If necessary. Benzodiazepine withdrawl may occur in dependent 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, chlorpromazine may impair the metabolism of isoniazid.	Co-administration should be avoided. If considered necessary, patients should be monitored carefully for isoniazid toxicity.
Haloperidol + Rifampicin	Haloperidol clearance is substantially increased by rifampicin.	If co-treatment with haloperidol is deemed necessary, monitor the clinical efficacy of haloperidol. A dose increase may be required.
Amitriptyline + Rifampicin Nortriptyline	Case reports (supported by theoretical considerations) suggest that rifampicin considerably increases amitriptyline clearance.	Co-treatment should be avoided. If necessary, monitor efficacy and, if possible, plasma concentrations of amitriptyline.

HORMONES, OTHER ENDOCRINE MEDICINES AND CONTRACEPTIVES		
Prednisolone and other systemically administered corticosteroids + Rifampicin	Prednisolone AUC ↓ 66% Prednisolone exposure is likely to be substantially decreased when co-treating with rifampicin. This applies to other corticosteroids as well.	Co-administration of Rifampicin 150 mg/Isoniazid 75 mg Tablets with corticosteroids should be avoided. If necessary, the clinical status of the patient should be carefully monitored, and corticosteroid doses adjusted as needed.
Glibenclamide + Rifampicin	Glibenclamide AUC ↓ 34%	Monitor blood glucose concentration closely. 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.	Thyrotropin (thyroid stimulating hormone, TSH) levels should be monitored.
Ethinylestradiol + Rifampicin	Ethinylestradiol AUC ↓ 66%	Co-adminstration with Rifampicin 150 mg/Isoniazid 75 mg Tablets may be associated with decreased contraceptive effect. Barrier or other non-hormonal methods of contraception should be used.
Norethisterone + Rifampicin	Norethisterone AUC ↓ 51%	Co-adminstration with Rifampicin 150 mg/Isoniazid 75 mg Tablets may be associated with decreased contraceptive effect. Barrier or other non-hormonal methods of contraception should be used.

OTHERS		
Praziquantel + Rifampicin	Praziquantel AUC ↓ 80–99%	Co-treatment with Rifampicin 150 mg/Isoniazid 75 mg Tablets should be avoided.
Disulfiram + Isoniazid	Concurrent use of disulfiram and isoniazid may increase the incidence of effects on the central nervous system and concurrent use with ethambutol may increased risk for ocular toxicity.	Dose reduction or discontinuation of disulfiram may be necessary during therapy with Rifampicin 150 mg/Isoniazid 75 mg Tablets.
Theophylline + Rifampicin/Isoniazid	Isoniazid may increase the serum concentration of theophylline and rifampicin may increase it. The effects of combination are unknown.	Theophylline dose adjustments may be needed.
Enflurane + Isoniazid	Isoniazid may increase the formation of the potentially nephrotoxic inorganic fluoride metabolite of enflurane	Avoid co-administration of Rifampicin 150 mg/Isoniazid 75 mg Tablets with enflurane.

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.

Cheese and fish (histamine- or tyramine-rich food): isoniazid may inhibit monoamine oxidase and diamine oxidase thus interfering with the metabolism of histamine and tyramine. This may result in redness or itching of the skin, feeling hot, rapid or pounding heartbeat, sweating, chills or clammy feeling, headache, and 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 Pregnancy and Lactation

Pregnancy
No adverse effects of isoniazid on the human foetus have been reported. At very high doses in animals rifampicin has been shown to have 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 foetus is not known. Use of rifampicin in the third trimester has been associated with postnatal haemorrhages in the mother and infant. Rifampicin 150 mg/Isoniazid 75 mg Tablets should be used in pregnancy only if the benefits are considered to outweigh the risks. If Rifampicin 150 mg/Isoniazid 75 mg Tablets is used in the last weeks of pregnancy, the mother and neonate should be substituted with vitamin K.

Lactation
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 in the baby have been reported.

4.7 Effects on Ability to Drive and Use Machines

No studies on the effects on the ability to drive and use machines have been performed. Nevertheless, the clinical status of the patient and the adverse reaction profile of Rifampicin 150 mg/Isoniazid 75 mg Tablets 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 on 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.

Uncommon : headache, lethargia, ataxia, difficulties concentrating, dizziness, seizures, toxic encephalopathy.
Not known : tremor, vertigo, hyperreflexia, insomnia.

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 : metallic taste, 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 common : hyperuricaemia, especially in patients with gout.
Very rare : aggravated porphyria.
Not known : hyperglycaemia, metabolic acidosis, pellagra.

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, anaphylaxia, 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, Stephens Johnson Syndrome.

Eye disorders:
Common : Ocular redness. Permanent discolouration of soft contact lenses.
Visual disturbances due to optic neuritis (retrobulbar neuritis).
Rare : Exudative conjunctivitis.
Not known : Optic atrophy or neuritis

Reproductive system and breast disorders
Common : Disturbances of the menstrual cycle.

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 discoloration of the skin ('red man syndrome'). Further symptoms include facial edema, 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 latter dose is unknown an initial dose of 5 g in adults or 80 mg/kg BW in children should be considered), intravenous diazepam (in case of seizures not responding to pyridoxine) and haemodialysis may be of value. Further treatment should be supportive, with special attention to monitoring/support of ventilation and correction of metabolic acidosis. There is no specific antidote.

5. Pharmacological Properties

5.1 Pharmacodynamic Properties

Pharmacotherapeutic group **:** Antimycobacterial, 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*. 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 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

Rifampicin

Absorption:
Rifampicin is rapidly absorbed from the gastrointestinal tract. Its bioavailability is 90-95% in adults, but may be lower in children. Concomitant intake of food delays absorption and reduces the peak concentration, but does not decrease bioavailability.

Following single dose administration of Rifampicin 150 mg/Isoniazid 75 mg Tablets in healthy volunteers, used to compare the bioavailability of this product with the same dose of the individual reference formulations, the mean (± SD) rifampicin Cmax value was 1.79 µg/ml (± 0.55), and the corresponding value for AUC was 9.10 µg.h/ml (± 3.89). The mean (± SD) rifampicin tmax value was 2.33 (± 0.90) hours.

Distribution
Rifampicin is 60-90% bound to plasma proteins and has a volume of distribution of approximately 0.9 l/kg. CSF concentrations are in the same order of magnitude as the unbound concentrations in plasma. Rifampicin readily crosses the placenta.

Metabolism:
Rifampicin is metabolized by hydrolysis and desacetylation into several metabolites, including the active metabolite desacetylrifampicin. Rifampicin induces its own metabolism; after repeat doses bioavailability is reduced to approximately 70% and apparent clearance is increased.

Excretion:
The half-life of rifampicin after a single dose is approximately three hours. After repeat doses this is reduced to approximately 1-2 hours. Rifampicin and its metabolites are mainly excreted in bile, and rifampicin undergoes enterohepatic recirculation. Approximately 25% of a dose is excreted in the urine.

Special populations:
The half-life of rifampicin has been reported to be prolonged in patients with liver impairment or biliary obstruction.

Isoniazid
Absorption:
After oral administration, isoniazid is rapidly absorbed with a bioavailability of ≥80%, and peak serum concentrations reached after 1-2 hours. The rate and extent of absorption are reduced when isoniazid is administered with food. Isoniazid undergoes appreciable presystemic (first pass) metabolism in the gut wall and liver.

Following single dose administration of Rifampicin 150 mg/Isoniazid 75 mg Tablets in healthy volunteers, used to compare the bioavailability of this product with the same dose of the individual reference formulations, the mean (± SD) isoniazid Cmax value was 1.08 µg/ml (± 0.46), and the corresponding value for AUC was 4.77 µg.h/ml (± 2.56). The mean (± SD) isoniazid tmax value was 1.02 (± 0.61) hours.

Distribution:
Isoniazid is distributed in the body with an apparent volume of distribution volume of 0.57 to 0.76 l/kg; protein binding is very low (0-10%).

Metabolism:
Isoniazid undergoes extensive metabolism that takes place in the mucosal cells of the small intestine and in the liver. Firstly, isoniazid is inactivated through acetylation. Subsequently, acetyl-isoniazid is further hydrolysed. Isoniazid acetylation is dependent on the genetically determined metabolic rate of the individual patients, who are termed fast or slow acetylators (this is due to a genetic polymorphism in the metabolising enzyme N-acetyl transferase). Different ethnic groups contain differing proportions of acetylator phenotypes. Acetylator status is the main determinant of isoniazid exposure at a given dose. At recommended doses, exposure in fast acetylators is about half that seen in slow acetylators.

Excretion:
Up to 95% of the ingested isoniazid is excreted in the urine within 24 hours, primarily as inactive metabolites. Less than 10% of the dose is excreted in the faeces. The main excretion products in the urine are N-acetylisoniazid and isonicotinic acid.

Pharmacokinetics in renal impairment:
The documentation of the pharmacokinetics of isoniazid and its metabolites in patients with renal impairment is incomplete. However, the half-life of isoniazid is prolonged and exposure is increased, in slow acetylators. The exposure to the (inactive) metabolites of isoniazid is likely to be increased in both fast and slow acetylators.

5.3 Preclinical safety data

Rifampicin
After oral administration of 100 mg/kg bodyweight (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 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 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, carcinogenic potential, toxicity to reproduction.

6. Pharmaceutical Particulars

6.1 List of Excipients

- Colloidal Silicon Dioxide
- Magnesium Stearate
- Microcrystalline Cellulose
- Povidone
- Maize Starch
- Sodium Starch Glycolate
- Purified Talc
- Hydroxy Propyl Methyl Cellulose
- Titanium Dioxide
- Colour Lake Ponceau
- Isopropyl Alcohol
- Methylene Chloride

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

36 Months

6.4 Special Precautions for Storage

Store in cool and dry place below 25°C.
Protect from Light
Keep out of reach of children

6.5 Nature and Contents of Container

Primary Packing : 28 tablets packed in an ALU PVC blister.
Secondary Packing : Such 24 blisters are packed in a printed carton alongwith a insert. OR
Such 3 blisters are packed in a printed carton alongwith a insert

6.6 Special Precautions for Disposal

No special requirements.
Any unused product or waste material should be disposed of in accordance with local requirements.

7. Marketing Authorization Holder

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8. Marketing Authorization Number: --

9. Date of First Authorization/Renewal of Authorization: 29.09.2017

10. Date of Revision of the Text: 20.11.2025