SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Isoniazid/Rifampicin 150 mg/150 mg Tablets*

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains:
Isoniazid 150 mg
Rifampicin 150 mg

For the full list of excipients see section 6.1.

3. PHARMACEUTICAL FORM

Brown, round biconvex, film-coated tablets, with break line on one side and plain on the other side. The tablet can be divided into equal halves.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Isoniazid/Rifampicin 150 mg/150 mg Tablets is indicated for the continuation treatment phase of tuberculosis, caused by *Mycobacterium tuberculosis* in patients weighing more than 30 kg according to the guidelines of WHO (Treatment of Tuberculosis: guidelines 4th edition, WHO, available at: *http://whqlibdoc.who.int/publications/2010/9789241547833_eng.pdf*

Also, Companion handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis, 2014 available at:
(http://www.who.int/tb/publications/pmdt_companionhandbook/en/)

4.2 Posology and method of administration

Oral use

The recommended doses for adults and children weighing more than 30 kg are 10 mg/kg (8-12 mg/kg) three times weekly for isoniazid and 10 mg/kg (8-12 mg/kg) three times weekly for rifampicin.

The number of tablets, by weight band, to be taken three times weekly is shown below:

Body weight (Kg)	Number of Isoniazid/Rifampicin 150 mg/150 mg Tablets to be taken three times weekly
30 - 37.5	2
37.6 - 55	3
>55	4

Isoniazid/Rifampicin 150 mg/150 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.

* Trade names are not prequalified by WHO. This is the national medicines regulatory authority's (NMRA) responsibility. Throughout this WHOPAR the proprietary name is given as an example only.

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. Isoniazid/Rifampicin 150 mg/150 mg Tablets must not be used in patients with severe liver disease (see section 4.3).

Advice on a missed dose:
As missing a dose may impact on the efficacy of tuberculosis treatment, directly observed therapy is recommended for this regimen, if a dose is missed, this dose should be taken as soon as possible, unless the next regular dose is scheduled within 24 hours. Otherwise the missed dose should be skipped.

Patients with a body weight < 30 kg:
Isoniazid/Rifampicin 150 mg/150 mg Tablets is not recommended for patients with body weight of less than 30 kg.
For these patients formulations containing a different dose ratio of the actives 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 Isoniazid/ Rifampicin 150 mg/150 mg Tablets with voriconazole or any HIV- or HCV-protease inhibitor 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 Isoniazid/Rifampicin 150 mg/150 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 Isoniazid/Rifampicin 150 mg/150 mg Tablets. Patient groups especially at risk for developing hepatitis include:

- age > 35 years,
- daily users of alcohol (see section 4.5),
- patients with active chronic liver disease
- intravenous drug users.

Furthermore, the following patients should be carefully monitored:
- patients with concurrent use of any chronically administered medication (see section 4.5),
- existence of peripheral neuropathy or conditions predisposing to neuropathy,
- pregnant patients
- HIV positive patients.

Patients should be instructed to immediately report signs or symptoms consistent with liver damage or other adverse effects. These include any of the following: unexplained anorexia, nausea, vomiting, dark urine, icterus, rash, persistent paraesthesiae of the hands and feet, persistent fatigue and/or weakness of greater than 3 days duration and/or abdominal tenderness, especially of the right upper quadrant. If these symptoms appear or if signs suggestive of hepatic damage are detected, Isoniazid/Rifampicin 150 mg/150 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 Isoniazid/Rifampicin 150 mg/150 mg Tablets and periodically throughout treatment.

Increased liver function tests are common during therapy with Isoniazid/Rifampicin 150 mg/150 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 with continued therapy.

If abnormalities of liver function exceed three to five times the upper limit of normal, discontinuation of Isoniazid/Rifampicin 150 mg/150 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, Isoniazid/Rifampicin 150 mg/150 mg Tablets 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, Isoniazid/Rifampicin 150 mg/150 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, Isoniazid/Rifampicin 150 mg/150 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: This is the most common toxic effect of isoniazid (see section 4.8). The frequency depends on the dose and on predisposing conditions such as malnutrition, alcoholism or diabetes. Concomitant pyridoxine administration largely reduces the risk of developing neuropathy. Therefore, pyridoxine should be co-administered routinely with Isoniazid/Rifampicin 150 mg/150 mg Tablets at doses of 10 mg per day.

Epilepsy and psychotic disorders: Isoniazid/Rifampicin 150 mg/150 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, leucopenia and thrombocytopenia, full blood count should be monitored regularly throughout therapy with Isoniazid/Rifampicin 150 mg/150 mg Tablets. In case of severe haematological disturbances Isoniazid/Rifampicin 150 mg/150 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, adequate supplementation with pyridoxine (see above) should be given to avoid neurotoxicity.

Nephrotoxicity: Isoniazid/Rifampicin 150 mg/150 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 Isoniazid/Rifampicin 150 mg/150 mg Tablets may reduce exposure and efficacy of many therapeutic drugs, including antiretroviral agents, antiepileptic drugs, immunosuppressants and coumarin derivatives (see section 4.5).

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

Treatment with corticosteroids: Isoniazid/Rifampicin 150 mg/150 mg Tablets may reduce the efficacy of corticosteroids in Addison's disease and induce an Addisonian crisis (see section 4.5).

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

Discoloration of body fluids: Isoniazid/Rifampicin 150 mg/150 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 and liver function should be monitored prior to and at regular intervals during treatment with Isoniazid/Rifampicin 150 mg/150 mg Tablets.

4.5 Interactions 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 co-treating with other drugs. To maintain optimum therapeutic blood levels, dosages of drugs metabolized by these enzymes may require adjustment when starting or stopping the concomitant administration of Isoniazid/Rifampicin 150 mg/150 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 Isoniazid/Rifampicin 150 mg/150 mg Tablets, these effects are likely to be outweighed by the hepatic enzyme induction due to rifampicin. In so far 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, Isoniazid/Rifampicin 150 mg/150 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 reductions in drug exposure may occur. Whenever co-prescribing any drug together with Isoniazid/Rifampicin 150 mg/150 mg Tablets, the possibility of a drug-drug interaction should be considered. The following list of drug interactions with Isoniazid/Rifampicin 150 mg/150 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 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 required.
Tenofovir DF / 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.
Non-nucleoside analogues **Efavirenz** / rifampicin	Efavirenz AUC ↓ 26%	When co-treating with Isoniazid/Rifampicin 150 mg/150 mg Tablets, 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 Isoniazid/Rifampicin 150 mg/150 mg Tablets and nevirapine is not recommended.
Etravirine / rifampicin	Rifampicin is likely to significantly reduce exposure to etravirine.	Co-treatment of Isoniazid/Rifampicin 150 mg/150 mg Tablets and etravirine should be avoided.

Drugs by Therapeutic Area	Interaction	Recommendations concerning co-administration
Protease inhibitors **Fosamprenavir /** rifampicin **Saquinavir** **Indinavir** **Ritonavir** **Nelfinavir** **Lopinavir** **Atazanavir** **Tipranavir** **Darunavir** **Boceprevir** **Telaprevir**	Protease inhibitor (PI) exposure will be reduced to subtherapeutic level due to interaction with rifampicin. Attempts to compensate for this by increasing doses of the PIs, or an increase in ritonavir-boosting, have been ill-tolerated with a high rate of hepatotoxicity.	Isoniazid/Rifampicin 150 mg/150 mg Tablets 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.
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.
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.
Voriconazole / rifampicin	Voriconazole AUC ↓ 96%	Co-administration is contraindicated. If necessary, rifabutin should be substituted for rifampicin.
Antibacterials/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 AUC i.v.↓ 33%	The clinical relevance of the interaction is unknown. No dose adjustment is routinely recommended. Efficacy

		should be monitored.
Drugs by Therapeutic Area	**Interaction**	**Recommendations concerning co-administration**
Sulfamethoxazole / 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 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 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	Lumefantrine AUC ↓ 68%	Co-administration should be avoided.
Artemisinin and its derivatives / rifampicin	Artemether AUC ↓ 89% Dihydroartemisinin AUC ↓ 85%	Co-administration should be avoided.

Drugs by Therapeutic Area	Interaction	Recommendations concerning co-administration
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 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 hepatotoxicity on co-administration, but data are inconclusive.Concurrent use with isoniazid may increase hepatotoxicity.	Co-administration of Isoniazid/Rifampicin 150 mg/150 mg Tablets and acetaminophen (paracetamol) should be avoided.
ANTICONVULSANTS		
Carbamazepine / rifampicin / isoniazid	Rifampicin is expected to decrease the serum concentration of carbamazepine whereas isoniazid may increase them. Neurological side effects and the risk of hepatotoxicity increase when co-treating with carbamazepine.	Co-administration of Isoniazid/Rifampicin 150 mg/150 mg Tablets and carbamazepine should be avoided.
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 isonazid may increase the risk of hepatotoxicity.	Co-administration of Isoniazid/Rifampicin 150 mg/150 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 result in an increased risk of hepatotoxicity.	Co-treatment with phenytoin and Isoniazid/Rifampicin 150 mg/150 mg Tablets should be avoided.

Drugs by Therapeutic Area	Interaction	Recommendations concerning co-administration
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, 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 ↓ 68% Sirolimus AUC ↓ 82% Everolimus AUC ↓ 63%	Co-administration of Isoniazid/Rifampicin 150 mg/150 mg Tablets and mTOR inhibitors should be avoided. If deemed necessary, plasma drug concentrations should be monitored, and the dose increased as appropriate.
CARDIOVASCULAR MEDICINES		
Warfarin / rifampicin	Warfarin AUC ↓ 85%	Monitor closely and adjust warfarin dose as necessary (2-3 fold) and reduce dose after withdrawing rifampicin treatment.
Atenolol / rifampicin	Atenolol AUC ↓ 19%	No dose adjustment required.
Verapamil / rifampicin	S-verapamil p.o CL/F ↑ 32-fold. With i.v. S-verapamil, CL ↑ 1.3-fold	Isoniazid/Rifampicin 150 mg/150 mg Tablets 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 Isoniazid/Rifampicin 150 mg/150 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.
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 Isoniazid/Rifampicin 150 mg/150 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, doses may need to be increased (except midazolam and triazolam). Temazepam can be used as alternative benzodiazepine.
Zolpidem / rifampicin **Zopiclone** /rifampicin	Zolpidem AUC ↓73% Zopiclone AUC ↓82%	Co-administration should be avoided. Use other agents instead.
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 Isoniazid/Rifampicin 150 mg/150 mg Tablets with haloperidol or clozapine is deemed necessary, monitor clinical efficacy. A dose increase may be required.
Amitriptyline / rifampicin	Case reports (supported by theoretical considerations) suggest	Co-treatment should be avoided. If necessary, efficacy and, if

	that rifampicin considerably increases amitriptyline clearance.	possible, also plasma concentrations of amitriptyline should be monitored.
Drugs by Therapeutic Area	**Interaction**	**Recommendations concerning co-administration**
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 Isoniazid/Rifampicin 150 mg/150 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 (2-3 fold increase may be required).
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 expected.	No dose adjustment required
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 Isoniazid/Rifampicin 150 mg/150 mg Tablets 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 Isoniazid/Rifampicin 150 mg/150 mg Tablets 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 Isoniazid/Rifampicin 150 mg/150 mg Tablets should be avoided.
Disulfiram / isoniazid	Concurrent use of disulfiram together with isoniazid may result in increased incidence of adverse effects on the central nervous system.	Dose reduction or discontinuation of disulfiram may be necessary during therapy with Isoniazid/Rifampicin 150 mg/150 mg Tablets.

Drugs by Therapeutic Area	Interaction	Recommendations concerning co-administration
Theophylline / Isoniazid / Rifampicin	Isoniazid may increase the serum concentration of theophylline and rifampicin may increase it. The effects of combination are unknown.	Theophylline dose adjustment may be needed.
Enflurane / Isoniazid	Isoniazid may increase the formation of the potentially nephrotoxic inorganic fluoride metabolite of enflurane.	Coadministration of Isoniazid/Rifampicin 150 mg/150 mg Tablets 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 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 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 anti-tuberculosis 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. Isoniazid/Rifampicin 150 mg/150 mg Tablets should be used in pregnancy only if the benefits are considered to outweigh the risks. If Isoniazid/Rifampicin 150 mg/150 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 Isoniazid/Rifampicin 150 mg/150 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 to <1/10), uncommon (≥1/1000 to <1/100), rare (≥1/10,000 to <1/1000), very rare (≤1/10,000), 'not known' (frequency cannot be estimated from the available data)..

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 (see section 4.4),
Uncommon: headache, lethargia, 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.

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, Stevens - Johnson syndrome.

Eye disorders:
Common: ocular redness, permanent discolouration of soft contact lenses,
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 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 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

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*. 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

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 2 x Isoniazid/Rifampicin 150 mg/150 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 4.27 µg/ml (± 1.02), and the corresponding value for AUC was 26.06 µg.h/ml (± 6.31). The mean (± SD) rifampicin t_{max} value was 1.89 (± 0.73) 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 wall of small intestine and liver.

Following single dose of 2 x Isoniazid/Rifampicin 150 mg/150 mg Tablets administration in healthy volunteers, the mean (± SD) isoniazid Cmax value was 7.90 µg/ml (± 2.34), and the corresponding value for AUC was 28.1 µg.h/ml (± 14.0). The mean (± SD) isoniazid t_{max} value was .0 69± 0.27 hours.

Distribution

Isoniazid is distributed in the body with an apparent volume of distribution 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

Tablet core: Ascorbic acid, colloidal silicon dioxide, crospovidone, magnesium stearate, microcrystalline cellulose and pregelatinised starch.
Film-coating: Hypromellose, iron oxide red, iron oxide yellow, polyethylene glycol, simethicone emulsion, talc and titanium dioxide.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Shelf life for the bottle and blisters: 36 months

In-use period for the bottle, after first opening: 30 days.

6.4 Special precautions for storage

Store in a dry place below 25ºC, protected from excessive humidity and light.

6.5 Nature and contents of container

Bulk pack of 1000 tablets in a polypropylene bag, inside an HDPE container with aluminium tagger seal, also containing a silica gel bag and closed with a white LDPE cap.

PVC/PVDC-aluminium blister pack of 28 tablets (7x4), such 24 blisters are packed in a carton along with pack 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. SUPPLIER

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TB195

9. DATE OF FIRST PREQUALIFICATION

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10. DATE OF REVISION OF THE TEXT

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