

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Rimactazid 150 mg/75 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 150 mg of rifampicin and 75 mg of isoniazid.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Round, biconvex, dark-pink film-coated tablets, 9.5 ± 0.4 mm in diameter, plain on both sides.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

For continuation phase treatment of tuberculosis according to World Health Organisation (WHO) guidelines.

Consideration should also be given to other official guidance on the appropriate use of antituberculosis agents.

4.2 Posology and method of administration

Posology

Rimactazid should be administered under the supervision of a physician trained in the management of tuberculosis.

The recommended dose and dosage schedules for **Rimactazid** are based on WHO guidelines:

- Fixed-dose-combination tablets for the treatment of tuberculosis; WHO/CDS/CPC/TB/99.267, 1999.
- The rationale for recommending fixed-dose combination tablets for treatment of tuberculosis; Bulletin of the World Health Organisation, 2001, 79: 61-68.
- Informal Consultation on 4-drug Fixed-Dose Combination, Geneva 2001.

Treatment of Tuberculosis Guideline, 4th Ed. WHO/HTM/TB/2009.420.

These dose and dose schedules may differ from recommendations on the use of anti-tuberculosis agents given in other official guidance.

Rimactazid is a fixed combination product intended for use in the continuation phase of anti-tuberculous treatment. **Rimactazid** should be administered on a daily basis throughout the 4 month continuation phase of treatment.

Rimactazid is a fixed combination product that should only be used when the fixed ratio of rifampicin 150 mg and isoniazid 75 mg will permit treatment of an individual patient in line with official recommendations and practice.

Table 1: WHO-recommended essential anti-TB drugs

Essential drug	Abbreviation	Recommended dosage (dose range), mg/kg
----------------	--------------	--

Daily		
Isoniazid	H	5 (4-6)
Rifampicin	R	10 (8-12)
Pyrazinamide	Z	25 (20-30)
Streptomycine	S	15 (12-18)
Ethambutol	E	15 (15-20)

Method of administration

Rimactazid tablets are administered orally. The tablets should be given as a single dose (number of tablets depending on the patient's bodyweight, see table 2), in a fasting state at least 1 hour before a meal.

Table 2: WHO-recommended number of tablets with fixed-dose combinations of anti-TB drugs in adults

			Duration	Patient's bodyweight (in kg)			
				30-39	40-54	55-70	>70
Initial phase – daily							
either	Rimstar	HRZE (75 mg+150 mg+400 mg+275 mg)	2 months	2	3	4	5
or ⁽¹⁾	Rimcure	HRZ (75 mg+150 mg+400 mg) 1	2 months	2	3	4	5
or ⁽²⁾	Rimstar + S	HRZE (75 mg+150 mg+400 mg+275 mg) + S (vial 1 g) ²	2 months	2	3	4	5
	and (subsequent)	Rimstar		0.5	0.75	1	1
		HRZE (75 mg+150 mg+400 mg+275 mg) ²	1 month	2	3	4	5
Continuation phase – daily							
either	Rimactazid	HR (75 mg+150 mg)	4 months	2	3	4	5
or	Separate drugs	HE (150 mg+400 mg)	6 months	1.5	2	3	3
or ⁽²⁾	Rimactazid + E	HR (75 mg+150 mg) + E (400 mg) ²	5 months	2	3	4	5
				1.5	2	3	3

¹ In patients with non-cavitary, smear-negative pulmonary tuberculosis known to be HIV negative, patients known to be infected with fully drug susceptible bacilli and young children with primary TB.

² In patients with previously treated sputum smear-positive pulmonary tuberculosis: relapse, treatment after interruption, treatment failure, according to the category II of WHO recommendations.

In case of chronic and multidrug-resistant tuberculosis cases (still sputum-positive after supervised re-treatment), specially designed standardised or individualised regimens are suggested for this category of patients (category IV of WHO recommendations).

Use in patients with body weight less than 30 kg:

Rimactazid is not a suitable dosage form for use in the treatment of patients with a body weight of less than 30 kg (see section 4.4).

Paediatric population

Rimactazid is not a suitable dosage form for use in the treatment of children with a body weight of less than 30 kg. **Rimactazid** is not recommended in children under 6 years of age because of risk of aspiration (see section 4.4).

Older people:

No special dosage regimen is necessary, but concurrent hepatic and/or renal insufficiency should be taken into account. Supplementation of pyridoxine (vitamin B6) may be useful.

Hepatic insufficiency:

Rimactazid should be used with caution and under strict medical supervision in impaired liver function (see section 4.4). **Rimactazid** is contraindicated in patients with a history of drug induced hepatitis and in patients with acute liver diseases (see section 4.3).

Renal insufficiency:

Rimactazid should be used with caution in patients with moderate renal impairment (creatinine clearance 25 – 60 ml/min, see section 4.4). **Rimactazid** is contraindicated in patients with severe renal impairment (creatinine clearance < 25 ml/min, see section 4.3).

Interruption of treatment

If continuation phase treatment with **Rimactazid** is interrupted for any reason including non-compliance, a fixed drug combination product such as **Rimactazid** is contraindicated for the resumption of treatment. Rifampicin and isoniazid must be administered separately for the resumption of treatment, because rifampicin needs to be reintroduced at a lower dose. Reference should be made to official guidance on the appropriate resumption of treatment with anti-tuberculosis agents.

4.3 Contraindications

Hypersensitivity to rifamycins, isoniazid and/or to any of the excipients listed in section 6.1.

A history of drug induced hepatitis and acute liver diseases regardless of its origin.

Porphyria.

Severe renal impairment (creatinine clearance < 25 ml/min) (see section 4.4).

Concomitant use with voriconazole and proteaseinhibitors, except ritonavir when given at full dose or 600 mg twice daily (see section 4.5).

Rifampicin is contraindicated with medicines strongly affected by its potential to induce drug metabolizing enzymes and transporters such as: lurasidone, sofosbuvir, antiretrovirals: cabotegravir, fostemsavir and lenacapavir (see section 4.5).

4.4 Special warnings and precautions for use

Warnings

In cases of known acetylation phenotypes, patients with extremely fast or extremely slow acetylating capability should receive the two components separately in order to facilitate dose adjustment of isoniazid.

Rimactazid should be withdrawn immediately if severe acute hypersensitivity reactions occur, such as thrombocytopenia, purpura, haemolytic anaemia, dyspnoea and asthma-like attacks, shock or renal failure as these are side effects that rifampicin may provoke in exceptional cases. Patients developing such reactions must never again be treated with rifampicin.

Rimactazid should be withdrawn if other signs of hypersensitivity appear, such as fever or skin reactions. For safety reasons, treatment should not be continued or resumed with rifampicin.

Rimactazid is not recommended in children under 6 years of age because of risk of aspiration.

Rimactazid is not a suitable dosage form for use in the treatment of patients with a body weight of less than 30 kg.

Severe cutaneous adverse reactions (SCARs) such as Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS) and acute generalised exanthematous pustulosis (AGEP), which can be life-threatening or fatal, have been reported in association with **Rimactazid** treatment.

At the time of prescription patients should be advised of the signs and symptoms and monitored closely for skin reactions.

If signs and symptoms suggestive of these reactions appear, **Rimactazid** should be withdrawn immediately and an alternative treatment considered.

If the patient has developed a serious reaction such as SJS, TEN, DRESS or AGEP with the use of **Rimactazid**, treatment with **Rimactazid** must not be restarted in this patient at any time.

Paradoxical drug reaction

After initial improvement of tuberculosis under therapy with TM, the symptoms may worsen again. In affected patients, clinical or radiological deterioration of existing tuberculous lesions or the development of new lesions have been detected. Such reactions have been observed within the first few weeks or months of initiation of tuberculosis therapy. Cultures are usually negative, and such reactions do not usually indicate treatment failure.

The cause of this paradoxical reaction is still unclear, but an exaggerated immune reaction is suspected as a possible cause. In case a paradoxical reaction is suspected, symptomatic therapy to suppress the exaggerated immune reaction should be initiated if necessary. Furthermore, continuation of the planned tuberculosis combination therapy is recommended.

Patients should be advised to seek medical advice immediately if their symptoms worsen. The symptoms that occur are usually specific to the affected tissues. Possible general symptoms include cough, fever, tiredness, breathlessness, headache, loss of appetite, weight loss or weakness (see section 4.8).

Precautions

The precautions for the use of **Rimactazid** are the same as those that apply for the administration of rifampicin and isoniazid as individual medicinal product.

Patients should be advised against interrupting treatment.

Impaired liver function, undernourishment, alcoholism

Rifampicin and isoniazid are metabolised in the liver. Elevated transaminase levels, above the upper limit of normal (ULN), commonly occur. Liver dysfunction that may occur in the first few weeks of treatment usually returns to the normal range spontaneously, without interruption of treatment, and usually by the third month of treatment.

With rifampicin, although slight elevations of liver enzymes are common, clinical jaundice or evidence of hepatitis are rare. In patients taking both isoniazid and rifampicin, a cholestatic pattern with elevated alkaline phosphatase suggests that rifampicin is the causative agent, whereas a rise in transaminases may be caused by isoniazid, or rifampicin, or the combination of both agents.

Patients with impaired liver function should be treated with caution and under strict medical supervision.

In these patients, careful monitoring of liver function, especially serum glutamic pyruvic transaminase (SGPT/ALAT) and serum glutamic oxaloacetic transaminase (SGOT/ASAT) should be carried out prior to therapy and repeated weekly or fortnightly during therapy. If signs of hepatocellular damage occur, **Rimactazid** should be withdrawn.

A moderate rise in bilirubin and/or transaminase levels is not in itself an indication for interrupting treatment; rather, the decision should be made after repeating these liver function tests, noting trends in the levels and considering them in conjunction with the patient's clinical condition.

Interrupting isoniazid treatment is recommended when there is clinical jaundice or transaminases exceeding 3 times the ULN. The fixed drug combination, **Rimactazid**, should be replaced by individual component formulations of rifampicin and isoniazid in order to facilitate treatment in these clinical circumstances.

Withdrawing rifampicin is recommended if liver function does not return to normal or transaminases exceed 5 times the ULN. The fixed drug combination, **Rimactazid**, should be replaced by individual component formulations in order to facilitate treatment in these clinical circumstances.

Use of isoniazid should be carefully monitored in patients with chronic liver disease. Severe and sometimes fatal hepatitis caused by isoniazid may occur and may develop even after many months of treatment. Hepatotoxicity associated with isoniazid therapy (thought to be caused by the metabolite diacetylhydrazine) is rare in patients up to 20 years of age, but more common with increasing age and affecting up to 3% of patients aged over 50 years. The incidence of severe hepatotoxicity can be minimised by careful monitoring of liver function. Patients should be monitored with regard to the appearance of prodromal symptoms of hepatitis, such as fatigue, weakness, malaise, anorexia, nausea or vomiting. If these symptoms appear or if signs of hepatic damage are detected, treatment should be discontinued promptly. Continued use of **Rimactazid** in these patients may cause a more severe form of liver damage.

In patients with chronic liver disease, as well as in chronic alcoholics and undernourished patients, the therapeutic benefits of treatment with **Rimactazid** must be weighed against the possible risks.

If anti-tuberculous treatment is considered necessary, the dosage of rifampicin and isoniazid may need to be modified and **Rimactazid** should not be used in such patients because it is only possible to adjust the dosage by administering rifampicin and isoniazid separately.

For undernourished or elderly patients supplementation of pyridoxine (vitamin B6) may be useful, because isoniazid in high doses can lead to pyridoxine (vitamin B6) deficiency.

Impaired renal function

In severe renal insufficiency, the elimination of isoniazid can be delayed leading to a higher systemic exposure, which can result in an increase in adverse events. **Rimactazid** should be used with caution in patients with moderate renal impairment (creatinine clearance 25-60 ml/min).

Haematology

Full blood count should be monitored during prolonged treatment and in patients with hepatic disorders. Rifampicin should be withdrawn permanently if thrombocytopenia or purpura occur.

Diabetes mellitus

Increased difficulty has been reported in controlling diabetes mellitus when such patients are given isoniazid.

Epilepsy

Patients suffering from convulsive disorders must be kept under special observation during treatment with **Rimactazid** because of the neurotoxic effects of isoniazid.

Neuropathy

Caution should be exercised in subjects with peripheral neuritis. Regular neurological examination is necessary with special care in patients with a history of alcohol abuse. Use of pyridoxine (vitamin B6) may prevent or diminish neuropathy due to isoniazid treatment especially in elderly and in malnourished patients. Pyridoxine should be given in line with official guidelines.

Contraception

Additional non-hormonal means of contraception must be employed to prevent the possibility of pregnancy during treatment with rifampicin (see section 4.5).

Alcohol

Patients should abstain from alcohol while receiving treatment with **Rimactazid**.

Laboratory tests

Full blood counts and liver function tests (SGPT/ALAT, SGOT/ASAT) should be performed before treatment and at regular intervals during treatment.

Concomitant medications

Rifampicin is a potent inducer of the cytochrome P450 system, and may increase the metabolism of concomitantly administered drugs, resulting in subtherapeutic plasma levels and a lack of effect. Drugs that are eliminated by hepatic metabolism should only be used concomitantly with **Rimactazid** if the plasma level or clinical response / undesirable effects can be monitored and the dose can be adequately adjusted (see section 4.5).

Use of the following medicinal products concomitantly with **Rimactazid** is not recommended: nevirapine, simvastatin, oral contraceptives and ritonavir (when given in low doses as a booster a marked reduction of plasma concentration might occur) (see section 4.5).

Rifampicin has enzyme induction properties that can enhance the metabolism of endogenous substrates including adrenal hormones, thyroid hormones and vitamin D. Isolated reports have associated porphyria exacerbation with rifampicin administration.

Rimactazid contains sodium

This medicinal product contains less than 1 mmol sodium (23 mg) per film-coated tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Influence of other medicinal products on **Rimactazid**

Antacids reduce the bioavailability of rifampicin and isoniazid. To avoid this interaction, **Rimactazid** should be taken at least 1 hour before antacids. Corticosteroids can reduce the plasma levels of isoniazid, by increasing its metabolic and/or renal clearance.

Influence of Rimactazid on other medicinal products

Rifampicin is the most potent inducer of the cytochrome P450 system (CYP450), notably of the two subfamilies CYP3A and CYP2C, which represent more than 80% of the isoenzymes of CYP 450. Thus rifampicin may increase the metabolism of numerous concomitantly administered medicinal products which are metabolised, partially or totally, by these two subfamilies of CYP450. Moreover, rifampicin also induces UDP-glucuronyltransferase, another enzyme involved in the metabolism of several medicinal products. This can result in subtherapeutic plasma levels of the simultaneous administered medicinal products, with a decreased or even a loss of effect. Isoniazid inhibits the metabolism of some medicinal products leading to increased plasma concentrations.

Moreover, some medicinal products are affected in the opposite direction by rifampicin and isoniazid, e.g. phenytoin, warfarin and theophylline. The net effect cannot be predicted and may change over time.

Plasma concentrations of morphine may be reduced by rifampicin. The analgesic effect of morphine should be monitored and doses of morphine adjusted during and after treatment with rifampicin.

Medicinal products that are eliminated by metabolism should only be used concomitantly with Rimactazid if the plasma concentrations or clinical response/undesirable effects can be monitored and the dose can be adequately adjusted. Monitoring should be performed regularly during Rimactazid therapy and for 2-3 weeks after discontinuation of the therapy.

The enzyme inducing effects of rifampicin reach a peak within 10 days and gradually decrease over a period of 2 or more weeks after discontinuation of rifampicin treatment, factors that must be taken into account if the dose of other medicinal products is increased during treatment with Rimactazid.

When considering the impact of Rimactazid on the concentrations of other simultaneously administered medicinal products, recommendations are the following:

Interactions with rifampicin:

Use of the following medicinal products concomitantly with Rimactazid is contraindicated: voriconazole and proteaseinhibitors, except ritonavir when given at full dose or 600 mg twice daily (see section 4.3).

Use of the following medicinal products concomitantly with Rimactazid is not recommended: nevirapine, simvastatin, oral contraceptives and ritonavir (when given in low doses as a booster a marked reduction of plasma concentration might occur) (see section 4.4).

Use of the following medicinal products concomitantly with Rimactazid requires a precaution for use by monitoring specific parameters or through a clinical surveillance:

- .
- Analgesics (e.g. methadone, narcotic analgesics, morphine, etoricoxib, rofecoxib)
- Antiarrhythmics (disopyramide, mexiletine, quinidine, propafenone, tocainide, lorcainide)
- Antibacterials (e.g. chloramphenicol, clarithromycin, dapsone, doxycycline, fluoroquinolones, telithromycin, linezolid, p-aminosalicylic acid)
- Anticoagulants (e.g. coumarins)
- Antidiabetics
- Antiepileptics (e.g. phenytoine, tiagabine, carbamazepine)
- Antifungals (e.g. fluconazole, itraconazole, ketoconazole, voriconazole, terbinafine)
- Antipsychotics (e.g. haloperidol, clozapine, aripiprazole)
- Antivirals (e.g. saquinavir, indinavir, efavirenz, amprenavir, nilfinavir, atazanavir, lopinavir, nevirapine, zidovudine)
- Anxiolytics and hypnotics (e.g. diazepam, benzodiazepines, buspirone, zopiclone, zolpidem, zaleplon)
- Atovaquone

- Barbiturates (e.g. hexobarbital)
- Beta-blockers (e.g. bisoprolol, propranolol, metoprolol, carvedilol (because of its use in cardiac insufficiency and its low therapeutic margin in this indication))
- Calcium channel blockers (e.g. diltiazem, nifedipine, verapamil, nimodipine, isradipine, nicardipine, nisoldipine, amlodipine)
- Corticosteroids
- Cardiac glycosides (digitoxin, digoxin)
- Cimetidine
- Clofibrate
- Cytotoxics (e.g. imatinib, gefitinib, irinotecan)
- Diuretics (e.g. eplerenone)
- Oestrogen, progestogens
- Fexofenadine
- Hormone antagonists (antioestrogens e.g. tamoxifen, toremifene; gestrinone)
- Immunosuppressive agents (e.g. ciclosporin, sirolimus, tacrolimus, leflunomide, azathioprine)
- Losartan, imidapril, enalapril
- Praziquantel
- Quinine
- Selective 5-HT₃ receptor antagonists (e.g. ondansetron, tropisetron)
- Statins metabolised by CYP 3A4 (e.g. simvastatin)
- Fluvastatin
- Systemic hormonal contraceptives
- Theophylline
- Thyroid hormone (e.g. levothyroxine)
- Tricyclic antidepressants (e.g. amitriptyline, nortriptyline)

Rifampicin is contraindicated with medicines strongly affected by its potential to induce drug metabolizing enzymes and transporters such as: lurasidone, sofosbuvir, antiretrovirals: cabotegravir, fostemsavir and lenacapavir. Significant decrease in their plasma concentrations is observed because of potent induction of CYP 3A4, P-gp, UGT1A1 by rifampicin which is likely to result in loss of their therapeutic effectiveness.

Interactions with isoniazid:

Use of the following medicinal products concomitantly with **Rimactazid** requires a precaution for use by monitoring specific parameters or through a clinical surveillance: halogenated volatile anaesthetics, glucocorticoids, ketoconazole, phenytoin, pyrazinamide, stavudine, carbamazepine, benzodiazepines, ethosuximide, theophylline.

Rifampicin may reduce the effectiveness of oral contraceptives and patients treated with **Rimactazid** should use a non-hormonal method of contraception.

Oral typhoid vaccine might be inactivated by concomitant antibiotic administration.

Food with a high content of tyramine or histamine should be avoided. Isoniazid may inhibit monoamine oxidase and diamine oxidase. Intake of food containing tyramine (e.g. cheese, red wine) or histamine (e.g. tuna fish) may lead to headache, palpitations, flushing etc.

Rifampicin can delay the biliary excretion of contrast media during gallbladder radiographic examination.

Microbiological methods used to determinate folic acid and cyanocobalamine (vitamin B12) plasma concentrations can not be used during rifampicin treatment as rifampicin is in competition with bilirubin and BSP. To avoid false positive reactions, BSP test should be carried out the morning before rifampicin administration.

4.6 Fertility, pregnancy and lactation

Pregnancy

Treatment should be considered on a case by case basis after benefit of medicinal product combination has been assessed. Consequently, Rimactazid could be given during pregnancy if the potential benefit for the mother is judged to outweigh the potential risk to the foetus.

Rifampicin

At very high doses in animals rifampicin has been shown to have teratogenic effects (see section 5.3). There are no well controlled studies with rifampicin in pregnant women. Although rifampicin has been reported to cross the placental barrier and appear in cord blood, the effect of rifampicin, alone or in combination with other antituberculosis drugs, on the human foetus is not known. Therefore, rifampicin should be used in pregnant women or in women of child bearing potential only if the potential benefit justifies the potential risk to the foetus.

Administration of rifampicin during the last few weeks of pregnancy can cause postnatal haemorrhage in the mother and newborn infant.

Isoniazid

On limited data, congenital malformations have not been observed to be any more frequent than what may be expected in a normal population. Isoniazid crosses the placenta. Isoniazid might exert neurotoxic effects on the child. Animal studies have shown reproductive toxicity (see section 5.3).

- In case of third trimester exposure, maternal administration of oral phytomenadione (vitamin K) during the last month of pregnancy and neonatal administration at delivery are recommended, because rifampicin can lead to maternal or neonatal haemorrhage.
- Supplementation of pyridoxine (vitamin B6) is recommended during pregnancy, because isoniazid might exert neurotoxic effects on the child.

Breast-feeding

Rifampicin and isoniazid pass into the breast milk, but no adverse effects on breast-fed infants have been observed. Breast-feeding is, however, not recommended in view of the theoretical possibility of neurotoxic effects due to isoniazid.

4.7 Effects on ability to drive and use machines

Rimactazid has minor to moderate influence on the ability to drive and use machines.

4.8 Undesirable effects

Frequency estimates:

<i>Common:</i>	$\geq 1/100$
<i>Uncommon:</i>	$\geq 1/1,000$ and $< 1/100$
<i>Rare:</i>	$\geq 1/10,000$ and $< 1/1,000$
<i>Very rare:</i>	$< 1/10,000$
<i>Not known:</i>	cannot be estimated from the available data

Undesirable effects of rifampicin which may occur during continuous daily or intermittent therapy

Blood and lymphatic system disorders

Rare: Transient leucopenia, eosinophilia agranulocytosis. Thrombocytopenia and thrombocytopenic purpura are encountered more frequently with intermittent therapy than with continuous daily treatment, during which they occur only in very rare cases. When rifampicin administration has been continued after the occurrence of purpura, cerebral haemorrhage and fatalities have been reported. (see section

4.4). Haemolysis, haemolytic anaemia. Disseminated intravascular coagulation has also been reported.

Endocrine disorders	<i>Rare:</i> Menstrual disturbances (in extreme cases amenorrhoea); induction of crisis in Addison patients (see section 4.5)
Psychiatric disorders	<i>Rare:</i> Mental confusion, psychosis.
Nervous system disorders	<i>Common:</i> Tiredness, drowsiness, headache, light-headedness, dizziness <i>Rare:</i> Ataxia, muscular weakness, myopathy.
Eye disorders	<i>Common:</i> Reddening of the eyes, permanent discolouration of soft contact lenses <i>Rare:</i> Visual disturbances, Severe signs and symptoms, such as e.g. exudative conjunctivitis
Gastrointestinal disorders	<i>Common:</i> Anorexia, nausea, abdominal pain, bloatedness <i>Rare:</i> Vomiting or diarrhoea, isolated occurrences of erosive gastritis and pseudomembranous colitis, pancreatitis.
Skin and subcutaneous tissue disorders	<i>Common:</i> Flushing, itching with or without skin rash, urticaria <i>Rare:</i> Severe skin reactions such as Stevens-Johnson syndrome and generalised hypersensitivity reactions, e.g. exfoliative dermatitis, Lyell's syndrome and pemphigoid reactions.
Hepatobiliary disorders	<i>Common:</i> Asymptomatic increase in liver enzymes (see section 4.4) <i>Rare:</i> Hepatitis or jaundice, induction of porphyria (see section 4.3)
Renal and urinary disorders	<i>Rare:</i> Elevations of BUN (blood urea nitrogen) and serum uric acid have been reported. Acute renal failure due to haemoglobinuria, haematuria, interstitial nephritis, glomerulonephritis and tubular necrosis has been reported.
General disorders and administration site conditions	<i>Common:</i> Reddish discoloration of body fluids and secretions such as e.g. urine, sputum, lacrimal fluid, faeces, saliva and sweat, paradoxical drug reaction (Recurrence or appearance of new symptoms of tuberculosis, physical and radiological signs in a patient who had previously shown improvement with appropriate anti-tuberculosis treatment is called a paradoxical reaction, which is diagnosed after excluding poor compliance of the patient to treatment, drug resistance, side effects of antitubercular therapy, secondary bacterial/fungal infections.)* <i>Rare:</i> Collapse, shock, oedema

*Incidence of paradoxical drug reaction: Lower frequency is reported as 9.2% (53/573) (data between October 2007 and March 2010) and higher frequency is reported as 25% (19/76) (data between 2000 and 2010).

Undesirable effects of rifampicin mainly occurring during intermittent therapy or on resumption of treatment after temporary interruption

In patients taking rifampicin other than on a daily basis or in those resuming treatment with the medicinal product after a temporary interruption, an influenza-like syndrome may occur, this being very probably of immunopathological origin. It is characterised by fever, shivering and possibly headache, dizziness and musculoskeletal pain. In rare cases this “flu-like syndrome” may be followed by thrombocytopenia, purpura, dyspnoea, asthma-like attacks, haemolytic anaemia, shock and acute renal failure. These serious complications may, however, also set in suddenly without preceding “flu-like syndrome”, mainly when treatment is resumed after a temporary interruption or when rifampicin is given only once a week in high doses (≥ 25 mg/kg) (see section 4.4). When rifampicin is administered in lower doses (600 mg) 2-3 times a week, the syndrome is encountered less commonly, its incidence then being comparable to that observed during daily medication (see section 4.4).

Undesirable effects of isoniazid

Blood and lymphatic system disorders	<i>Rare:</i> Eosinophilia, thrombocytopenia, anaemia (haemolytic, sideroblastic) <i>Very rare:</i> Agranulocytosis
Endocrine disorders	<i>Rare:</i> Isoniazid may interfere with liver metabolism of several hormones, resulting in menstrual disturbances, gynaecomastia, Cushing syndrome, pubertas praecox, and difficult controllable diabetes, hyperglycaemia (see section 4.4) and metabolic acidosis
Psychiatric disorders	<i>Rare:</i> Psychoses, hyperactivity, euphoria, insomnia
Nervous system disorders	<i>Common:</i> Peripheral neuropathy (dose dependent and more common in undernourished patients, alcoholics, slow acetylators and diabetics), usually preceded by paresthesias of feet and hands (see section 4.4) <i>Rare:</i> Damage to the optic nerve (see section 4.4), convulsions, dizziness, light-headedness, headache, toxic encephalopathy. High doses may increase seizure frequency in epileptics (see section 4.4)
Vascular disorders	<i>Not known:</i> Vasculitis
Gastrointestinal disorders	<i>Common:</i> Nausea, vomiting, epigastric distress <i>Not known:</i> Pancreatitis
Hepatobiliary disorders	<i>Common:</i> Disturbances of liver function (usually mild and transient elevation of serum transaminase level). The most common prodromal symptoms are anorexia, nausea, vomiting, fatigue, malaise and weakness. (see section 4.4). <i>Uncommon:</i> Hepatitis <i>Rare:</i> Severe hepatitis

	<i>Very rare:</i> Fulminant hepatitis
Skin and subcutaneous tissue disorders	<i>Rare:</i> Toxic epidermal necrolysis, eosinophilia systemic symptoms <i>Unknown:</i> Acute generalised exanthematous pustulosis
General disorders and administration site conditions	<i>Common:</i> Allergic and other reactions, like drug exanthema and fever <i>Rare:</i> Allergic and other reactions, like dry mouth, heartburn, disorders of micturition, rheumatic syndrome, lupus erythematosus-like signs and symptoms, pellagra, lymphadenopathy, acne.
Musculoskeletal and connective tissue disorders	<i>Unknown:</i> Lupus-like syndrome

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions **via the national reporting system listed in Appendix V.**

4.9 Overdose

Rifampicin

Signs and Symptoms:

Nausea, vomiting, abdominal pain, pruritus, headache and increasing lethargy will probably occur within a short time after acute ingestion; unconsciousness may occur when there is severe hepatic disease. Transient increases in liver enzymes and/or bilirubin may occur. Brownish-red or orange colouration of the skin, urine, sweat, saliva, tears and faeces will occur, and its intensity is proportional to the amount ingested. Facial or periorbital oedema has also been reported in paediatric patients. Hypotension, sinus tachycardia, ventricular arrhythmias, seizures and cardiac arrest were reported in some fatal cases.

The minimum acute lethal or toxic dose is not well established. However, nonfatal acute overdoses in adults have been reported with doses ranging from 9 to 12 g rifampicin. Fatal acute overdoses in adults have been reported with doses ranging from 14-60 g. Alcohol or a history of alcohol abuse was involved in some of the fatal and nonfatal reports.

Nonfatal overdoses in paediatric patients ages 1 to 4 years old of 100 mg/kg for one to two doses have been reported.

Management:

Intensive supportive measures should be instituted and individual symptoms treated as they arise. Since nausea and vomiting are likely to be present, gastric lavage is probably preferable to induction of emesis. Following evacuation of the gastric contents, the instillation of activated charcoal slurry into the stomach may help absorb any remaining drug from the gastrointestinal tract. Antiemetic medication may be required to control severe nausea and vomiting. Active diuresis (with measured intake and output) will help promote excretion of the drug. Haemodialysis may be of value in some patients.

Isoniazid

Toxicity: The toxicity is potentiated by alcohol. Lethal dose 80-150 mg/kg bodyweight. 5 g to 15-year old resulted in lethal intoxication. 900 mg to 8-year old resulted in moderate intoxication. 2-3 g to 3-year old resulted in severe intoxication. 3 g to 15-year old and 5 - 7.5 g to adults resulted in extremely severe intoxication.

Symptoms: Typical symptoms are seizures, metabolic acidosis, ketonuria, hyperglycemia. In addition, periorbital myoclonus, dizziness, tinnitus, tremor, hyperreflexia, paresthesias, hallucinations, impaired consciousness. Respiratory depression, apnoea. Tachycardia, arrhythmias, hypotension. Nausea, vomiting. Fever, rhabdomyolysis, DIC, hyperglycaemia, hyperkalaemia. Liver involvement.

Doses of isoniazid exceeding 10 mg/kg may adversely affect the nervous system, e.g. in the form of peripheral neuropathy, and thus impair the patient's ability to drive or operate machinery.

Management: If authorised, evacuation of the stomach (provided the patient is not experiencing seizures), charcoal. Blood samples must be collected for immediate determination of blood gases, electrolytes, BUN, glucose etc. In the event of seizures and metabolic acidosis, pyridoxine is given at 1 g per g isoniazid. In the event of seizures and unknown dose, 5 g pyridoxine is given iv. In the absence of seizures, 2 - 3 g pyridoxine is given prophylactically intravenously. Pyridoxine should be diluted to reduce vascular irritation and is administered for 30 minutes via infusion pump or syringe pump. The dose is repeated if necessary. Diazepam potentiates the effect of pyridoxine. A high dose of diazepam can also be tried to combat seizures if pyridoxine is unavailable. In severe cases, respiratory therapy. Correction of metabolic acidosis and electrolyte disturbances. Ensure good diuresis. Haemodialysis or haemoperfusion in the event of extremely severe intoxication. Symptomatic treatment.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Combinations of drugs for treatment of tuberculosis (rifampicin and isoniazid).

ATC code J04A M02.

Rifampicin is a rifamycin antibiotic. Isoniazid is a bactericidal antituberculous agent.

Mechanism of action

Rifampicin exerts, both *in vitro* and *in vivo* bactericidal effects on *Mycobacterium tuberculosis*. It also exhibits variable activity against other atypical species of *Mycobacterium*.

In vivo rifampicin exerts its bacterial effect not only on micro-organisms in the extracellular spaces but also on those located intracellularly.

Rifampicin inhibits the DNA-dependent RNA polymerase of sensitive bacterial strains, but without affecting the host enzymatic systems.

Isoniazid exerts a bactericidal effect mainly on rapidly growing populations of *Mycobacterium tuberculosis*. Its mechanism of action is probably based chiefly on inhibition of mycolic acid synthesis, mycolic acid being an important constituent of the mycobacterial cell wall.

Susceptibility

Rifampicin in concentrations of 0.005 to 0.2 µg/ml inhibits the growth of *M. tuberculosis in vitro*. Rifampicin increases the *in vitro* activity of streptomycin and isoniazid against *M. tuberculosis*, but not that of ethambutol.

Isoniazid is bacteriostatic for "dormant" bacteria but is bactericidal for rapidly dividing micro-organisms. The minimal tuberculostatic concentration is 0.025 to 0.05 µg/ml.

The following resistance rates have been observed in new pulmonary TB cases (never treated patients) within the EU and EEA countries (data according to the ECDC Surveillance Report, 2012):

Agent	Resistance
Isoniazid	7.8% (range: 0 - 31.3%)
Rifampicin	3.0% (range: 0 – 19.1%)
Isoniazid and Rifampicin (Multidrug resistance)	2.6% (range: 0 – 18.6%)
Ethambutol	No data provided
Pyrazinamide	No data provided

Extrapulmonary tuberculosis

The treatment of extrapulmonary tuberculosis with short-course chemotherapy is recommended by WHO, IUATLD and several national committees like the American Thoracic Society although there have not been the same kinds of carefully conducted trials for extrapulmonary tuberculosis as for pulmonary tuberculosis.

5.2 Pharmacokinetic properties

Rifampicin

Rifampicin is well absorbed when taken on an empty stomach. The rate and extent of absorption is decreased when taken with food. Maximum plasma concentrations are reached about 2 h after administration. Rifampicin is rapidly distributed throughout the body. The concentration in cerebrospinal fluid is, however, generally low, except in meningitis. The volume of distribution is about 55 L. The protein binding is high (80%). Rifampicin is deacetylated to the active metabolite desacetyl-rifampicin. Rifampicin and desacetyl-rifampicin are excreted in the bile and rifampicin undergoes enterohepatic recycling. About 10% of the dose is excreted unchanged in urine.

The elimination half-life initially is 3 to 5 hours, decreasing to 2-3 hours on repeated administration. The rate of elimination is increased during the first 6 to 10 days of therapy, due to auto-induction of hepatic microsomal oxidative enzymes. After high doses excretion may be slower because of saturation of the biliary excretion.

Isoniazid

Isoniazid is rapidly absorbed following oral administration. The rate and extent of absorption is decreased when taken with food. Maximum plasma concentrations are reached 1-2 h after a dose. Isoniazid is widely distributed to most body fluids and tissues. The volume of distribution is about 43 L. Protein binding is very low, approximately 0 to 10%. Isoniazid is acetylated by N-acetyltransferase to N-acetylisoniazid. It is then biotransformed to isonicotinic acid and monoacetylhydrazine. Monoacetylhydrazine is associated with hepatotoxicity via formation of a reactive intermediate metabolite. The rate of acetylation is genetically determined; slow acetylators are characterised by a relative lack of hepatic N-acetyltransferase. Approximately 50 % of Caucasians and African Americans are slow acetylators. The majority of Eskimos and Asians with Mongolese ethnicity such as Japanese, Chinese and Vietnamese are rapid acetylators.

The half-life is generally between 1 and 4 hours, but can vary between 0.5 to 6 hours, depending of the rate of acetylation. Approximately 75-95% of the dose is excreted by the kidneys within 24 hours, primarily as the inactive metabolites N-acetylisoniazid and isonicotinic acid.

Characteristics in special risk groups

Rifampicin

With impaired renal function, the elimination half-life becomes prolonged at doses exceeding 600 mg daily (10 mg/kg). Rifampicin is not removed from the blood by haemodialysis.

In patients with impaired liver function, the plasma concentrations are raised and the elimination half-life prolonged. For treatment of patients with impaired liver function, see section 4.4.

Isoniazid

In slow acetylators with severely impaired renal function, accumulation of isoniazid may occur. In such cases, the serum concentration of isoniazid should be closely monitored and, if necessary, the dosage reduced.

In the presence of impaired liver function the elimination half-life of isoniazid is prolonged. For use in patients with impaired liver function, see section 4.4.

5.3 Preclinical safety data

Rifampicin

In female mice a significant increase in hepatomas was observed after 1 year of treatment with rifampicin in quantities equivalent to 2-10 times the maximum clinical doses.

In mice of another strain and in rats carcinogenicity studies were negative.

Rifampicin is thought not to be mutagenic in bacteria, *Drosophila melanogaster* or mice *in vivo*. An increase in chromatid breaks was noted when whole blood cell cultures were treated with rifampicin. Rifampicin has been reported to possess immunosuppressive potential in rabbits, mice, rats, guinea pigs, human lymphocytes *in vitro* and humans.

In pregnant rats, mice and rabbits, an unspecific embryotoxic effect occurred after doses exceeding 150 mg/kg daily. In rats and mice increased occurrence of spina bifida and cleft palate was observed within the same dose range.

Isoniazid

Isoniazid has a weak direct genotoxic effect and is a promutagenic substance through formation of the toxic metabolites hydrazine and acetylhydrazine via metabolic activation. Chromosomal changes have not been documented in lymphocytes from patients who were treated with isoniazid, while an increased frequency of chromosomal changes were documented in connection with combination treatment.

Conflicting data are reported on the isoniazid potential to induce teratogenic effects in animal models. Isoniazid may exert an embryocidal effect. No effects on fertility have been noted.

Limited evidence shows that isoniazid produces lung tumours in mice after various modes of administration. Available evidence of human exposure has not suggested that isoniazid is carcinogenic in humans at doses applicable to the treatment and prophylaxis of tuberculosis.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Pregelatinised maize starch

Maize starch

Sodium laurilsulfate

Crospovidone

Magnesium stearate

Talc

Copovidone

Hypromellose 3 cPs

Hypromellose 6 cPs

Hypromellose 50 cPs

Titanium dioxide (E 171)

Macrogol 400

Macrogol 6000

Red iron oxide (E 172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf-life

PVC/PE/PVDC-Alu blisters: 3 years

PP containers and HDPE bottle pack: 2 years

6.4 Special precautions for storage

Blisters: Do not store above 25°C. Store in the original package in order to protect from moisture.

Containers: Do not store above 30°C. Keep the container tightly closed in order to protect from moisture.

6.5 Nature and contents of container

Box containing 30, 60, 120, 240, 672 or 1000 film-coated tablets in PVC/PE/PVDC-aluminium blister.

White, opaque polypropylene container with polyethylene cap containing 500 film-coated tablets.

White, opaque polyethylene container with polypropylene cap containing 500 film-coated tablets.

Pack sizes of 500 and 1000 film-coated tablets are intended for clinical use.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

[To be completed nationally]

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: {DD month YYYY}

Date of latest renewal: {DD month YYYY}

[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

2026-02-23