**IRISH MEDICINES BOARD ACTS 1995 AND 2006**

**MEDICINAL PRODUCTS(CONTROL OF PLACING ON THE MARKET)REGULATIONS,2007**

**(S.I. No.540 of 2007)**

**PA0111/006/001**
Case No: 2064363

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

**Sandoz GmbH**

**Biochemiestrasse 10**, **A-6250 Kundl**, **Austria**

an authorisation, subject to the provisions of the said Regulations, in respect of the product

**Rimcure, film-coated tablet**

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **10/11/2009** until **05/03/2013**.

Signed on behalf of the Irish Medicines Board this

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A person authorised in that behalf by the said Board.

# Part II

# Summary of Product Characteristics

## 1 NAME OF THE MEDICINAL PRODUCT

Rimcure, film-coated tablet

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 150 mg rifampicin, 75 mg isoniazid and 400 mg pyrazinamide.
For a full list of excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM

Film-coated tablet.
The tablet is pink, ovaloid and biconvex.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic Indications

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

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

### 4.2 Posology and method of administration

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

The recommended dose and dosage schedules for Rimcure 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: Guidelines for national programmes; WHO/CDS/TB/2003.313, 2003.

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

Rimcure is a fixed combination product intended for use in the initial intensive phase of anti-tuberculous treatment. Rimcure should be administered on a daily basis throughout the 2 month initial phase of treatment. When indicated, other anti-tuberculous medicinal products such as streptomycin or ethambutol may be added in the initial phase of treatment.

Rimcure is a fixed combination product that should only be used when the fixed ratio of rifampicin 150 mg, isoniazid 75 mg and pyrazinamide 400 mg will permit treatment of an individual patient in line with official recommendations and practice.
Rimcure 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 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) |

**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) | 2 months | 2 | 3 | 4 | 5 |
| | | + S (vial 1 g) **2** | | 0.5 | 0.75 | 1 | 1 |
| | *and (subsequent)* **Rimstar** | 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) | 5 months | 2 | 3 | 4 | 5 |
| | | + E (400 mg) **2** | | 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:*
Rimcure 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).

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

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

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

Interruption of treatment
If initial intensive phase treatment with Rimcure is interrupted for any reason including non-compliance, a fixed drug combination product such as Rimcure is contraindicated for the resumption of treatment.
Rifampicin, isoniazid and pyrazinamide 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

Known or suspected hypersensitivity to rifamycins, isoniazid, pyrazinamide and/or to any of the excipients.

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

Porphyria.

Acute gouty arthritis.

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.).

## 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 three components separately in order to facilitate dose adjustment of isoniazid.

Rimcure 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.

Rimcure 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.

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

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

*Precautions*

The precautions for the use of Rimcure are the same as those that apply for the administration of rifampicin, isoniazid and pyrazinamide as individual medicinal products.

Patients should be advised against interrupting treatment.

Impaired liver function, undernourishment, alcoholism

Rifampicin, isoniazid and pyrazinamide 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 pyrazinamide, or the combination of the three 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, Rimcure 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, Rimcure, should be replaced by individual component formulations of rifampicin, isoniazid and pyrazinamide in order to facilitate treatment in these clinical circumstances.

Withdrawing rifampicin and pyrazinamide is recommended if liver function does not return to normal or transaminases exceed 5 times the ULN. The fixed drug combination, Rimcure, 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 Rimcure 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 Rimcure must be weighed against the possible risks.

If anti-tuberculous treatment is considered necessary, the dosage of rifampicin, isoniazid and pyrazinamide may need to be modified and Rimcure should not be used in such patients because it is only possible to adjust the dosage by administering rifampicin, isoniazid and pyrazinamide 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 and pyrazinamide can be delayed leading to a higher systemic exposure, which can results in an increase in adverse events. Rimcure should be used with caution in patients with moderate renal impairment (creatinine clearance 25-60 ml/min).

Gout
Pyrazinamide should be used with caution in patients with a history of gout. Regular monitoring of serum uric acid should be undertaken. Rimcure treatment should be stopped in gouty arthritis.

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. The possibility of pyrazinamide having an undesirable effect on blood clotting time or vascular integrity should be borne in mind in patients with haemoptysis.

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 Rimcure 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 Rimcure.

Laboratory tests
Full blood counts, liver function tests (SGPT/ALAT, SGOT/ASAT), renal function tests and monitoring serum uric acid 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 Rimcure 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 Rimcure 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.).

## 4.5 Interaction with other medicinal products and other forms of interaction

Influence of other medicinal products on Rimcure
Antacids reduce the bioavailability of rifampicin and isoniazid. To avoid this interaction, Rimcure 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 Rimcure 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.

Medicinal products that are eliminated by metabolism should only be used concomitantly with Rimcure 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 Rimcure 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 Rimcure.

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

*Interactions with rifampicin:*
Use of the following medicinal products concomitantly with Rimcure 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 Rimcure 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 Rimcure requires a precaution for use by monitoring specific parameters or through a clinical surveillance: calcium antagonists, class Ia antiarrhythmics (quinidine, disopyramide), oral anticoagulants, azole antifungals (except voriconazole), buspirone, carvedilol (because of its use in cardiac insufficiency and its low therapeutic margin in this indication), immunosuppressive agents (like ciclosporine, tacrolimus, sirolimus), clozapine, corticosteroids, gestrinone, estrogens and progestagens given as hormonal replacement therapy, haloperidol, thyroid hormones, methadone, morphine, efavirenz, propafenone, terbinafine, tiagabine, zidovudine, zolpidem, zaleplon, carbamazepine, phenytoine, theophylline, benzodiazepines, digitalis, dapsone, atovaquone, repaglinide or oral antidiabetics of sulfonylurea type, beta-receptor antagonists (if hepatically metabolised such as metoprolol, propranolol), chloramphenicol, clarithromycin, telithromycin, tricyclic antidepressants, p-aminosalicylic acid, cimetidine, mexiletine, nevirapine, fluvastatin, etorocoxib, rofecoxib, imidapril, tropisetron, linezolid.

*Interactions with isoniazid:*
Use of the following medicinal products concomitantly with Rimcure 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.

*Interactions with pyrazinamide:*
Use of the following medicinal products concomitantly with Rimcure requires a precaution for use by monitoring specific parameters or through a clinical surveillance: probenecid, sulfinpyrazon.

Rifampicin may reduce the effectiveness of oral contraceptives and patients treated with Rimcure 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 Pregnancy and lactation

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

*Rifampicin*
On limited clinical data on exposed pregnancy, no increase in the rate of foetal malformation was found. Rifampicin crosses the placenta. Administration of rifampicin during the last few weeks of pregnancy can cause postnatal haemorrhage in the mother and newborn infant. Studies in animals have shown reproductive toxicity at doses ≥150 mg/kg (see section 5.3.).

*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).

*Pyrazinamide*
No animal reproductive studies have been conducted with pyrazinamide. Nor is it known whether pyrazinamide can cause foetal damage when administered to a pregnant woman.

- 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.

Rifampicin, isoniazid and pyrazinamide 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

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

## 4.8 Undesirable effects

| | | |
|---|---|---|
| Frequency estimates: | *Common:* | ≥ 1/100 to <1/10 |
| | *Uncommon:* | ≥ 1/1,000 to < 1/100 |
| | *Rare:* | ≥ 1/10,000 to < 1/1,000 |
| | *Very rare:* | < 1/10,000 |

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

| | | |
|---|---|---|
| Blood and lymphatic system disorders | *Rare:* | Transient leucopenia, eosinophilia. Thrombocytopenia and thrombocytopenic purpura are encountered more frequently with intermittent therapy than with continuous daily treatment, during which they occur only in very care 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 |
| Endocrine disorders | *Rare:* | Menstrual disturbances (in extreme cases amenorrhoea); induction of crisis in Addison patients (see section 4.5) |
| Psychiatric disorders | *Rare:* | Mental confusion |
| Nervous system disorders | *Common:* | Tiredness, drowsiness, headache, light-headedness, dizziness |
| | *Rare:* | Ataxia, muscular weakness |
| Eye disorders | *Common:* | Reddening of the eyes, permanent discolouration of soft contact lenses |
| | *Rare:* | Visual disturbances, Severe signs and symptoms, such as e.g. exudative conjunctivitis |
| Gastrointestinal disorders | *Common:* | Anorexia, nausea, abdominal pain, bloatedness |
| | *Rare:* | Vomiting or diarrhoea, isolated occurrences of erosive gastritis and pseudomembranous colitis |
| Skin and subcutaneous tissue disorders | *Common:* | Flushing, itching with or without skin rash, urticaria |
| | *Rare:* | Severe skin reactions such as generalised hypersensitivity reactions, e.g. exfoliative dermatitis, Lyell's syndrome and pemphigoid reactions |
| Hepatobiliary disorders | *Common:* | Asymptomatic increase in liver enzymes (see section 4.4) |
| | *Rare:* | Hepatitis or jaundice, induction of porphyria (see section 4.3) |
| Renal and urinary disorders | *Rare:* | 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 | *Common:* | Reddish discoloration of body fluids and secretions such as e.g. urine, sputum, lacrimal fluid, faeces, saliva and sweat. |
| | *Rare:* | Collapse, shock, oedema |

**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).

**Undesirable effects of isoniazid**

| | | |
|---|---|---|
| Blood and lymphatic system disorders | *Rare:* | Eosinophilia, thrombocytopenia, anaemia (haemolytic, sideroblastic) |
| | *Very rare:* | Agranulocytosis |
| Endocrine disorders | *Rare:* | 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 | *Rare:* | Psychoses, hyperactivity, euphoria, insomnia |
| Nervous system disorders | *Common:* | 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) |
| | *Rare:* | 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) |
| Gastrointestinal disorders | *Common:*<br>*Very Rare:* | Nausea, vomiting, epigastric distress<br>Pancreatitis |
| Hepatobiliary disorders | *Common:* | 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). |
| | *Rare:* | Hepatitis, severe hepatitis |
| | *Very rare:* | Fulminant hepatitis |

| | | |
|---|---|---|
| General disorders and administration site conditions | *Common:* | Allergic and other reactions, like drug exanthema and fever |
| | *Rare:* | Allergic and other reactions, like dry mouth, heartburn, disorders of micturition, rheumatic syndrome, lupus erythematosus-like signs and symptoms, pellagra, vasculitis, lymphadenopathy, acne. |

**Undesirable effects of pyrazinamide**

| | | |
|---|---|---|
| Blood and lymphatic system disorders | *Rare:* | Thrombocytopenia, sideroblastic anaemia, undesirable effects on blood clotting mechanisms, splenomegaly |
| Gastro-intestinal disorders | *Common:* | Nausea, vomiting, anorexia, abdominal pain |
| Hepatobiliary disorders | *Common:* | Moderate and transient rises in serum transaminase level during the early phase of treatment (see section 4.4). Porphyria (see section 4.3) |
| | *Rare:* | Severe hepatotoxicity appears to be related to dose; hepatomegaly, jaundice |
| Renal and urinary disorders | *Common:* | Hyperuricaemia (often asymptomatic), gout requiring treatment (see section 4.3 and section 4.4). |
| | *Rare:* | Interstitial nephritis, dysuria |
| General disorders and administration site conditions | *Common:* | Allergic and other reactions, like mild arthalgia and myalgia |
| | *Rare:* | Allergic and other reactions, like skin rash, photosensitivity, urticaria, pruritus, fever, acne |

## 4.9 Overdose

*Rifampicin*
Toxicity: Overdose symptoms and outcomes are variable as appears from practice: Doses of 15 g and 60 g to adults resulted in fatal outcomes, whereas 9 g in adults led to severe intoxication and 12 g to adolescents resulted in moderate intoxication.

Symptoms: Gastrointestinal complaints, vomiting, sweating, dyspnoea, seizures, renal failure, liver involvement, impaired consciousness, generalised pruritus. Reddish-orange discoloration of skin and urine, facial oedema. Possibly pulmonary oedema.

Treatment: If authorised, evacuation of the stomach, repeated doses of charcoal. Symptomatic treatment. Dialysis may be required in the event of renal failure.

*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.

Treatment: 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.

*Pyrazinamide*
Abnormal liver function tests, hyperuricaemia.

# 5 PHARMACOLOGICAL PROPERTIES

## 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Combinations of drugs for treatment of tuberculosis (rifampicin, pyrazinamide and isoniazid).
ATC-code J04A M05.

Rifampicin is a rifamycin antibiotic. Isoniazid and pyrazinamide are bactericidal antituberculous agents.

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.

*Pyrazinamide*: The exact mechanism of action is unknown. *In vitro* and *in vivo* studies have demonstrated that pyrazinamide is only active at a slightly acidic pH (pH 5.5).

Microbiological sensitivity

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 pyrazinamide MIC for *M. tuberculosis* has been reported to be in the range 12.5-20 µg/ml.

Once the initial intensive phase of treatment has been completed treatment can be continued with the combination rifampicin-isoniazid on a daily basis.
This regimen (initial intensive phase followed by continuation phase treatment) is appropriate in case of new tuberculosis patients, in case of relapse, in case of treatment after interruption or treatment failure.

The following resistance rates have been observed in new cases (never treated patients) within western and central Europe (data according to the EuroTB project, March 2002):

| **Agent** | **Resistance** |
|---|---|
| Isoniazid | 4.1% (range: 0 - 9.3%) |
| Rifampicin | 0.7% (range: 0 – 2.1%) |
| Isoniazid and Rifampicin (Multidrug resistance) | 0.5% (range: 0 – 2.1%) |
| 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 desacetylrifampicin. Rifampicin and desacetylrifampicin 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.

*Pyrazinamide*
Pyrazinamide is well absorbed from the gastrointestinal tract. The absorption is not affected by concomitant food intake. Maximum plasma concentrations are reached after 1-2 hours in adults and about 3 hours in children. Pyrazinamide is rapidly distributed throughout the body. Pyrazinamide is hydrolysed by a microsomal deaminase to pyrazinoic acid, an active metabolite, and then hydroxylated by xanthine oxidase to 5-hydroxypyrazinoic acid. Pyrazinamide is renally excreted, mainly as metabolites. Only 3% of the dose is excreted unchanged in urine. The half-life is about 10 hours.

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..

*Pyrazinamide*
Patients with hepatic cirrhotic insufficiency exhibit a marked reduction of the pyrazinamide clearance and an increase in half-life. The area under the curve of pyrazinoic acid (the main metabolite) is increased three-fold (see also section 4.4.).

There is no information regarding the pharmacokinetics of pyrazinamide in renal impairment. Pyrazinamide is removed from blood by haemodialysis.

## 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, *Drosophilia 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.

*Pyrazinamide*
Pyrazinamide was not found to be carcinogenic in rats or male mice while no conclusion was possible for female mice. Pyrazinamide was not mutagenic in the Ames bacterial test, but induced chromosomal aberrations in human lymphocytes.

*Ethambutol*
Conflicting results are available on genotoxicity (negative in human lymphocyte cell cultures, positive in mouse micronucleus). In mice, ethambutol administered together with sodium nitrite gave rise to an increased frequency of lymphomas and lung tumours, while ethambutol alone did not cause any increase in tumour frequency.

Cleft palate, exencephaly and vertebral column abnormalities have been observed with high doses in studies of reproduction toxicity in mice. Studies in rats and rabbits have shown that ethambutol in high doses causes minor abnormalities of the cervical vertebrae and monophthalmia, limb reduction defects, hare lip and cleft palate in the offspring.

# 6 PHARMACEUTICAL PARTICULARS

## 6.1 List of excipients

*Tablet core:*
Pregelatinised maize starch
Maize starch
Sodium laurilsulfate
Crospovidone
Magnesium stearate
Talc

*Film-coating:*
Copovidone
Hypromellose
Talc
Titanium dioxide (E171)
Opadry pink 03B54929 [hypromellose, titanium dioxide (E171), macrogol 400, red iron oxide (E172)]
Opadry clear OY-S-29019 [hypromellose, macrogol 6000]

## 6.2 Incompatibilities

Not applicable.

## 6.3 Shelf Life

30 months

## 6.4 Special precautions for storage

Blisters: Do not store above 30ºC. Store in the original package in order to protect from moisture.
Containers: Do not store above 30ºC. Keep the container tightly closed in order to protect from moisture.

## 6.5 Nature and contents of container

Box containing 30, 60, 120, 240 or 1000 tablets in PVC/PE/PVDC-aluminium blister.
White, opaque polypropylene container with polyethylene cap containing 500 tablets.

Pack sizes of 500 and 1000 tablets are intended for clinical use. Not all packsizes may be marketed.

## 6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

## 7 MARKETING AUTHORISATION HOLDER

Sandoz GmbH
Biochemiestrasse 10
A-6250 Kundl
Austria

## 8 MARKETING AUTHORISATION NUMBER

PA 111/6/1

## 9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 12th August 2005
Date of last renewal: 6th March 2008

## 10 DATE OF REVISION OF THE TEXT

October 2008