APPROVED PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

RISOPET film coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains:

150 mg of rifampicin, 75 mg of isoniazid, 400 mg of pyrazinamide and 275 mg of ethambutol hydrochloride.

Contains ascorbic acid as an anti-oxidant.

RISOPET tablets are sugar free.

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Film coated tablets.

Brown coloured, capsule shaped film coated tablets with a break line on one side and plain on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

RISOPET is indicated for the initial phase treatment of pulmonary and extra-pulmonary tuberculosis in new adult patients and re-treatment of adult cases.

4.2 Posology and method of administration

The recommended treatment dosages, based on the patient's body weight, given daily for the 2 month initial-phase treatment in adults and children older than 13 years of age are as follows:

- 30 - 37 kg 2 tablets
- 38 - 54 kg 3 tablets
- 55 - 70 kg 4 tablets
- 71 kg and over 5 tablets

Special populations

Use in patients with body weight less than 30 kg

RISOPET 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).

Elderly

No special dosage regimen is necessary, but concurrent hepatic and/or renal insufficiency should be taken into account. Supplementation of pyridoxine (vitamin B_6) may be useful.

Hepatic insufficiency

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

Renal insufficiency

RISOPET should be used with caution in patients with moderate renal impairment (creatinine clearance 30 – 60 ml/min, see section 4.4). RISOPET is contraindicated in patients with severe renal impairment (creatinine clearance < 30 ml/min, see section 4.3).

Paediatric population

RISOPET is not a suitable dosage form for use in the treatment of children with a body weight of less than 30 kg and is not recommended in children under 13 years of age because of risk of aspiration and possible difficulties in evaluation of changes of visual acuity (see sections 4.3 and 4.4).

Method of administration

RISOPET tablets should be taken with a full glass of water 1 hour before, or 2 hours after a meal. If RISOPET tablets result in gastrointestinal irritation, it may be taken with food. If aluminium-containing antacids are taken, RISOPET tablets should be administered one hour after the antacid tablet dose.

Missed dose:

Doctors should advise patients who forget to take RISOPET to take a dose as soon as possible and then continue with the normal dose. Patients should not take a double dose to compensate for the missed dose.

4.3 Contraindications

RISOPET tablets are contraindicated in:

- hypersensitivity to rifampicin, isoniazid, pyrazinamide, ethambutol, any other chemically related medication, or to any of the ingredients of RISOPET
- patients with jaundice or active hepatic disease
- patients with severe renal function impairment (creatinine clearance < 30 ml/min)
- patients with optic neuritis
- pregnancy and lactation (see section 4.6)
- children younger than 13 years of age
- concomitant use with voriconazole and the combination of saquinavir / ritonavir, protease inhibitors except ritonavir when given at full dose or 600 mg twice daily (see section 4.5)
- porphyria.

Rifampicin very markedly reduces ketoconazole levels. Rifampicin levels are halved by ketoconazole (see section 4.5).

4.4 Special warnings and precautions for use

Liver function should be assessed before and regularly during treatment as each active ingredient contained in RISOPET has been associated with liver dysfunction.

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

Hypersensitivity

Treatment should be discontinued permanently should shock, renal failure, haemolytic anaemia, dyspnoea and asthma-like attacks, thrombocytopenia or purpura occur as these are side effects that rifampicin may provoke in exceptional cases.
Patients developing such reactions must never again be treated with rifampicin.
Patients should be advised against interrupting treatment. Use of RISOPET after interruption has been associated with increased risk of serious adverse effects.
Treatment with RISOPET tablets should be stopped immediately and the patient evaluated should rash and fever occur.

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN)

Cases of severe cutaneous reactions including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), some with a fatal outcome, have been reported with the use of isoniazid (see section 4.8). Patients should be advised of the signs and symptoms and monitored closely for skin reactions. If signs or symptoms of SJS or TEN (e.g.

progressive skin rash often with blisters or mucosal lesions) develop, the patient should be advised to consult their doctor immediately. RISOPET should be permanently discontinued if an
alternative aetiology for the signs and symptoms cannot be established.

Impaired liver function, undernourishment, alcoholism

Rifampicin, isoniazid, pyrazinamide and ethambutol 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.

Patients with impaired liver function should only be given rifampicin in cases of necessity and then with caution and under strict medical supervision. In these patients, careful monitoring of liver function, especially serum alanine aminotransferase (ALT) and serum aspartate
aminotransferase (AST) should be carried out prior to therapy and then every 2 to 4 weeks during therapy. If signs of hepatocellular damage occur, rifampicin should be withdrawn.
In some cases, hyperbilirubinaemia resulting from competition between rifampicin and bilirubin for excretory pathways of the liver at cell level can occur in the early days of treatment.

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.

Use of isoniazid should be carefully monitored in patients with current chronic liver disease or severe renal dysfunction.

Severe and sometimes fatal hepatitis associated with isoniazid therapy may occur and may develop even after months of treatment. The risk of developing hepatitis is age related. Therefore, patients should be monitored for the prodromal symptoms of hepatitis, such as fatigue, weakness, malaise, anorexia, nausea or vomiting.

Treatment with RISOPET tablets should be stopped immediately and the patient evaluated in the following cases: jaundice or elevated liver enzymes associated with the clinical signs of hepatitis since continued use of the medicine in these cases has been reported to cause a more severe form of liver damage.

Special care should be exercised in alcoholic patients, the elderly (patients of 50 years and older have the highest incidence of hepatitis with the use of isoniazid) or those with pre-existing hepatic disease.

Risk of neuropathy or pyridoxine deficiency, including those who are alcoholic, malnourished, diabetic, uremic, HIV infected or pregnant, supplementation with

pyridoxine (in a 10 mg to 50 mg daily dose) is usually required under these circumstances.

Medicine reaction with eosinophilia and systemic symptoms ("DRESS")

Severe, systemic hypersensitivity reactions, including fatal cases, such as medicine reaction with eosinophilia and systemic symptoms (DRESS) syndrome have been observed during treatment with anti-tuberculosis therapy (see section 4.8).

It is important to note that early manifestations of hypersensitivity, such as fever, lymphadenopathy or biological abnormalities (including eosinophilia, liver abnormalities) may be present even though rash is not evident. If such signs or symptoms are present, the patient should be advised to consult their doctor immediately. RISOPET should be discontinued if an alternative aetiology for the signs and symptoms cannot be established.

Impaired renal function

Impaired kidney function: dosage adjustment may be necessary according to the ethambutol serum concentration.

In severe renal insufficiency, the elimination of isoniazid, pyrazinamide and ethambutol can be delayed leading to a higher systemic exposure, which can result in an increase in adverse events. RISOPET should

be used with caution in patients with moderate renal impairment (creatinine clearance 30 - 60 ml/min).

Gout

In patients with a history of gout, regular monitoring of serum uric acid should be undertaken. RISOPET 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

Pyrazinamide may interfere with the measurement of urine ketone levels (see section 4.5).
Increased difficulty has been reported in controlling diabetes mellitus when such patients are given isoniazid.

Epilepsy/psychosis

Caution should be observed with the use of RISOPET in patients with

- Epilepsy, as convulsions may be triggered
- History of psychosis

Visual defects

Should visual disturbances arise during treatment with RISOPET tablets (especially in the elderly, and in children in whom evaluation of changes in visual acuity may be difficult), it must be reported immediately, and the medicine discontinued pending visual evaluation. Periodic eye examinations during treatment are suggested.

Contraception

The efficacy of oral contraceptives may be affected by rifampicin; patients should be advised to change to non-hormonal methods for effective birth control (see section 4.5).

Antacids

The absorption of rifampicin may be reduced by antacids, but this interaction can be overcome by giving RISOPET an hour before any antacid. Similarly, RISOPET and preparations containing bentonite (e.g. some amino-salicylic acid preparations) should be given 8 hours apart (see section 4.5).

Discolouration of teeth, body fluids and contact lenses

Treatment with RISOPET tablets may lead to reddish-orange colouration of faeces, saliva, sputum, urine, tears and sweat. Soft contact lenses may be stained irreversibly. Avoid the wearing of soft contact lenses during treatment.

4.5 Interaction with other medicines and other forms of interaction

Influence of other medicines on RISOPET

Antacids reduce the bioavailability of rifampicin, isoniazid and ethambutol. To avoid this interaction, RISOPET should be taken at least 1 hour before antacids (see section 4.4).

Glucocorticosteroids may increase hepatic metabolism and/or excretion of isoniazid.

Influence of RISOPET on other medicines

Rifampicin and isoniazid

Cytochrome P-450 enzyme interaction

Rifampicin induces and isoniazid inhibits certain cytochrome P-450 enzymes. Care should be taken when RISOPET tablets are prescribed with medicines metabolised by cytochrome P-450. To maintain optimum therapeutic plasma levels, the dosages of medicines metabolised by cytochrome P-450 enzymes may require adjustment when initiating or stopping concomitant administration of RISOPET tablets.

Some medicines 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.

Medicines that are eliminated by metabolism should only be used concomitantly with RISOPET 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 RISOPET 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 RISOPET.

Rifampicin

Combinations contraindicated

Enzyme induction

When RISOPET is given concurrently with the combination saquinavir/ritonavir, the potential for hepatotoxicity is increased. Concomitant use with voriconazole and saquinavir/ritonavir, protease inhibitors, except ritonavir when given at full dose or 600 mg twice daily is contraindicated (see section 4.3).

Combinations not recommended

Use of the following medicines concomitantly with RISOPET 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).

When rifampicin is given concomitantly with either halothane or isoniazid, the potential for hepatotoxicity is increased. The concomitant use of rifampicin and halothane should be avoided. Patients receiving both rifampicin and isoniazid should be monitored closely for hepatotoxicity.

Combinations requiring precaution

Rifampicin increases the rate of metabolism of certain medicines by inducing microsomal enzymes, resulting in decreases in the plasma levels of such medicines.
Examples of medicines metabolised by cytochrome P-450 enzymes include analgesics (e.g. methadone, narcotic analgesics, morphine, etoricoxib, rofecoxib), antidysrhythmics (e.g. disopyramide, mexiletine, quinidine, propafenone, tocainide, verapamil), antibacterials (e.g. chloramphenicol, clarithromycin, dapsone, doxycycline, fluoroquinolones, telithromycin, linezolid, p-aminosalicylic acid) anticoagulants (e.g. warfarin), anticonvulsants (e.g. phenytoin, tiagabine, carbamazepine), antiestrogens (e.g. tamoxifen, toremifene, gestrinone), antifungals (e.g. fluconazole, itraconazole, ketoconazole, voriconazole, terbinafine), antipsychotics (e.g. haloperidol, clozapine, aripiprazole), antiretrovirals (e.g. zidovudine, delavidine, saquinavir, indinavir, efavirenz and protease inhibitors), atovaquone, barbiturates (e.g. hexobarbitone), beta-blockers,

benzodiazepines (e.g. diazepam), benzodiazepine-related medicines (e.g. zopiclone, zolpidem), calcium channel blockers (e.g. diltiazem, nifedipine, verapamil, nimodipine, isradipine, nicardipine, nisoldipine, amlodipine), cardiac glycosides (e.g. digoxin), cimetidine, clofibrate, clofazimine, co-trimoxazole, cytotoxics (e.g. imatinib, geftinib, irinotecan), diuretics (e.g. eplerenone), systemic hormonal contraceptives, corticosteroids, estrogens, fexofenadine, , oral hypoglycaemic agents (sulfonylureas), immunosuppressive agents (e.g. azathioprine, cyclosporine, tacrolimus), irinotecan, levothyroxine, losartan, imidapril, enalapril, praziquantel, progestins, quinine, riluzole, selective 5-HT_3 receptor antagonists (e.g. ondansetron), statins metabolised by CYP 3A4, fluvastatin, sulphasalazine, thiazolidinediones (e.g. rosiglitazone), theophylline, thyroid hormone (e.g. levothyroxine), tricyclic antidepressants (e.g. amitriptyline).
It may be necessary to adjust the dosages of these medicines if they are given concurrently with rifampicin.

The effectiveness of estrogen-containing oral preparations is reduced.
Patients using systemic hormonal contraceptives should be advised to use additional precautions or to switch to non-hormonal methods of contraception during rifampicin therapy (see section 4.4).

Concurrent use of alcohol, isoniazid, paracetamol, and other hepatotoxic medicines may increase the incidence of rifampicin-induced hepatotoxicity.

Concurrent use of enalapril has resulted in decreased concentrations of enalaprilat, the active metabolite of enalapril. Dosage adjustments should be made if indicated by the patient's clinical condition.

Interference with laboratory and diagnostic tests

Therapeutic levels of rifampicin have been shown to inhibit standard microbiological assays for serum folate and vitamin B12. Thus, alternative assay methods should be considered.

Transient elevation of serum bilirubin has also been observed. RISOPET tablets may impair biliary excretion of contrast media used for visualisation of the gallbladder, due to competition for biliary excretion. Therefore, these tests should be performed before the morning dose of rifampicin.

Isoniazid

Combinations requiring precaution

Chronic use of isoniazid may decrease the plasma clearance and prolong the duration of action of alfentanil, benzodiazepines (diazepam, triazolam), carbamazepine, chlorzoxazone, coumarin anticoagulants, ethosuximide, primidone, theophylline, disulfiram and phenytoin. Appropriate adjustment of the anticonvulsant dose may be required.

Isoniazid has been associated with increased concentrations or toxicity of cycloserine and warfarin.

Concurrent use of alcohol, paracetamol, rifampicin and other hepatotoxic agents, may increase the potential for isoniazid-induced hepatotoxicity.

Aluminium-containing antacids may delay absorption and decrease serum concentrations of isoniazid.

Glucocorticosteroids may increase hepatic metabolism and/or excretion of isoniazid.

Para-Aminosalicylic acid may increase the plasma concentration and elimination half-life of isoniazid.

Concurrent use of ciclosporin, disulfiram, cycloserine and other neurotoxic medicines may increase the potential for CNS toxicity.

Isoniazid may increase the formation of potentially nephrotoxic inorganic fluoride metabolites when used concomitantly with enflurane.

Interactions with miconazole and ketoconazole have been reported.

Copper sulphate urine glucose tests may show false positive reactions.

Consumption of red wine, cured meat, beer and certain types of cheese e.g. Swiss or Cheshire (tyramine-containing foods), or foods containing histamine e.g. fish such as tuna, skipjack, other tropical fish, salmon, mackerel may result in chills or headache, sweating, flushing, hypotension, itching of the skin and a rapid or pounding heart. Tyramine-and histamine-containing foods should be avoided by patients on RISOPET therapy.

Pyrazinamide

Combinations requiring precaution

Pyrazinamide may decrease the efficacy of medicines used in the treatment of gout (e.g. allopurinol, colchicine, probenecid or sulphinpyrazone). Dosage adjustments of these medicines may be necessary.

The dosage of pyrazinamide may be decreased by zidovudine.

Pyrazinamide may interfere with the measurement of urine ketone levels in patients with diabetes (see section 4.4).

Ethambutol

Combinations requiring precaution

Concurrent use of ethambutol with neurotoxic medicines may potentiate neurotoxic effects such as optic and peripheral neuritis.

4.6 Fertility, pregnancy and lactation

Pregnancy

The safety of RISOPET tablets in pregnancy has not been established.

Rifampicin has been reported to cross the placental barrier. When administered during the last weeks of pregnancy, rifampicin can cause post-natal haemorrhages in the mother and infant, for which treatment with vitamin K may be indicated.

Breastfeeding

All components of RISOPET tablets are excreted in breast milk.

The safety of RISOPET tablets in breast feeding has not been established.

4.7 Effects on ability to drive and use machines

RISOPET can cause side-effects such as confusion, disorientation, dizziness or drowsiness and visual disturbances. RISOPET may impair your ability to drive and use machinery. Patients should be advised to not drive, operate machinery, or do anything else that could be dangerous until they know how RISOPET affects them.

4.8 Undesirable effects

Tabulated summary of adverse reactions

Side effects associated with rifampicin

System Organ Class	Frequency	Side effects
Infections and Infestations	Less frequent	Fungal overgrowth (sore mouth or tongue)

Blood and lymphatic system disorders	Frequent Less frequent Frequency unknown	Thrombocytopenia, purpura Leucopenia, blood dyscrasias (sore throat, unusual bleeding or bruising), eosinophilia, haemolytic anaemia, agranulocytosis, oedema, haemolysis
Immune system disorders	Less frequent Frequency unknown	Anaphylaxis, shock Lupus-like syndrome, 12-hour “flu” syndrome, chills, fever, malaise, bone pain, wheezing, shortness of breath
Endocrine disorders	Less frequent	Induction of crisis in Addison patients, pancreatitis
Metabolism and nutrition disorders	Frequency unknown	Decreased appetite
Psychiatric disorders	Less frequent	Mental confusion, psychosis
Nervous system disorders	Frequent Frequency unknown	Headache, numbness, tiredness, drowsiness, light-headedness, dizziness, ataxia Generalised numbness, cerebral haemorrhage and fatalities have been reported when rifampicin administration has been continued or resumed after the appearance of purpura
Eye disorders	Frequent Frequency unknown	Eye irritation, visual disturbances (blurred vision), exudative conjunctivitis Permanent discolouration of soft contact lenses, tear discolouration

Vascular disorders	Frequency unknown	Disseminated intravascular coagulation, decrease in blood pressure, shock, flushing, vasculitis
Respiratory, thoracic and mediastinal disorders	Less frequent Frequency unknown	Shortness of breath, wheezing Dyspnoea, discoloured sputum
Gastrointestinal disorders	Frequent Frequency unknown	nausea, vomiting, diarrhoea Gastrointestinal disorder, abdominal discomfort, epigastric distress (which may be alleviated by administration with food), tooth discolouration
Hepatobiliary disorders	Frequency unknown	Prodromal symptoms of hepatitis, transient abnormalities in liver function, hepatotoxicity, hyperbilirubinemia
Skin and subcutaneous tissue disorders	Less frequent Frequency unknown	Cutaneous syndrome, flushing, itching with or without skin rash, urticaria Pemphigoid reactions, toxic epidermal necrolysis, vasculitis and erythema multiforme, including Stevens-Johnson syndrome, toxic epidermal necrolysis, exfoliative dermatitis, fixed-medicine eruptions, acute generalised exanthematous pustulosis, sweat discolouration

Musculoskeletal, connective tissue and bone disorders	Frequency unknown	Muscular weakness and myopathy, bone pain, myalgia
Renal and urinary disorders	Frequency unknown	Alteration in kidney function, interstitial nephritis (bloody or cloudy urine, greatly decreased frequency of urination or amount of urine), renal failure
Pregnancy, puerperium and perinatal conditions	Frequency unknown	Post-partum haemorrhage, foetal-maternal haemorrhage
Reproductive system and breast disorders	Frequency unknown	Menstrual disturbances
Congenital and familial/genetic disorders	Frequency unknown	Porphyria exacerbation
General disorders and administrative site conditions	Frequent Frequency unknown	Reddish-orange discoloration of urine, faeces, saliva, sputum, sweat and tears, pyrexia, chills Collapse, shock, oedema
Investigations	Frequent Frequency unknown	Increased blood bilirubin, increased aspartate aminotransferase (AST), increased alanine aminotransferase (ALT) Decreased blood pressure, increased blood creatinine, increased hepatic enzyme

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Side effects associated with isoniazid

System Organ Class	Frequency	Side effects
Blood and lymphatic system disorders	Frequency unknown	Blood dyscrasias, including various anaemias (aplastic anaemia, sideroblastic anaemia, haemolytic anaemia), agranulocytosis, eosinophilia, thrombocytopenia and neutropenia
Immune system disorders	Less frequent Frequency unknown	Hypersensitivity reactions, systemic lupus erythematosus-like syndrome Anaphylactic reactions
Endocrine disorders	Less frequent Frequency unknown	Pancreatitis Menstrual disturbances, Cushing syndrome, pubertas praecox, and difficult controllable diabetes
Metabolism and nutrition disorders	Frequency unknown	Pellagra, hyperglycaemia, metabolic acidosis
Psychiatric disorders	Frequency unknown	Psychotic reactions, convulsions, toxic psychosis, memory impairment and toxic encephalopathy, increased seizure frequency in epileptics, hyperactivity, euphoria, insomnia, delusions, hallucinations, ataxia, cerebellar toxicity, stupor

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Nervous system disorders	Frequent Less frequent	Polyneuritis, paraesthesia, neurotoxicity, peripheral neuropathy Dizziness, light-headedness, headache, toxic encephalopathy, high doses may increase seizure frequency
Eye disorders	Frequency unknown	Optic neuritis and atrophy
Ear and labyrinth disorders	Frequency unknown	Vertigo, tinnitus
Vascular disorders	Frequency unknown	Vasculitis
Gastrointestinal disorders	Frequent Frequency unknown	Diarrhoea, constipation, dry mouth Nausea and vomiting, epigastric distress
Hepatobiliary disorders	Frequent Less frequent	Raised liver enzymes Hepatitis, severe hepatitis, fulminant hepatitis, hepatotoxicity
Skin and subcutaneous tissue disorders	Frequency unknown	Acne, rash, Stevens-Johnson syndrome, pemphigus, exfoliative dermatitis medicine reaction with eosinophilia and systemic symptoms (DRESS) syndrome, toxic epidermal necrolysis (TEN), lupus-like reactions, erythema multiforme, vasculitis, urticaria, purpura, pellagra, alopecia

Musculoskeletal, connective tissue and bone disorders	Frequency unknown	Rheumatoid syndrome, loss of tendon reflexes, muscle weakness, hyperreflexia, muscle twitching, arthritic symptoms, arthralgia
Renal and urinary disorders	Frequency unknown	Urinary retention
Reproductive system and breast disorders	Frequency unknown	Gynecomastia
General disorders and administrative site conditions	Frequency unknown	Lymphadenopathy, fever

Side effects associated with pyrazinamide

System Organ Class	**Frequency**	**Side effects**
Blood and lymphatic system disorders	Frequency unknown	Sideroblastic anaemia, thrombocytopenia, undesirable effects on blood clotting mechanisms, splenomegaly
Immune system disorders	Less frequent	Allergic reactions
Metabolism and nutrition disorders	Frequency unknown	Anorexia
Gastrointestinal disorders	Frequency unknown	Nausea, vomiting, anorexia, abdominal pain aggravation of peptic ulcer
Hepatobiliary disorders	Frequency unknown	Hepatotoxicity (frequency appears to be dose-related), increases in liver enzymes hepatomegaly, jaundice, porphyria

Skin and subcutaneous tissue disorders	Less frequent Frequency unknown	Angioedema Itching, skin rash, photosensitivity, pellagra, urticaria, pruritus, acne, medicine reaction with eosinophilia and systemic symptoms (DRESS) syndrome
Musculoskeletal, connective tissue and bone disorders	Frequent Frequency unknown	Arthralgia, myalgia Gouty arthritis
Renal and urinary disorders	Frequency unknown	Dysuria
General disorders and administrative site conditions	Frequent	Fever, malaise

Side effects associated with ethambutol

System Organ Class	**Frequency**	**Side effects**
Blood and lymphatic system disorders	Less frequent Frequency unknown	Thrombocytopenia Eosinophilia, leucopenia, neutropenia
Immune system disorders	Less frequent	Hypersensitivity reactions, anaphylactic reactions
Metabolism and nutrition disorders	Frequency unknown	Hyperuricaemia
Psychiatric disorders	Less frequent	Hallucinations, disorientation, confusion
Nervous system disorders	Less frequent Frequency unknown	Headache, dizziness, malaise Peripheral neuritis

Eye disorders	Frequency unknown	Retrobulbar optic neuritis with a reduction in visual acuity, constriction of visual field, central or peripheral scotoma, green-red colour blindness, retinal haemorrhage.
Respiratory, thoracic and mediastinal disorders	Less frequent	Pulmonary infiltrates
Gastrointestinal disorders	Frequent	Gastrointestinal disturbances including metallic taste, anorexia, loss of appetite, abdominal pain, nausea, vomiting
Hepatobiliary disorders	Frequency unknown	Jaundice, transient liver dysfunction
Skin and subcutaneous tissue disorders	Frequency unknown	Skin rash, pruritus, urticaria, toxic epidermal necrolysis, lichenoid and erythema multiforme eruptions, Stevens-Johnson syndrome, dermatitis, medicine reaction with eosinophilia and systemic symptoms (DRESS) syndrome
Musculoskeletal, connective tissue and bone disorders	Less frequent Frequency unknown	Gout (acute), arthritic joint pains Arthralgia
Renal and urinary disorders	Frequency unknown	Renal clearance of urate may be reduced, interstitial nephritis, acute renal failure

General disorders and administrative site conditions	Frequency unknown	Fever, malaise

The adverse effects for each of the active ingredients as listed above are possible side effects when taking the combination tablet RISOPET.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the online service for adverse drug reaction reporting by following the link: https://www.sahpra.org.za/Publications/Index/8.

An email can be sent directly to the company, pharmacovigilance@pharmadynamics.co.za to ensure safety of the product.

4.9 Overdose

Signs and symptoms:

The symptoms of an overdose with RISOPET are unknown, but may include diarrhoea, nausea, vomiting, abdominal cramps, anorexia, reddish-orange discolouration of secretions, myopathy, muscle weakness, oedema, peripheral neuropathy, constipation, dry mouth, arthralgia and hyperuricaemia, jaundice, rash and fever, elevated liver enzymes with the clinical signs of hepatitis, visual impairment.

Rifampicin

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 discolouration 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

dysrhythmias, seizures and cardiac arrest were reported in some fatal cases.

Nonfatal acute overdoses in adults have been reported with doses ranging from 9 g to 12 g rifampicin. Fatal acute overdoses in adults have been reported with doses ranging from 14 g to 60 g. Non-fatal overdoses in paediatric patients ages 1 to 4 years old of 100 mg/kg for one or two doses have been reported.

Isoniazid

Isoniazid overdosage produces signs and symptoms within 30 minutes to 3 hours after ingestion. Nausea, vomiting, dizziness, slurring of speech, blurring of vision and visual hallucinations are among the early manifestations. With marked overdosage, respiratory distress and CNS depression, progressing rapidly from stupor to profound coma are to be expected, along with severe, intractable seizures. Severe metabolic acidosis, acetonuria and hyperglycaemia are typical laboratory findings.

Pyrazinamide

There is limited information related to pyrazinamide overdosage. Liver toxicity and hyperuricaemia may occur with overdosage.

Ethambutol

There is limited information related to ethambutol overdose. Loss of appetite, gastro-intestinal disturbances, fever, headache, dizziness, confusion and hallucinations may occur.

Management of overdose:

Symptomatic and supportive therapy is required.

Intensive support measures should be instituted, including airway patency and individual symptoms treated as they arise.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

ATC code: J04A M06.

Pharmacological classification: A.20.2.3 Tuberculostatics

Mechanism of action

This medicine is a combination of four medicines used to treat tuberculosis.

Rifampicin is a semi-synthetic, broad-spectrum antibiotic which is bactericidal for both intracellular and extracellular microorganisms.

Isoniazid is a synthetic, anti-tubercular medicine that acts as a bacteriostatic agent against semi-dormant bacilli and as a bactericidal agent against actively dividing mycobacteria.

Depending on its concentration and the susceptibility of the organism, pyrazinamide may be bactericidal or bacteriostatic.

Ethambutol is a synthetic, bacteriostatic anti-tubercular medicine and suppresses the growth of most isoniazid- and streptomycin-resistant *tubercle bacilli*.

5.2 Pharmacokinetic properties

Rifampicin

Absorption:

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 hours after administration.

Distribution:

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 %).

Biotransformation:

Rifampicin is deacetylated to the active metabolite desacetylrifampicin. Rifampicin and desacetylrifampicin are excreted in the bile and rifampicin undergoes enterohepatic recycling.

Elimination:

The elimination half-life initially is 3 to 5 hours, decreasing to 2 to 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

Absorption:

Isoniazid is absorbed following oral administration. The rate and extent of absorption is decreased when taken with food. Maximum plasma concentrations are reached 1 to 2 hours after a dose.

Distribution:

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 %.

Biotransformation:

Isoniazid is acetylated by N-acetyltransferase to N-acetylisoniazid. It is then bio-transformed 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.

Elimination:

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

Absorption:

Pyrazinamide is well absorbed from the gastrointestinal tract. The absorption is not affected by concomitant food intake. Maximum plasma concentrations are reached after 1 to 2 hours in adults and about 3 hours in children.

Distribution:

Pyrazinamide is rapidly distributed throughout the body.

Biotransformation:

Pyrazinamide is hydrolysed by a microsomal deaminase to pyrazinoic acid, an active metabolite, and then hydroxylated by xanthine oxidase to 5-hydroxypyrazinoic acid.

Elimination:

Pyrazinamide is renally excreted, mainly as metabolites.

Only 3 % of the dose is excreted unchanged in urine. The half-life is about 10 hours.

APPROVED PROFESSIONAL INFORMATION

Ethambutol

Absorption:

Ethambutol is absorbed following oral administration. The bioavailability is approximately 80 %. The absorption is not affected by concomitant food intake. Maximum plasma concentrations are reached 2 to 4 hours after a dose.

Distribution:

Ethambutol is widely distributed to most tissues. It is not distributed to cerebrospinal fluid. However, in patients with tuberculous meningitis the concentration in cerebrospinal fluid may reach therapeutic levels. Concentrations in erythrocytes are 2 to 3 times higher than in serum. Protein binding is low (10 to 40 %). The volume of distribution is about 20 L.

Biotransformation:

Ethambutol is metabolised in the liver, up to 15 % to inactive metabolites. The half-life of ethambutol is 3 to 4 hours, but increases up to 8 hours in patients with impaired renal function.

Elimination:

Up to 80 % excreted renally within 24 hours (at least 50 % unchanged and up to 15 % as inactive metabolites). About 20 % is excreted unchanged in the faeces.

Pharmacokinetics in special patient 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 section 4.4).

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

Ethambutol

The elimination half-life of ethambutol is increased in patients with impaired renal function, which may require an adjustment of dosage. Ethambutol is not removed from the blood by haemodialysis.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet cores:

Ascorbic acid

Bone gelatine

Colloidal silicon dioxide

Crospovidone

Magnesium stearate

Microcrystalline cellulose

Pre-gelatinised starch.

Film coating:

Iron oxide red

Lecithin (Soya)

Polyvinyl alcohol-part hydrolysed

Talc

Titanium dioxide

Xanthan gum.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Store in a cool place, at or below 25 °C in a well closed container.

Protect from light.

Keep the blisters in the outer carton until required for use.

6.5 Nature and contents of container

Amber PVC/ACLAR & ALU/ALU blister packs of 28, 56, 84 and 112 tablets, packed into an outer cardboard carton.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF THE CERTIFICATE OF REGISTRATION

Pharma Dynamics (Pty) Ltd

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Silverwood Close

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7945, South Africa

8. REGISTRATION NUMBER

A42/20.2.3/0890

9. DATE OF FIRST AUTHORISATION

Date of registration: 20 June 2013

10. DATE OF REVISION OF THE TEXT

15 November 2023