1. Name of the medicinal product

Rifater Tablets

2. Qualitative and quantitative composition

Rifampicin Ph Eur	120 mg
Isoniazid Ph Eur	50 mg
Pyrazinamide Ph Eur	300 mg

3. Pharmaceutical form

Tablets

4. Clinical particulars

4.1 Therapeutic indications

Rifater is indicated in the treatment of pulmonary tuberculosis.

4.2 Posology and method of administration

Rifater is recommended in the initial intensive phase of the short-course treatment of pulmonary tuberculosis. During this phase, which lasts for 2 months, Rifater should be administered on a daily continuous basis. The concomitant administration of ethambutol or intramuscular streptomycin over the same period of time is advised.

Each Rifater tablet contains isoniazid (INH), pyrazinamide (Z) and rifampicin (RAMP) in such a ratio that the administration of 9-12mg/kg RAMP, 4-5mg/kg INH and 23-30mg/kg Z can be achieved by giving 3 tablets daily to patients weighing less than 40kg, 4 tablets to patients weighing 40-49kg, 5 tablets to patients weighing 50-64kg and 6 tablets to patients weighing 65kg or more.

Rifater should be given as a single dose and preferably on an empty stomach at least 30 minutes before a meal, or 2 hours after a meal to ensure rapid and complete absorption.

Once the initial intensive phase of treatment has been completed treatment can be continued with the combination rifampicin-isoniazid (Rifinah) always on a daily basis.

This regimen, if correctly applied, is 100% effective with very few, if any, relapses. The clinical evidence indicates that these occur generally in the first 6 months after stopping treatment with bacilli fully sensitive to the drugs employed, so that changes in the drugs to be utilised for further treatment are not required. The regimen has been found to be fully effective also in the presence of a bacillary population resistant to isoniazid, to streptomycin or to both drugs.

Children: The ratio of the three drugs in Rifater may not be appropriate in children (eg higher mg/kg doses of INH are usually given in children than in adults). Rifater can be used only in special cases, after careful consideration of the mg/kg dose of each component.

Use in the Elderly: Caution should be exercised in such patients, in view of the possible decrease of the excretory function of the kidney and of the liver.

4.3 Contraindications

Rifater is contra-indicated in patients who are hypersensitive to any one of the components of the combination or any of the excipients. Rifater is contra-indicated in the presence of jaundice.

Rifater use is contraindicated when given concurrently with the combination of saquinavir/ritonavir (see section 4.5 Interactions).

4.4 Special warnings and precautions for use

The precautions for the use of Rifater are the same as those considered when a triple individual administration of rifampicin, isoniazid and pyrazinamide is required. Rifater should only be given under supervision. Each of these drugs has been associated with liver dysfunction.

Rifater should be given under the supervision of a respiratory or other suitably qualified physician.

All tuberculosis patients should have pre-treatment measurements of liver function.

Adults treated for tuberculosis with Rifater should have baseline measurements of hepatic enzymes, bilirubin, serum creatinine, a complete blood count and a platelet count (or estimate).

Patients should be seen at least monthly during therapy and should be questioned specifically about symptoms associated with adverse reactions. All patients with abnormalities should have follow-up, including laboratory testing, if necessary.

However, because there is a higher frequency of isoniazid-associated hepatitis among persons older than 35 years of age, a transaminase measurement should be obtained at baseline and at least monthly during therapy in this age group. Other factors associated with an increased risk of hepatitis include daily use of alcohol, chronic liver disease, intravenous drug use and being a black or Hispanic woman.

<u>Paradoxical drug reaction</u>

After initial improvement of tuberculosis under therapy with Rifater, 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)

If the patient has no evidence of pre-existing liver disease and normal pre-treatment liver function, liver function tests need only be repeated if fever, vomiting, jaundice or other deterioration in the patient's condition occur.

Patients with impaired liver function should only be given Rifater in cases of necessity and then with caution and under strict medical supervision. In these patients, careful monitoring of liver function, especially serum glutamic pyruvic transaminase (SGPT) and serum glutamic oxaloacetic transaminase (SGOT) should be carried out prior to therapy and then every two to four weeks during therapy.

If signs of hepatocellular damage or clinically significant changes in hepatic function occur, Rifater should be withdrawn. The need for other forms of antituberculosis therapy and a different regimen should be considered. Urgent advice should be obtained from a specialist in the management of tuberculosis. If Rifater is reintroduced after liver function has returned to normal, liver function should be monitored daily.

Severe, systemic hypersensitivity reactions, including fatal cases, such as Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) syndrome have been observed during treatment with anti-tuberculosis therapy (See section 4.8).

Rifater should be discontinued if an alternative etiology for the signs and symptoms cannot be established.

Rifampicin

Cautions should be taken in cases of renal impairment if dose > 600 mg/day.

In patients with impaired liver function, elderly patients, malnourished patients and possibly children under two years of age, caution is particularly recommended when instituting therapeutic regimens in which isoniazid is to be used concurrently with rifampicin.

In some cases, hyperbilirubinaemia resulting from competition between rifampicin and bilirubin for excretory pathways of the liver at the cell level can occur in the early days of treatment. An isolated report showing a moderate rise in bilirubin and/or transaminase level is not in itself an indication for interrupting treatment; rather, the decision should be made after repeating the tests, noting trends in the levels and considering them in conjunction with the patient's clinical condition.

Because of the possibility of immunological reaction including anaphylaxis (see section 4.8 Undesirable effects) occurring with intermittent rifampicin therapy (less than 2 or 3 per week) patients should be closely monitored. Patients should be cautioned against interruption of dosage regimens since these reactions may occur.

Severe cutaneous adverse reactions (SCARs) including Steven-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), acute generalized exanthematous pustulosis (AGEP), which can be life-threatening or fatal, have been reported with a not known frequency in association with Rifater treatment.

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

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 immediately their physician.

If signs and symptoms suggestive of these reactions appear, Rifater should be withdrawn immediately and an alternative treatment considered (as appropriate).

Most of these reactions occurred within 2 days to 2 months after treatment initiation; the time to onset can vary depending on the conditions.

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.

Rifampicin may produce a discoloration (yellow, orange, red, brown) of the teeth, urine, sweat, sputum and tears, and the patient should be forewarned of this. Soft contact lenses have been permanently stained (see section 4.8)

Rifampicin is a well characterized and potent inducer of drug metabolizing enzymes and transporters and might therefore decrease or increase concomitant drug exposure, safety and efficacy (see Section 4.5).

Therefore, potential drug interactions should be considered whether beginning or discontinuing rifampicin treatment.

Rifampicin may cause vitamin K dependent coagulopathy and severe bleeding (see Section 4.8). Monitoring of occurrence of coagulopathy is recommended for patients at particular bleeding risk. Supplemental vitamin K administration should be considered when appropriate (vitamin K deficiency, hypoprothrombinemia).

Isoniazid

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 many 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. If these symptoms appear or if signs suggestive of hepatic damage are detected, isoniazid should be discontinued promptly, since continued use of the drug in these cases has been reported to cause a more severe form of liver damage.

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) develops, the patient should be advised to consult immediately their physician. Isoniazid should be permanently discontinued if an alternative etiology for the signs and symptoms cannot be established.

Care should be exercised in the treatment of elderly or malnourished patients who may also require Vitamin B6 supplementation with the isoniazid therapy.

Use of isoniazid should be carefully monitored in patients with slow acetylator status, epilepsy, history of psychosis, history of peripheral neuropathy, diabetes, alcohol dependence, HIV infection or porphyria.

Pyrazinamide

Rifater should be used with caution in patients with a history of gout. If hyperuricaemia accompanied by an acute gouty arthritis occurs, the patient should be transferred to a regimen not containing pyrazinamide (e.g. Rifinah 150 or 300).

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

4.5 Interaction with other medicinal products and other forms of interaction

Food Interaction

Isoniazid is an inhibitor of monoamine oxidase (MAO) and diamine oxidase (DAO), therefore can reduce tyramine and histamine metabolism, causing symptoms such as headache, sweating, palpitations, flushing, and hypotension. Patients should be advised against ingesting foods rich in tyramine and/or histamine during treatment with isoniazid, such as cured meat, some cheeses (e.g. matured cheeses), wine, beer and some fish (e.g. tuna, mackerel, salmon).

Interactions with other medicinal products

When Rifater is given concomitantly with the combination saquinavir/ritonavir, the potential for hepatotoxicity is increased. Therefore, concomitant use of Rifater with saquinavir/ritonavir is contraindicated (see section 4.3 Contraindications).

Cytochrome P-450 enzyme interaction

Rifampicin is known to induce and isoniazid is known to inhibit certain cytochrome P-450 enzymes. In general, the impact of the competing effects of rifampicin and isoniazid on the metabolism of drugs that undergo biotransformation through the affected pathways is unknown. Therefore, caution should be used when prescribing Rifater with drugs metabolised by cytochrome P-450. To maintain optimum therapeutic blood levels, dosages of drugs metabolised by these enzymes may require adjustment when starting or stopping Rifater.

Interactions with Rifampicin

Pharmacodynamic interactions

The potential for hepatotoxicity is increased with an anaesthetic.

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.

The concomitant use of rifampicin with other antibiotics causing vitamin K dependent coagulopathy such as cefazolin (or other cephalosporins with N-methyl-thiotetrazole side chain) should be avoided as it may lead to severe coagulation disorders, which may result in fatal outcome (specially with high doses).

Effect of rifampicin on other medicinal products

<u>Induction of Drug Metabolizing Enzymes and Transporters</u>

Rifater is a well characterized and potent inducer of drug metabolizing enzymes and transporters. Enzymes and transporters reported to be affected by Rifater include cytochromes P450 (CYP) 1A2, 2B6, 2C8, 2C9, 2C19, and 3A4, UDP-glucuronyltransferases (UGT), sulfotransferases, carboxylesterases, and transporters including P-glycoprotein (P-gp) and multidrug resistance-associated protein 2 (MRP2). Most drugs are substrates for one or more of these enzyme or transporter pathways, and these pathways may be induced by Rifater simultaneously. Therefore, Rifater may accelerate the metabolism and decrease the activity of certain co-administered drugs, or increase the activity of a coadministered pro-drug (where metabolic activation is required) and has the potential to perpetuate clinically important drug-drug interactions against many drugs and across many drug classes (Table 1). To maintain optimum therapeutic blood levels, dosages of drugs may require adjustment when starting or stopping concomitantly administered Rifater.

Examples of drugs or drug classes affected by Rifater:

• Antiarrhythmics (e.g. disopyramide, mexiletine, quinidine, propafenone, tocainide),

• Antiepileptics (e.g. phenytoin),

• Hormone antagonist (antiestrogens e.g. tamoxifen, toremifene, gestinone),

• Antipsychotics (e.g. haloperidol, aripiprazole),

• Anticoagulants (e.g. coumarins),

• Antifungals (e.g. fluconazole, itraconazole, ketoconazole, voriconazole),

• Antivirals (e.g. saquinavir, indinavir, efavirenz, amprenavir, nelfinavir, atazanavir, lopinavir, nevirapine),

• Barbiturates

• Beta-blockers (e.g. bisoprolol, propanolol),

• Anxiolytics and hypnotics (e.g. diazepam, benzodiazepines, zopiclone, zolpidem),

• Calcium channel blockers (e.g. diltiazem, nifedipine, verapamil, nimodipine, isradipine, nicardipine, nisoldipine),

• Antibacterials (e.g. chloramphenicol, clarithromycin, dapsone, doxycycline, fluoroquinolones, telithromycin),

• Corticosteroids

• Cardiac glycosides (digitoxin, digoxin),

• Clofibrate,

• Systemic hormonal contraceptives including estrogens and progestogens,

• Antidiabetic (e.g. chlorpropamide, tolbutamide, sulfonylureas, rosiglitazone),

• Immunosuppressive agents (e.g. ciclosporin, sirolimus, tacrolimus)

• Irinotecan,

• Thyroid hormone (e.g. levothyroxine),

• Losartan,

• Analgesics (e.g. methadone, narcotic analgesics),

• Praziquantel,

• Quinine,

• Riluzole,

• Selective 5-HT3 receptor antagonists (e.g. ondansetron)

• Statins metabolised by CYP 3A4 (e.g. simvastatin),

• Theophylline,

• Tricyclic antidepressants (e.g. amitriptyline, nortriptyline),

• Cytotoxics (e.g. imatinib),

• Diuretics (e.g. eplerenone)

• Enalapril: decrease enalapril active metabolite exposure. Dosage adjustments should be made if indicated by the patient's clinical condition

• Hepatitis-C antiviral drugs (eg. daclatasvir, simeprevir, sofosbuvir, telaprevir): Concurrent use of treatment of hepatitis-C antiviral drugs and rifampicin should be avoided.

• Morphine: 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.

• Clopidogrel: Increases active metabolite exposure. Rifater strongly induces CYP2C19, resulting in both an increased level of clopidogrel active metabolite and platelet inhibition, which in particular might potentiate the risk of bleeding. As a precaution, concomitant use of clopidogrel and rifampicin should be discouraged.

Rifampicin treatment reduces the systemic exposure of oral contraceptives. Patients using oral contraceptives should be advised to change to non-hormonal methods of birth control during Rifater therapy. Also diabetes may become more difficult to control.

Rifampicin may reduce the effect of ACE inhibitors (e.g. enalapril, imidapril), antiemetics (e.g. aprepitant), antineoplastic agents (e.g. imatinib), diuretics (e.g. eplerenone), drugs used in erectile dysfunction (e.g. tadalafil), oral hypoglycemic agents (e.g. nateglinide, repaglinide) and NSAIDS (e.g. etoricoxib).

If p-aminosalicylic acid and rifampicin are both included in the treatment regimen, they should be given not less than eight hours apart to ensure satisfactory blood levels.

Effect of other medicinal products on rifampicin

Concomitant antacid administration may reduce the absorption of rifampicin. Daily doses of rifampicin should be given at least 1 hour before the ingestion of antacids.

Other drug interactions with rifampicin

When the two drugs were taken concomitantly, decreased concentrations of atovaquone and increased concentrations of rifampicin were observed.

Interactions with Isoniazid

The following drugs may interact with isoniazid:

• Antiepileptics (e.g. carbamazepine and phenytoin)

There may be an increased risk of distal sensory neuropathy when isoniazid is used in patients taking stavudine.

Concomitant use of zalcitabine with isoniazid has been shown to approximately double the renal clearance if isoniazid in HIV infected patients.

Administration of prednisolone 20mg to 13 slow acetylators and 13 fast acetylators for receiving isoniazid 10mg/kg reduced plasma concentrations of isoniazid by 25% and 40%, respectively. The clinical significance of this effect has not been established.

The effect of acute alcohol intake (serum levels 1g/L maintained for 12 hours) on the metabolism of isoniazid (300mg/d for 2 days) was studies in 10 healthy volunteers in a controlled cross over design. The metabolism of isoniazid and its metabolite, acetyl isoniazid, was not modified by this acute alcohol intake. The metabolism of isoniazid may be increased in chronic alcoholics; however this effect has not been quantified.

Other Interactions

Para-aminosalicylic acid may increase the plasma concentration and elimination half-life of isoniazid by competing for acetylating enzymes.

General anaesthetics may increase the hepatotoxicity of isoniazid.

The absorption of isoniazid is reduced by antacids.

The risk of CNS toxicity is increased when isoniazid is given with cycloserine.

Isoniazid may reduce plasma concentration of ketoconazole and increase plasma concentration of theophylline.

Pyrazinamide

Pyrazinamide antagonizes the effects of probenecid and sulfinpyrazone.

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 BSP and serum bilirubin has been reported. Rifampicin may impair biliary excretion of contrast media used for visualization of the gallbladder, due to competition for biliary excretion. Therefore, these tests should be performed before the morning dose of rifampicin.

4.6 Pregnancy and lactation

Pregnancy

Rifampicin

At very high doses in animals rifampicin has been shown to have teratogenic effects. There are no well controlled studies with Rifater 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. When administered during the last few weeks of pregnancy, rifampicin may cause post-natal haemorrhages in the mother and infant, for which treatment with Vitamin K1 may be indicated.

Isoniazid

It has been reported that in both rats and rabbits, isoniazid may exert an embryocardial effect when administered orally during pregnancy, although no isoniazid-related congenital anomalies have been found in reproduction studies in mammalian species (mice, rats, rabbits).

Therefore, Rifater 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.

Lactation

Rifampicin, isoniazid and pyrazinamide are excreted in breast milk and infants should not be breast fed by a patient receiving Rifater unless in the physician's judgement the potential benefit to the patient outweighs the potential risk to the infant.

In breast-fed infants whose mothers are taking isoniazid, there is a theoretical risk of convulsions and neuropathy (associated with vitamin B6 deficiency), therefore they should be monitored for early signs of these effects and consideration should be given to treating both mother and infant prophylactically with pyridoxine.

4.7 Effects on ability to drive and use machines

Isoniazid has been associated with vertigo, visual disorders and psychotic reactions (see section 4.8). Patients should be informed of these, and advised that if affected, they should not drive, operate machinery or take part in any activities where these symptoms may put either themselves or others at risk.

4.8 Undesirable effects

The following CIOMS frequency rating is used, when applicable:

Very common (≥ 1/10); 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), not known (cannot be estimated from available data).

Rifampicin

Reactions occurring with either daily or intermittent dosage regimens include:

System organ class	**Frequency**	**Preferred Term**
Infections and infestations	Unknown	Pseudomembranous colitis Influenza
Blood and lymphatic system disorders	Common	Thrombocytopenia with or without purpura, usually associated with intermittent therapy, but is reversible if drug is discontinued as soon as purpura occurs.
	Uncommon	Leukopenia
	Unknown	Disseminated intravascular coagulation Eosinophilia Agranulocytosis Hemolytic anemia Vitamin K dependent coagulation disorders
Immune system disorders	Unknown	Anaphylactic reaction
Endocrine disorders	Unknown	Adrenal insufficiency in patients with compromised adrenal function have been observed
Metabolism and nutritional disorders	Unknown	Decreased appetite
Psychiatric disorders	Unknown	Psychotic disorder
Nervous system disorders	Common	Headache Dizziness
	Unknown	Cerebral hemorrhage and fatalities have been reported when rifampicin administration has been continued or resumed after the appearance of purpura
Eye disorders	Unknown	Tear discolouration
Vascular disorders	Unknown	Shock

		Flushing Vasculitis Bleeding
Respiratory, thoracic and mediastinal disorders	Unknown	Dyspnoea Wheezing Sputum discoloured
Gastrointestinal disorders	Common	Nausea Vomiting
	Uncommon	Diarrhea
	Unknown	Gastrointestinal disorder Abdominal discomfort Tooth discolouration (which may be permanent)
Hepatobiliary disorders	Unknown	Hepatitis Hyperbilirubinaemia (see section 4.4)
Skin and subcutaneous tissue disorders	Unknown	Erythema multiforme Stevens-Johnson syndrome (SJS) Toxic epidermal necrolysis (TEN) Drug reaction with eosinophilia and systemic symptoms (DRESS) Acute generalized exanthematous pustulosis (AGEP) (see section 4.4) Skin reaction Pruritus Rash pruritic Urticaria Dermatitis allergic Pemphigoid Sweat discoloration
Musculoskeletal and connective tissue disorders	Unknown	Muscle weakness Myopathy

		Bone pain
Renal and urinary disorders	Unknown	Acute kidney injury usually due to renal tubular necrosis or tubulointerstitial nephritis Chromaturia
Pregnancy, puerperium and perinatal conditions	Unknown	Post-partum haemorrhage Fetal-maternal haemorrhage
Reproductive system and breast disorders	Unknown	Menstrual disorder
Congenital, familial and genetic disorders	Unknown	Porphyria
General disorders and administration site conditions	Very common	Pyrexia Chills
	Common	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).*
	Unknown	Edema
Investigations	Common	Blood bilirubin increased Aspartate aminotransferase increased Alanine aminotransferase increased
	Unknown	Blood pressure decreased Blood creatinine increased Hepatic enzyme increased

* 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).

Isoniazid

System organ class	**Frequency**	**Preferred Term**

Hepatobiliary disorders	Uncommon	Severe and sometimes fatal hepatitis may occur with isoniazid therapy
Nervous system disorders	Uncommon	Other neurotoxic effects, which are uncommon with conventional doses, are convulsions, toxic encephalopathy, optic neuritis and atrophy, memory impairment and toxic psychosis.
	Not known	Vertigo Polyneuritis associated with isoniazid, presenting as paraesthesia, muscle weakness, loss of tendon reflexes etc, is unlikely to occur with the recommended daily dose of Rifater. The incidence is higher in “slow acetylators”. The possibility that the frequency of seizures may be increased in patients with epilepsy should be borne in mind.
Immune system disorders	Not known	Anaphylactic reactions
Blood and lymphatic system disorders	Not known	Eosinophilia Agranulocytosis Thrombocytopenia and anaemia Aplastic anaemia Haemolytic anaemia
Skin and subcutaneous tissue disorders	Not known	Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) syndrome (See section 4.4) Rash Acne Toxic epidermal necrolysis (TEN) Stevens-Johnson syndrome Exfoliative dermatitis Pemphigus
Vascular disorders	Not known	Vasculitis
Endocrine disorders	Not known	Gynecomastia
Gastrointestinal disorders	Not known	Constipation Dry mouth

		Nausea Vomiting Epigastric distress Pancreatitis
Metabolism and nutrition disorders	Not known	Hyperglycaemia Pellagra
Investigations	Not known	Anti-nuclear bodies
General disorders and administration site conditions	Not known	Fever
Musculoskeletal and connective tissue disorders	Not known	Systemic lupus erythromatosus-like syndrome

Pyrazinamide

System organ class	**Frequency**	**Preferred Term**
Hepatobiliary disorders	Rare	Acute yellow atrophy Death
	Not known	The hepatic reaction is the most common adverse reaction and varies from a symptomless abnormality of hepatic cell function detected only through laboratory liver function tests, through a mild syndrome of fever, malaise and liver tenderness, to more serious reactions such as clinical jaundice
Musculoskeletal and connective tissue disorders	Not known	Arthralgia
Blood and lymphatic system disorders	Not known	Sideroblastic anaemia Thrombocytopenia with or without purpura
Metabolism and nutritional disorders	Not known	Active gout (pyrazinamide has been reported to reduce urate excretion) Anorexia
Gastrointestinal disorders	Not known	Nausea Vomiting Aggravation of peptic ulcer

Renal and urinary disorders	Not known	Dysuria
General disorders and administration site conditions	Not known	Malaise Fever
Skin and subcutaneous tissue disordrs	Very Rare	Angioedema
	Not known	Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) syndrome Urticaria Pruritus Erythema Rash

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation 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 Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

There is limited overdose information involving rifampicin, isoniazid and pyrazinamide in combination.

Signs and Symptoms

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 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 to 60 g. Alcohol or a history of alcohol abuse was involved in some of the fatal and nonfatal reports. Nonfatal overdoses in paediatrics patients ages 1 to 4 years old of 100 mg/kg for one to 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 (including bright colours and strange designs), 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 overdose. Liver toxicity and hyperuricemia may occur with overdosage.

Management

In cases of overdosage with Rifater, gastric lavage should be performed as soon as possible. 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.

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

Isoniazid

If acute isoniazid overdose is suspected, even in asymptomatic patients, the administration of intravenous pyridoxine (vitamin B6) should be considered. In patients with seizures not controlled with pyridoxine (vitamin B6), anticonvulsant therapy should be administered. Sodium bicarbonate should be given to control metabolic acidosis. Haemodialysis is advised for refractory cases; if this is not available, peritoneal dialysis can be used along with forced diuresis.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Rifampicin, isoniazid and pyrazinamide are all active bactericidal antituberculosis drugs. Rifampicin and isoniazid are particularly active against the rapidly growing extracellular organisms. Pyrazinamide is active against intracellular organisms, particularly in the acid pH environment of macrophages. Rifampicin and isoniazid also have bactericidal activity intracellularly. Rifampicin has activity against slow and intermittently-growing M tuberculosis. Thus, the three agents, rifampicin, isoniazid and pyrazinamide have activity against the three different bacterial populations.

Rifampicin inhibits DNA-dependent RNA polymerase activity in susceptible cells. Specifically, it interacts with bacterial RNA polymerase but does not inhibit the mammalian enzyme. Cross-resistance to rifampicin has only been shown after the development of resistance to other rifamycins.

5.2 Pharmacokinetic properties

Rifampicin

Rifampicin is readily absorbed from the stomach and the duodenum. Peak serum concentrations of the order of 10 µg/ml occur about 2-4 hours after a dose of 10mg/kg body weight on an empty stomach.

In normal subjects the biological half-life of rifampicin in serum averages about 3 hours after a 600mg dose and increases to 5.1 hours after 900mg dose. With repeated administration, the half-life decreases and reaches average values of approximately 2-3 hours. At a dose of up to 600 mg/day the half-life does not differ in patients with renal failure and, consequently, no dosage adjustment is required. The half-life of rifampicin may be decreased when isoniazid is administered concurrently.

After absorption, rifampicin is rapidly eliminated in the bile and an enterohepatic circulation ensues. During this process, rifampicin undergoes progressive deacetylation, so that nearly all the drug in the bile is in this form in about 6 hours. This metabolite retains essentially complete antibacterial activity. Intestinal reabsorption is reduced by deacetylation and elimination is facilitated. Up to 30% of a dose is excreted in

the urine with about half of this being unchanged drug. Absorption of rifampicin is reduced when the drug is ingested with food.

Rifampicin is widely distributed throughout the body. It is present in effective concentrations in many organs and body fluids, including cerebrospinal fluid. Rifampicin is about 80% protein bound. Most of the unbound fraction is not ionized and therefore is diffused freely in tissues.

Isoniazid

After oral administration, isoniazid produces peak blood levels within 1 to 2 hours, which decline to 50% or less within 6 hours. Ingestion of isoniazid with food may reduce its absorption. It diffuses readily into all body fluids (cerebrospinal, pleural, and ascitic fluids), tissues, organs and excreta (saliva, sputum and faeces). The drug also passes through the placental barrier and into the milk in concentrations comparable to those in the plasma. From 50 to 70% of a dose of isoniazid is excreted in the urine in 24 hours.

Isoniazid is metabolised primarily by acetylation and dehydrazination. The rate of acetylation is genetically determined. Approximately 50% of Black and Europeans are 'Slow inactivators', the majority of Asians are 'rapid inactivators'.

Pyridoxine deficiency (B_6) is sometimes observed in adults with high doses of isoniazid, probably due to its competition with pyridoxal phosphate of the enzyme apotryptophanase.

Pyrazinamide

Pyrazinamide is well absorbed from the gastrointestinal tract and rapidly distributed throughout the body, with peak plasma levels in 2 hours. It is hydrolysed to pyrazinoic acid and then metabolised to 5-hydroxypyrazinoic acid. Glomerular filtration is the primary route of excretion. It is bactericidal in acid pH, and has intracellular antibacterial activity against *M. tuberculosis*.

Pharmacokinetic studies in normal volunteers have shown that the three ingredients in Rifater have comparable bioavailability whether they are given together as individual dose forms or as Rifater.

5.3 Preclinical safety data

Not applicable

6. Pharmaceutical particulars

6.1 List of excipients

Polyvinylpyrrolidone

Sodium Carboxymethylcellulose

Sodium Lauryl Sulphate

Calcium Stearate

Sucrose

Acacia Gum

Talc

Light Magnesium Carbonate

Kaolin

Titanum Dioxide

Colloidal Silicon Dioxide

Aluminium Hydroxide Gel

Iron Oxide

6.2 Incompatibilities

None stated

6.3 Shelf life

3 years from date of manufacture

6.4 Special precautions for storage

Do not store above 25°C. Store in the original container.

6.5 Nature and contents of container

PDVC and PVC/PVDC aluminium foil blisters packed in cardboard cartons.

Pack size: 100 tablets

6.6 Special precautions for disposal and other handling

Not applicable

7. Marketing authorisation holder

Aventis Pharma Limited

410 Thames Valley Park Drive

Reading

Berkshire

RG6 1PTUK

Trading as:

Sanofi

410 Thames Valley Park Drive

Reading

Berkshire

RG6 1PTUK

8. Marketing authorisation number(s)

PL 04425/0060

9. Date of first authorisation/renewal of the authorisation

Date of First authorisation: 27 April 1984

Date of last renewal: 21 March 2006

10. Date of revision of the text

20/07/2021

LEGAL STATUS

POM

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