Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Rifater 50 mg/300 mg/120 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains :

Isoniazid. 50 mg
Pyrazinamide 300 mg
Rifampicin 120 mg

Excipient: Contains 104.99 mg sucrose

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Coated tablet.
Smooth, circular, pink-beige sugar-coated tablets.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Indications for use

In the treatment of pulmonary tuberculosis.

4.2 Posology and method of administration

Recommended Dosage

For oral administration.

Adults:

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.

Rifater should only used under the supervision of specialists having the appropriate facilities for clinical and laboratory monitoring of effects.

Each Rifater tablet contains isoniazid (INH), pyrazinamide (Z) and rifampicin (RAMP) in such a ratio that the administration of 9-12 mg/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 1-2 hours before a meal to ensure rapid and complete absorption. Once the initial intensive phase of treatment has been completed the treatment can be continued with the combination rifampicin-isoniazid (Rifinah) always on a daily basis.

Children:
There is insufficient experience of use in children.

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.

In patients with renal insufficiency dosage should be reduced.

4.3 Contraindications

Rifater is contra-indicated in patients with a history of hypersensitivity to rifamycin, isoniazid, pyrazinamide or any one of the components of the combination. Rifater is contra-indicated in the presence of jaundice or hepatic disease.

Rifater use is contra-indicated when given concurrently with the combination of saquinavir/ritonavir *(see section 4.5)*.

Use during pregnancy or lactation in women who are breast feeding infants.

4.4 Special warnings and precautions for use

Rifater is a combination of three drugs, each of which has been associated with liver dysfunction, but the combination may have a greater potential for inducing abnormalities in liver function particularly in patients with pre-existent liver disorders, in the elderly, the very young and the malnourished.

Applies to rifampicin:
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 biochemical state, especially serum alanine aminotransferase (ALT) and serum aspartate aminotransferase (AST) should be carried out prior to therapy and then every 2-4 weeks during therapy. If signs of hepatocellular damage occur, Rifampicin should be discontinued.

Cases of mild to severe cholestasis have been reported with rifampicin therapy. Patients should be instructed to contact their physician immediately if they experience symptoms such as itching, weakness, loss of appetite, nausea, vomiting, abdominal pain, yellowing of eyes or skin or dark urine.
If cholestasis is confirmed, Rifater should be discontinued.

In some cases, hyperbilirubinaemia 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 patients clinical condition.

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

Severe bullous reactions:
Cases of severe bullous skin reactions such as Stevens Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and acute generalized exanthematous pustulosis (AGEP) have been reported with rifampicin. If symptoms or signs of AGEP, SJS or TEN are present, rifampicin treatment must immediately be discontinued.
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 discolouration (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.

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 patients should be advised not to take any other medication without medical advice.

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).

There have been reports of interstitial lung disease (ILD) or pneumonitis in patients receiving rifampicin for treatment of tuberculosis (see section 4.8). ILD/pneumonitis is a potentially fatal disorder. Careful assessment of all patients with an acute onset and/or unexplained worsening of pulmonary symptoms (dyspnoea accompanied by dry cough) and fever should be performed to confirm the diagnosis of ILD/pneumonitis. If ILD/pneumonitis is diagnosed, rifampicin should be permanently discontinued in case of severe manifestations (respiratory failure and acute respiratory distress syndrome) and appropriate treatment initiated as necessary.

Applies to 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.

Applies to pyrazinamide:
Rifater should be used with caution in patients with a history of gout. If hyperuricaemia accompanied by acute gouty arthritis occurs, the treatment should be discontinued and the patient should be transferred to a regimen not containing pyrazinamide.

Applies to Rifater:
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).
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.

Rifater should be discontinued if an alternative etiology for the signs and symptoms cannot be established.
Adults treated for tuberculosis with Rifater should have baseline measurements of hepatic enzymes, bilirubin, serum creating, a complete blood count and a platelet count. Baseline tests are unnecessary in children unless a complicating condition is known or clinically suspected.

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.

Rifater should be used with caution in patients with diabetes mellitus, alcoholism, convulsive disorders, manic or hypomanic psychosis.

If sideroblastic anaemia or peptic ulceration occurs treatment with Rifater may need to be discontinued. The possibility of pyrazinamide having an adverse effect on blood clotting time or vascular integrity should be bourne in mind in patients with haemoptysis.

Paradoxical drug reaction
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).

Sodium:
This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium free'.

4.5 Interaction with other medicinal products and other forms of interaction

4.5.1 Pharmacodynamic Interactions

Concomitant use of paracetamol with rifampicin may increase the risk of hepatotoxicity.

When Rifadin is given concomitantly with the combination saquinavir/ritonavir, the potential for hepatotoxicity is increased. Therefore, concomitant use of Rifadin with saquinavir/ritonavir is contra-indicated (See Section 4.3).
When Rifadin is given concomitantly with either halothane or isoniazid, the potential for hepatotoxicity is increased. The concomitant use of Rifadin and halothane should be avoided. Patients receiving both Rifadin 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 (especially in high doses).

If *p*-aminosalicyclic 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.

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 have been reported. Rifampicin may impair billiary excretion of contrast media used for visualisation of the gall bladder. Therefore these tests should be performed before the morning dose of rifampicin.

Induction of Drug Metabolizing Enymes and Transporters

Rifadin is a well characterized and potent inducer of drug metabolizing enzymes and transporters. Enzymes and transporters reported to be affected by Rifadin 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 Rifadin simultaneously. Therefore, Rifadin 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 Rifadin.

Table 1 Effect of Rifampicin Coadministration on Drugs or Drug Classes

Drug or Drug Class	Effect	Comment
antiretroviral drugs (eg zidovudine, saquinavir, indinavir, efavirenz)	↓ antiretroviral exposure	Rifampicin 600mg daily reduced zidovudine exposure (AUC) by 47% via induction of zidovudine glucuronidation and amination metabolism pathways . Rifampicin 600mg daily reduced saquinavir exposure (AUC) by 70% in healthy volunteers and by 47% in HIV-infected patients most likely via induction of CYP3A4 and possibly P-gp pathways . Rifampicin 600mg daily reduced efavirenz exposure (AUC) by 60% primarily via induction of efavirenz CYP2B6-mediated 8-hydroxylation pathway (See Section 4.3: Contraindications)
hepatitis-C antiviral drugs (eg, daclatasvir, simeprevir, sofosbuvir, telaprevir)4	↓ exposure to hepatitis-C antiviral drug exposure	The hepatitis C antivirals are cleared by various drug metabolizing enzymes and transporters which are susceptible to induction by multiple dose rifampicin. Rifampicin 600 mg daily reduced the exposure (AUC) of daclatasvir by 79% , simeprevir by 48% , sofosbuvir by 77% and telaprevir by 92% compared to control subjects. Concurrent use of treatment of hepatitis-C antiviral drugs and rifampicin should be avoided.
systemic hormonal contraceptives including estrogens and progestins	↓ Contraceptive exposure	Rifampicin treatment reduces the systemic exposure of oral contraceptives Patients using systemic hormonal contraceptives should be advised to change to non-hormonal methods of birth control during rifampicin therapy and to continue using this form of contraception for two weeks after completing the course of treatment
Enalapril	↓ enalapril active metabolite exposure	Dosage adjustments should be made if indicated by the patient's clinical condition.
Anticonvulsants (e.g. phenytoin)	↓ phenytoin exposure	Phenytoin is metabolized mainly by CYP2C9/2C19. Rifampicin 450 mg daily doubled the clearance of phenytoin and reduced the half-life by about 50% .
Antiarrhythmics (e.g. disopyramide, mexiletine, quinidine, propafenone, tocainide)	↓ antiarrhythmic drug exposure	Rifampicin 600 mg daily reduced the exposure (AUC) of mexiltine by 41% , quinidine by about 80% , propafenone by 87% , and tocainide by 25% .
antiestrogens (e.g. tamoxifen, toremifen)	↓ tamoxifen and toremifen exposure	Tamoxifen and toremifen are predominantly substrates of CYP3A4. Rifampicin 600 mg daily reduced the systemic exposure (AUC) of tamoxifen by 86% and of toremifen by 87% .
antipsychotics (e.g. haloperidol)	↓ haloperidol exposure	Coadministration of rifampicin to schizophrenic patients receiving haloperidol decreased haloperidol trough concentrations up to 70% .
oral anticoagulants (e.g. warfarin)	↓ warfarin exposure	S-Warfarin is a clinical index substrate for CYP2C9. Rifampicin 600 mg daily reduced the exposure (AUC) of S-warfarin by 74%.
Clopidogrel	↑ active metabolite exposure	Rifadin 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.
antifungals (e.g. fluconazole, itraconazole, ketoconazole)	↓ antifungal exposure	Rifampicin 600 mg daily reduced fluconazole exposure (AUC) by approximately 23% , itraconazole by 88% and ketoconazole by about 80% .

barbiturates	↓ barbiturate exposure	Rifampicin has been shown to increase hexobarbital metabolic clearance by 2- to 3-fold in healthy volunteers and patients, and to significantly decrease hexobarbital half-life
beta blockers	↓ beta blocker exposure	Rifampicin 600 mg daily reduced the exposure (AUC) of metoprolol by 33% and increased the clearance of propranolol by 169%
benzodiazepines (e.g. diazepam)	↓ diazepam exposure	Rifampicin 600 and 1200 mg daily increased the clearance of diazepam by 60% and 98%, respectively .
benzodiazepine related drugs (e.g. zolpiclone, zolpidem),	↓ zopiclone and zolpidem exposure	Rifampicin 600 mg daily reduced the exposure (AUC) of zolpiclone by 82% and of zolpidem by 27% .
calcium channel blockers (e.g. diltiazem, nifedipine, verapamil),	↓ calcium channel blocker exposure	Calcium channel blockers are primarily substrates of CYP3A4. Rifampicin 1200 mg administered as a single oral dose 8 h before administering a single oral dose of nifedipine 10 mg reduced nifedipine exposure (AUC) by 64% . Rifampicin 600 mg daily reduced the exposure (AUC) of verapamil by 93% .
chloramphenicol	↓ chloramphenicol exposure	In two children treated concomitantly with intravenous chloramphenicol and rifampicin, peak chloramphenicol serum concentrations were reduced by 85.5% in one patient and by 63.8% in the other
clarithromycin	↓ clarithromycin exposure	Rifampicin 600 mg daily markedly reduced plasma concentrations of clarithromycin and increased clarithromycin metabolite concentrations .
corticosteroids	↓ corticosteroid exposure	Numerous cases appear in the literature describing a decrease in glucocorticoid effect when rifampicin is prescribed concurrently. The literature contains reports of acute adrenal crisis or adrenal insufficiency induced by the combination of rifampicin-isoniazid- ethambutol or rifampicin-isonizid in patients with Addison's disease. In patients receiving concomitant rifampicin, prednisolone AUC was reduced by 48% to 66% and clearance was increased by 45% to 91%.
cardiac glycosides	↓ cardiac glycoside exposure	Digoxin is a clinical index substrate for P-gp activity. Rifampicin 600 mg daily reduced the bioavailability of oral digoxin by 30% and increased intestinal P-gp content 3.5-fold, which correlated with the AUC after oral digoxin. Several reports have been published regarding the interaction of digitoxin and rifampicin. Decreased serum digitoxin levels were observed during antituberculosis therapy with rifampicin-isoniazid- ethambutol or with rifampicin alone; serum digitoxin levels decreased by 53% and 54% respectively.
clofibrate	↓ clofibrate exposure	Rifampicin 600 mg daily significantly reduced steady- state plasma concentrations of clofibrate's main circulating metabolite, chlorophenoxyisobutyric acid (CPIB), from 50 µg/mL to 33 µg/mL. Although CPIB plasma half-life of individual subjects was decreased during rifampicin treatment, the change was not significant .
dapsone	↓ dapsone exposure ↑ exposure to hydroxylamine metabolite, responsible for adverse effects that include methemoglobinemia, haemolytic anaemia, agranulocytosis, and haemolysis.	Dosage adjustment may be required for dapsone and necessitate monitoring of haematological adverse events.
doxycycline	↓ doxycycline exposure	In a group of hospitalized patients rifampicin (10 mg/kg daily) reduced the exposure (AUC) of doxycycline by about 50% .
fluoroquinolones	↓ fluoroquinolone	Rifampicin 900 mg daily modestly reduced the AUC of perfloxacin by about 35%.

	exposure	Rifampicin 450 mg to 600 mg daily has been shown to reduce the exposure (AUC) of moxifloxacin by about 30%.
oral hypoglycemic agents (sulfonylureas)	↓ sulfonylurea exposure	Sulfonylureas are primarily substrates of CYP2C9. Rifampicin 600 mg daily reduced the exposure (AUC) of glyburide by 39% and of glipizide by 22%, and reduced the half-life of both drugs. It is probable that the blood glucose–lowering effect of glyburide is reduced during concomitant treatment with rifampicin.
immunosuppressive agents (e.g., cyclosporine, tacrolimus)	↓ cyclosporine, tacrolimus exposure	Cyclosporine and tacrolimus are substrates of CYP3A4 and P-gp. In 6 healthy volunteers oral bioavailability of cyclosporine was reduced from 33% to 9% with coadministration of rifampicin 600 mg daily . In 4 kidney transplant patients coadministration of rifampicin 600 mg daily reduced the exposure of cyclosporine (AUC) by approximately 60% . In 6 healthy volunteers oral bioavailability of tacrolimus was reduced by 51% with coadministration of rifampicin 600 mg daily via induction of CYP3A4 and P-gp .
irinotecan	↓ irinotecan active metabolite exposure	Irinotecan is extensively metabolized by various enzyme systems, including carboxyl esterases, UGT, and CYP3A4. Rifampicin 450mg/day was administered to a patient as part of an antibiotic regimen including isoniazid (300 mg/day) and streptomycin (0.5 g/day im). Although there was no change in irinotecan exposure (AUC), irinotecan active metabolite exposure (AUC) decreased by 20% and its glucuronide metabolite decreased by 58.8%, possibly via induction of CYP3A4.
levothyroxine	↓ levothyroxine exposure	Rifampicin 600 mg daily was administered to a patient previously treated with levothyroxine. Approximately 2 weeks after initiation of rifampicin, thyroid stimulating hormone (TSH) concentration increased by 202% compared to the pretreatment concentration. TSH concentration returned to normal 9 days after discontinuance of rifampicin .
Losartan	↓ losartan and active metabolite exposure	Losartan is metabolized by CYP2C9 and CYP3A4 to an active metabolite, E3174, which has greater antihypertensive activity than the parent compound. Rifampicin 600 mg daily reduced the exposure (AUC) of losartan by 35% and E3174 by 40%. Losartan oral clearance was increased by 44%. The half-life values of both compounds were decreased by 50% .
narcotic analgesics	↓ narcotic analgesics exposure	Various studies and case reports have been reviewed between rifampicin and both opioid analgesics. Rifampicin 600 mg daily decreased the mean AUC for IV and oral oxycodone by 53% and 86%, respectively, while oral oxycodone's mean bioavailability decreased by 70%. Rifampicin 600 mg daily reduced morphine Cmax by 41% and AUC by 28%. The analgesic effect of morphine should be monitored and doses of morphine adjusted during and after treatment with rifampicin.
methadone	↓ methadone exposure	Methadone is predominantly metabolized by CYP2B6 and CYP3A4. Rifampicin 600 mg daily reduced the oral bioavailability of methadone from 70% to 50% .
praziquantel	↓ praziquantel exposure	Praziquantel is extensively metabolized by CYP enzymes. Rifampicin 600 mg daily reduced plasma concentrations of praziquantel to below detectable levels in 7 of 10 subjects administered single dose praziquantel; of the 3 subjects with detectable concentrations, praziquantel exposure (AUC) was reduced by 85%. In the same study, rifampicin reduced multiple dose praziquantel concentrations

		below detectable levels in 5 of 10 subject; of the 5 subjects with detectable concentrations, praziquantel exposure was reduced by 80% .
Quinine	↓ quinine exposure	Quinine is mainly metabolized by CYP3A4. Rifampicin 600 mg daily increased quinine clearance by 6.9-fold and reduced quinine exposure (AUC) and half-life .
selective 5-HT3 receptor antagonists (e.g. ondansetron)	↓ ondansetron exposure	Ondansetron is metabolized by multiple CYP Enzymes Rifampicin 600 mg daily reduced the exposure (AUC) of orally administered ondansetron by 65% compared with placebo and the elimination half-life (t1⁄2) by 38%. The oral bioavailability of ondansetron was reduced from 60% to 40% .
statins metabolized by CYP3A4 (e.g., simvastatin)	↓ simvastatin exposure	Simvastatin is a clinical index substrate of CYP3A4. Rifampicin 600 mg daily reduced simvastatin exposure (AUC) by 87% compared to placebo. Because the elimination half-life of simvastatin was not affected by rifampicin, induction of the CYP3A4-mediated first-pass metabolism of simvastatin in the intestine and the liver probably explains this interaction.
teithromycin	↓ telithromycin exposure	Telithromycin is metabolized primarily by CYP3A4. Rifampicin 600 mg daily reduced telithromycin exposure (AUC) by 86%
theophylline	↓ theophylline exposure	Theophylline is a clinical index inhibitor of CYP1A2. Rifampicin 600 mg daily increased theophylline clearance by 40%, reduced theophylline exposure (AUC) by 27%, and reduced elimination half-life by 30%.
thiazolidinediones (e.g.rosiglitazone)	↓ rosiglitazone exposure	Rosiglitazone is primarily metabolized by CYP2C8 and to a lesser extent by CYP2C9. Rifampicin 600 mg daily increased rosiglitazone apparent oral clearance by 3-fold, reduced rosiglitazone exposure (AUC) by 65%, and reduced elimination half-life from 3.9 to 1.5 h.
tricyclic antidepressants (eg nortriptyline)	↓ nortriptyline exposure	Higher than expected doses of nortriptyline were required to obtain a therapeutic drug level when it was associated with Rifampicin 600 mg daily given as part of a tuberculosis treatment regimen that included isoniazid 300 mg daily, pyrazinamide 500 mg 3x per day and pyridoxine 25 mg. Following the discontinuation of rifampicin, the patient became drowsy and the serum nortriptyline levels rose precipitously (3-fold) into the toxic range .
Mifepristone	↓ Mifepristone exposure	Rifampicin was shown to decrease mifepristone AUC by 6.3-fold and its metabolites 22-hydroxy mifepristone and N-demethyl mifepristone by 20-fold and 5.9-fold, respectively. Therefore, reduced efficacy can be expected when mifepristone is given concomitantly with rifampicin. If concomitant use is necessary, the dose of mifepristone should be increased.

↓ : decrease ↑ : increase
Effect of other medicinal products on Rifadin
Concomitant antacid administration may reduce the absorption of Rifadin. Daily doses of Rifadin should be given at least 1 hour before the ingestion of antacids.

Other Drug Interactions with Rifadin
When the two drugs were taken concomitantly, decreased concentrations of atovaquone and increased concentrations of rifampicin were observed.

Concurrent use of ketoconazole and Rifadin has resulted in decreased serum concentration of both drugs.

4.6 Fertility, pregnancy and lactation

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. 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.

Rifampicin and isoniazid and pyrazinamide areknown to pass into maternal breast milk. Therefore Rifater should be used in a nursing mother only if the potential benefit to the patient outweighs the potential risk to the infant.

4.7 Effects on ability to drive and use machines

Not relevant.

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).

Applies to Rifampicin:
Infections and Infestations:
Unknown: Pseudomembranous colitis, influenza
Hepatobiliary disorders:
Hepatitis may be caused by rifampicin and liver function tests should be monitored. (See 4.4 Special Warnings and Precautions for Use).

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, haemolytic 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 discoloration

Vascular disorders
Unknown: Shock, flushing, vasculitis **,** bleeding

Respiratory, thoracic and mediastinal disorders
Unknown: Dyspnoea, wheezing, sputum discoloured, Interstitial lung disease (including pneumonitis)

Gastrointestinal disorders
Common: Nausea, vomiting
Uncommon: Diarrhea
Unknown: Gastrointestinal disorder, abdominal discomfort, tooth discoloration (which may be permanent)

Hepatobiliary disorders
Unknown: Hepatitis, hyperbilirubinaemia, cholestasis(see section 4.4: Special warnings and precautions for use)

Skin and subcutaneous tissue disorders
Unknown: Erythema multiforme, acute generalized exanthematous pustulosis (AGEP), Stevens-Johnson syndrome and toxic epidermal necrolysis, Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) syndrome (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

* 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).

Investigations
Common: Blood bilirubin increased, aspartate aminotransferase increased, alanine aminotransferase increased
Unknown: Blood pressure decreased, blood creatinine increased, hepatic enzyme increased

If serious complications arise, e.g., renal failure, thrombocytopenia or haemolytic anaemia, Rifater should be stopped and never restarted.

Rifampicin may produce a discolouration (yellow, orange, red, brown) of the teeth, urine, sputum and tears. The patient should be forewarned of this. Soft contact lenses may be permanently stained.

Applies to Isoniazid:
Immune system disorders:
Anaphylactic reactions.

Endocrine disorders - Gynecomastia

Nervous system disorders:
Polyneuritis, presenting a sparathesia, muscle weakness, loss of tendon reflexes etc. The incidence is higher in 'slow acetylators'. Other neurotoxic effects, which are uncommon with conventional doses, are convulsions (see Section 4.9 Overdose), toxic enceophalopathy, optic neuritis and atrophy, memory impairment, and toxic psychosis. The possibility that the frequency of seizures may be increased in patients with epilepsy should be bourne in mind.

Vascular disorders:
Not known: Vasculitis

Skin and subcutaneous tissue disorders:
Rash, acne Stevens-Johnson syndrome (SJS) (see section 4.4), exfoliative dermatitis, pemphigus.
Rare: Toxic epiderman necrolysis, dress reaction with eosinophilia and systemic symptoms (DRESS) (see section 4.4).

Blood and lymphatic system disorders:
Eosinophilia, agranulocytosis, thrombocytopenia, anaemia.

Gastrointestinal disorders:
Not known: Pancreatitis, nausea, vomiting, epigastric distress.

Hepatobiliary disorders:
Severe and sometimes fatal hepatitis.
Uncommon: Hepatitis

Metabolism and nutrition disorders:
Pellagra

Musculoskeletal and connective tissue disorders:
Systemic lupus erythematosus-like syndrome.

General disorders and administration site conditions:
Fever.

Applies to Pyrazinamide:

Blood and lymphatic system disorders:
Sideroblastic anaemia, thrombocytopenia with or without purpura.
Not Known: vasculitis

Metabolism and nutrition disorders:
Gout, anorexia.

Gastrointestinal disorders:
Nausea, vomiting and aggravation of peptic ulcer.

Not known: pancreatitis

Hepatobiliary disorders:
Hepatitis. The hepatic reaction is the most common adverse reaction and varies from a symptom less abnormality of hepatic cell function through a mild syndrome of fever, malaise and liver tenderness, to more serious reactions as clinical jaundice and rare cases of acute yellow atrophy and death.

Skin and subcutaneous tissue disorders:
Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) syndrome (see section 4.4), urticaria, pruritus, erythema, rash
Very rarely, angioedema has been reported.
Not known:Photosensitivity reaction.

Musculoskeletal and connective tissue disorders:
Arthralgia.

Renal and urinary disorders:
Dysuria.

General disorders and administration site conditions:
Malaise, fever.

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 HPRA Pharmacovigilance, Website: www.hpra.ie

* 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).

4.9 Overdose

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

Signs and symptoms:

Applies to rifampicin:
Nausea, vomiting, abdominal pain, prutitis, 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 arrhythmias, seizure and cardiac arrest were reported in some fatal cases.

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

Applies to 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 hyperglycemia are typical laboratory findings.

Applies to pyrazinamide:
There is limited information related to pyrazinamide overdose. Liver toxicity and hyperuriceamia may occur with overdosage.

Management:

Applies to Rifater:
In cases of overdosage with Rifater, gastric lavage should be performed as soon as possible. Following evacuation of the gastric contents, the installation of activated charcoal slurry into the stomach may help absorb any remaining drug from the gastrointestinal tract. Antiemetic medication may be required tocontrol severe nausea and vomiting. Intensive supportive measures should be instituted including airway patency and individual symptoms treated as they arise.

Applies to isoniazid only:
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, 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

ATC: J04 AM02.

Rifampicin, isoniazid and pyrazinamide are all active bactericidal antituberculous 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 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 10mcg/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. 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. It diffuses readily into 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 (B6) is sometimes observed in adults with high doses of isoniazid, probably due to its competition with pyridoxal phosphate for 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

Povidone
Carmellose sodium
Sodium laurilsulfate
Calcium stearate
Sucrose
Acacia gum
Talc
Light magnesium carbonate
Kaolin
Titanium dioxide (E171)
Colloidal Silicon dioxide
Aluminium hydroxide Dried gel
Iron oxide (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

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

6.5 Nature and contents of container

Blister strips of 20 in packs of 100.
Blister material is 250mcg PVC/60 gm^2 PVDC and 67.5 gm^2 aluminium/118-20 gm^2 PVDC.

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

Sanofi-Aventis Ireland Limited T/A SANOFI
Citywest Business Campus
Dublin 24
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0540/067/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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Date of last renewal: 09 February 2007

10 DATE OF REVISION OF THE TEXT

March 2024