Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Rifinah 300 / 150 mg Film Coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 300mg Rifampicin and 150mg Isoniazid.

Excipients: Sucrose 181.03mg
Sodium 1.3mg

For a full list of excipients, see 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablets (Tablets).
Orange, smooth, shiny, capsule-shaped, sugar-coated tablets.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

For the treatment of tuberculosis, and other mycobacterial infections.

4.2 Posology and method of administration

Rifinah should be given at least 30 minutes before a meal or 2 hours after a meal.

Adults Only: Rifampicin 450-600mg (10mg/kg b.w) daily as a single dose combined with Isoniazid 5mg/kg b.w.

Use in the elderly: Caution should be exercised in using rifampicin in such patients especially if there is evidence of liver function impairment.

Use in impaired liver function: A daily dose of 8mg/kg/day should not be exceeded in patients with impaired liver function.

4.3 Contraindications

Use in patients with jaundice.

Use in patients with known hypersensitivity to the rifamycins, isoniazid or any of the components.

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

Administration at the same time as some formulations of para-aminosalicylic acid, since such a combination will not permit adequate blood levels of either. Dosage of each should be separated by at least eight hours, unless the formulation of PAS has been shown not to inhibit absorption.

Use in patients with manic or hypomanic psychoses.

4.4 Special warnings and precautions for use

Rifinah is a combination of two drugs, each of which has been associated with liver dysfunction.

Patients with impaired liver function or chronic alcoholism should only be given Rifinah 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 Rifinah 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, Rifinah should be discontinued

In some cases, hyperbilirubinemia resulting from competition between rifampicin and bilirubin for excretory pathyways 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 patients clinical condition.

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

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 as a result of induction of delta amino levulinic acid synthetase.

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.

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

Care should be exercised in the treatment of elderly or malnourished patients who may also require vitamin B_6 supplementation with the isoniazid therapy.

Certain individuals, who may metabolise isoniazid more slowly than usual (the "slow acetylators") are susceptible to drug-induced peripheral neuropathy.

Isoniazid should only be administered with great caution in patients with convulsion disorders, chronic alcoholism, and severe impairment of liver/kidney function.
Adults treated for tuberculosis with Rifinah should have baseline measurements of hepatic enzymes, bilirubin, serum creatinine, and a complete blood count and a platelet count (or estimate).

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.

Severe cutaneous reactions:

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

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.

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 into his 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.

The combination of rifampicin with isoniazid 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, the malnourished.

Certain hypersensitivity phenomena affecting platelets and vascular tissue may occur. Adequate surveillance should be maintained to permit early detection of these effects.

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

Paradoxical drug reaction
After initial improvement of tuberculosis under therapy with Rifinah, 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).

This medicinal product 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,	↓ 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% .

quinidine, propafenone, tocainide)		
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 exposure	Rifampicin 900 mg daily modestly reduced the AUC of perfloxacin by about 35%. 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	Various studies and case reports have been reviewed between rifampicin and

	exposure	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 exposure	Higher than expected doses of nortriptyline were required to obtain a therapeutic drug level when it was associated with Rifampicin 600 mg daily

nortriptyline)		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

Rifampicin has been shown to be teratogenic in rodents when given in large doses. There are no well controlled studies with rifanah in pregnant women. Therefore, Rifinah 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.

When administered during the last few weeks of pregnancy, rifampicin can cause postnatal haemorrhages in the mother and infant, for which treatment with Vitamin K1 may be indicated.

Rifampicin and isoniazid are excreted in breast milk and infants should not be breast fed by a patient receiving Rifinah unless in the physicians judgement the potential to the patient outweighs the potential risk to the infant.

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).

Applies to Rifampicin:
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 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, rifampicin should be stopped and never restarted.

Applies to Isoniazid:
Blood and lymphatic system disorders
Eosinophilia, agranulocytosis, thrombocytopenia, anemia.

Immune system disorders
Anaphylactic reactions

Endocrine disorders - Gynecomastia

Metabolism and nutrition disorders
Pellagra

Nervous system disorders
Polyneuritis, presenting as paresthesia, 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 12: Overdose), toxic encephalopathy, optic neuritis and atrophy, memory impairment, and toxic psychosis.

Vascular disorders:
Not known: Vasculitis

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

Hepatobiliary disorders
Severe and sometimes fatal hepatitis.
Uncommon: hepatitis

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

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

General disorders and administration site conditions
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.

4.9 Overdose

In cases of overdosage with Rifinah, gastric lavage should be performed as soon as possible. Intensive supportive measures should be instituted including airway patency and individual symptoms treated as they arise. Parenteral pyridoxine (Vitamin B1) should be given. Symptoms are more likely to be related to isoniazid, including coma, respiratory distress, hyperglycaemia and metabolic ketoacidosis.

Applies to rifampicin
Nausea, vomiting, abdominal pain, pruritus, headache and increasing lethargy will probably occur within a short time after acute ingestion; unconciousness may occur when there is severe hepatic disease. Transient increases in liver enzymes and/or bilirubin may occur. Facial or periorbital edema 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 overdose in adults have been reported with doses ranging from 14 to 60g. Alcohol or history of alcohol abuse was involved in some fatal and nonfatal reports. Nonfatal overdoses in paediatric patients ages 1 – 4 years old of 100mg/kg for one to 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 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. 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 and isoniazid are active bactericidal anti-tuberculosis drugs. Rifampicin and isoniazid are particularly active against the rapidly growing extracellular organisms. Rifampicin and isoniazid also have bactericidal activity intracellularly. Rifampicin has activity against slow and intermittently-growing *M. tuberculosis*.

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 with other rifamycins.

Isoniazid acts against actively growing tubercle bacilli.

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 a 900mg dose. With repeated administration, the half-life decreases and reaches average values of approximately 2-3 hours.

After absorption, rifampicin is rapidly eliminated in the bile, and an enterohepatic circulation ensues. During this process, rifampicinundergoes 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 with 1 to 2 hours which decline to 50% of less within 6 hours. It diffuses readily into all body fluids (cerebrospinal, pleural and ascitic fluids), tissues, organs and excreta (saliva, sputum and faeces). From 50 to 70% of a dose of isoniazid is excreted in the urine in 24 hours.

Isoniazid is metabolized primarily by acetylation and dehydration. The rate of acetylation is genetically determined.

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

5.3 Preclinical safety data

Not applicable.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium laurilsulfate
Calcium stearate
Carmellose sodium
Magensium stearate
Microcrystalline cellulose
Acacia
Gelatin
Kaolin, heavy
Magnesium carbonate light
Talc
Titanium dioxide (E171)
Silica, colloidal ahydrous
Povidone
Yellow A1 lake (E110)
Sucrose
Carnauba wax
Colophony
White beeswax
Hard paraffin

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 25°C.

Keep the container tightly closed (bottles).

Store in the original package in order to protect from moisture (blisters).

6.5 Nature and contents of container

PVC/aluminium foil blisters containing 56 tablets.
Amber glass bottle, with LDPE screw cap, containing 100 tablets.

Not all pack sizes may be marketed.

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

No special requirements.

7 MARKETING AUTHORISATION HOLDER

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

8 MARKETING AUTHORISATION NUMBER

PA0540/068/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 01 April 1977

Date of last renewal: 24 January 2008

10 DATE OF REVISION OF THE TEXT

March 2024