Safety update: CCDS v2-8 (resubmission)

PROFESSIONAL INFORMATION (CLEAN), dated 18 August 2022

SCHEDULING STATUS: S4

1 NAME OF THE MEDICINE

RIFINAH® 150/75 Film-coated tablets

RIFINAH® 300 FC Film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

RIFINAH® 150/75 contains 150 mg rifampicin and 75 mg isoniazid.

RIFINAH® 300 FC contains 300 mg rifampicin and 150 mg isoniazid

Sugar free.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

RIFINAH150/75: Film-coated tablets.

Rust brown, 9,1 mm round, biconvex, film-coated tablets.

RIFINAH 300 FC: Film-coated tablets.

Warm orange, 11 mm round, biconvex, film-coated tablets.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Continuation phase treatment of pulmonary and extra-pulmonary tuberculosis in newly diagnosed patients and re-treatment of adult cases.

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4.2 Posology and method of administration

Posology

RIFINAH Tablets are recommended in the continuation phase of the treatment of pulmonary and extra-pulmonary tuberculosis.

South African National Tuberculosis Control Programme dosage recommendation:

New, smear positive patients, new smear negative patients and extra-pulmonary TB: During this phase, which lasts for 4 months, this medicine should be administered daily for 5 consecutive days per week.

WHO dosage recommendation*:* During this phase, which lasts for 4 months, this medicine should be administered on a continuous daily basis.

The total dosage requirement is as follows:

	Daily	
Rifampicin	10 mg/kg (8-12 mg/kg)	maximum 600 mg per day
Isoniazid	5 mg/kg (4-6 mg/kg)	maximum 300 mg/kg

Patient body mass (kg)	Number of tablets (daily)	
	RIFINAH 150/75	RIFINAH 300 FC
30 – 37	2	--
38 – 54	3	--
55 or more	--	2

Paediatric population:

RIFINAH tablets are unsuitable for children under 12 years.

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4.3 Contraindications

Contraindicated in patients with a history of hypersensitivity to rifamycins, isoniazid or any of the components.

RIFINAH is contraindicated in jaundice and acute porphyria.

Rifampicin can cause thrombocytopenia and purpura usually with intermittent tuberculosis regimens; further administration is contraindicated (see section 4.4).

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

4.4 Special warnings and precautions for use

RIFINAH 150/75 and RIFINAH 300 FC are a combination of two medicines, each of which has been associated with liver dysfunction.

Adults treated for tuberculosis with RIFINAH 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 and chronic liver disease and intravenous drug use.

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Severe, systemic hypersensitivity reactions, including fatal cases, such as Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) syndrome have been observed during treatment with antituberculosis 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 doctor. RIFINAH should be discontinued if an alternative etiology for the signs and symptoms cannot be established.

Applies to rifampicin:

Liver: Patients with impaired liver function should only be given rifampicin in cases of necessity and then with caution and under strict medical supervision. In these patients, careful monitoring of liver function, especially serum alanine aminotransferase (ALT) and serum aspartate aminotransferase (AST) should be carried out prior to therapy and then every 2 to 4 weeks during therapy. If signs of hepatocellular damage occur, rifampicin should be discontinued.

Cases of mild to severe cholestasis have been reported with rifampicin therapy. Patients should be instructed to contact their doctor 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 pathways of the liver at 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 the trends in the levels and considering them in conjunction with the patient's clinical condition.

Immunological reactions/anaphylaxis:

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Because of the possibility of immunological reactions, including anaphylaxis (see section 4.8), 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 generalised 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.

Porphyria exacerbation and metabolism of endogenous substrates:

Rifampicin has enzyme induction properties that can enhance the metabolism of endogenous substrates including adrenal hormones, thyroid hormones and vitamin D.
Reports have associated porphyria exacerbation with rifampicin administration as a result of induction of delta amino levulinic acid synthetase (see section 4.3).

Discolouration of teeth, body fluids and contact lenses:

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 (see section 4.8).

Inducing of medicine metabolising enzymes and transporters:

Rifampicin is a well characterised and potent inducer of medicine metabolising enzymes and transporters and might therefore decrease or increase concomitant medicine exposure, safety and

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efficacy (see section 4.5). Therefore, patients should be advised not to take any other medication without medical advice.

Vitamin K dependent coagulopathy and severe bleeding:

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).

Applies to isoniazid:

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

Liver: Severe and sometimes fatal hepatitis associated with isoniazid therapy may occur and may develop even after months of treatment. The risk of developing hepatitis is age-related. Therefore, patients should be monitored for the prodromal symptoms of hepatitis, such as fatigue, weakness, malaise, anorexia, nausea or vomiting. If these symptoms appear or if signs suggestive of hepatic damage are detected, isoniazid should be discontinued promptly, since continued use of the medicine in these cases has been reported to cause a more severe form of liver damage.

Stevens-Johnson syndrome (SJS) and Toxic Epidermal Necrolysis (TEN):

Cases of severe cutaneous reactions including Stevens-Johnson syndrome (SJS) and Toxic Epidermal Necrolysis (TEN), some with a fatal outcome, have been reported with the use of isoniazid (see section 4.8). Patients should be advised of the signs and symptoms and monitored closely for skin reactions. If signs or symptoms of SJS or TEN (e.g. progressive skin rash often with blisters or mucosal lesions) develops, the patient should be advised to consult immediately their doctor.

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

Pyridoxine supplementation: Patients who are at risk of neuropathy or pyridoxine deficiency including those who are diabetic, alcoholic, elderly, malnourished, uraemic, pregnant or have HIV infection, should receive pyridoxine (Vitamin B_6) usually in a dose of 10 mg daily.

4.5 Interaction with other medicines and other forms of interaction

Applies to RIFINAH (rifampicin and isoniazid combination):

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

Cytochrome P-450 enzyme interaction:

Rifampicin is known to induce, and isoniazid is known to inhibit certain cytochrome P-450 enzymes. Therefore, caution should be used when prescribing RIFINAH with medicines metabolised by cytochrome P-450. To maintain optimum therapeutic blood levels, dosages of medicines metabolised by these enzymes may require adjustment when starting or stopping RIFINAH.

Applies to Rifampicin:

- **Pharmacodynamic interactions**

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

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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 with high doses).

- **Effect of rifampicin on other medicinal products**

Induction of Medicine Metabolising Enzymes and Transporters

RIFINAH is a well characterised and potent inducer of medicine metabolising enzymes and transporters. Enzymes and transporters reported to be affected by RIFINAH 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 medicines are substrates for one or more of these enzyme or transporter pathways, and these pathways may be induced by RIFINAH simultaneously. Therefore, RIFINAH may accelerate the metabolism and decrease the activity of certain coadministered medicines 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 medicines and across many medicine classes (Table 1). To maintain optimum therapeutic blood levels, dosages of medicines may require adjustment when starting or stopping concomitantly administered RIFINAH.

The following table provides examples of the induction effect of rifampicin on exposure of selected medicine metabolising enzymes and transporter substrate medicines

Table 1 Effect of Rifampicin Coadministration on Medicines or Medicine Classes		
Medicine or	**Effect**	**Comments**

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Medicine Class		
antiretroviral medicines (e.g. zidovudine, saquinavir, indinavir, efavirenz, atazanavir, lopinavir, nevirapine)	↓ antiretroviral exposure	Rifampicin 600 mg daily reduced zidovudine exposure (AUC) by 47 % via induction of zidovudine glucuronidation and amination metabolism pathways. Rifampicin 600 mg 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 600 mg daily reduced efavirenz exposure (AUC) by 60 % primarily via induction of efavirenz CYP2B6-mediated 8-hydroxylation pathway (see section 4.3).
hepatitis-C antiviral medicines (e.g. daclatasvir, simeprevir, sofosbuvir, telaprevir)	↓ exposure to hepatitis-C antiviral medicine 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.

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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.
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 metabolised mainly by CYP2C9/2C19. Rifampicin 450 mg daily doubled the clearance of phenytoin and reduced the half-life by about 50 %.
antidysrhythmics (e.g. disopyramide, flecainide, quinidine, propafenone)	↓ antidysrhythmic medicine exposure	Rifampicin 600 mg daily reduced the exposure (AUC) of quinidine by about 80 % and propafenone by 87 %.
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)

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		of S-warfarin by 74 %.
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 medicines (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 1 200 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)

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		of verapamil by 93 %.
chloramphenicol	↓ chloramphenicol exposure	In two children treated concomitantly with intravenous chloramphenicol and rifampin, 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

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		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	In a clinical probe cocktail study, rifampicin 600 mg daily, increased the metabolism of dapsone via induction of CYP2C9, CYP2E1 and CYP3A4.
doxycycline	↓ doxycycline exposure	In a group of hospitalised patients rifampicin (10 mg/kg daily) reduced the exposure (AUC) of doxycycline by about 50 %.
fluoroquinolones e.g. moxifloxacin, ciprofloxacin, levofloxacin	↓ fluoroquinolone 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 glipizide by 22 % and reduced its half-life. Diabetes may become more difficult to control.
immunosuppressive	↓ ciclosporine,	Ciclosporine and tacrolimus are substrates of

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agents (e.g. ciclosporine, tacrolimus, azathioprine, sirolimus)	tacrolimus exposure	CYP3A4 and P-gp. In 6 healthy volunteers oral bioavailability of ciclosporine 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 ciclosporine (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 metabolised by various enzyme systems, including carboxyl esterases, UGT, and CYP3A4. Rifampicin 450 mg/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

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		increased by 202 % compared to the pretreatment concentration. TSH concentration returned to normal 9 days after discontinuance of rifampin.
losartan	↓ losartan and active metabolite exposure	Losartan is metabolised by CYP2C9 and CYP3A4 to an active metabolite, E3174, which has greater antihypertensive activity than the parent compound. Rifampin 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 rifampin both opioid analgesics. Rifampin 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 C_{max} by 41 % and AUC by 28 %. Using the cold pressor test to determine pain sensation, the administration of rifampicin resulted in no analgesic effect of morphine.
methadone	↓ methadone exposure	Methadone is predominantly metabolised by CYP2B6 and CYP3A4. Rifampin 600 mg daily reduced the oral bioavailability of methadone from 70 % to 50 %.
praziquantel	↓ praziquantel exposure	Praziquantel is extensively metabolised by CYP enzymes.

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		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 metabolised 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 metabolised 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 ($t_{½}$) by 38 %. The oral bioavailability of ondansetron was reduced from 60 % to 40 %.
statins metabolised 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

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		affected by rifampicin, induction of the CYP3A4-mediated first-pass metabolism of simvastatin in the intestine and the liver probably explains this interaction.
telithromycin	↓ telithromycin exposure	Telithromycin is metabolised 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. pioglitazone)	↓ pioglitazone exposure	Pioglitazone is metabolised by CYP2C8.
tricyclic antidepressants (e.g. nortriptyline)	↓ nortriptyline exposure	Rifampicin 600 mg daily as part of a tuberculosis treatment regimen that included isoniazid 300 mg daily, pyrazinamide 500 mg 3 x per day and pyridoxine 25 mg was associated with higher than expected doses of nortriptyline were required to obtain a therapeutic medicine level. Following the discontinuation of rifampin, the patient became drowsy and the serum nortriptyline levels rose precipitously (3-fold) into the toxic range.
Clopidogrel	↑ active metabolite exposure	Rifampicin strongly induces CYP2C19, resulting in both an increased level of clopidogrel active metabolite and

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		platelet inhibition, which in particular might potentiate the risk of bleeding. As a precaution, concomitant use of clopidogrel and rifampicin should be discouraged.

↓ decrease ↑: increase

Decreased prothrombin time and INR with concurrent anticoagulant use:

The prothrombin time of patients receiving concurrent warfarin anticoagulant therapy may be decreased. Frequent monitoring of the prothrombin level in such patients with subsequent adjustment in anticoagulant dosage, is recommended.

Effect of other medicinal products on rifampicin:

The absorption of rifampicin may be reduced by concomitant administration with antacids, medicines that reduce gastric motility (anticholinergics and opioids), ketoconazole, or preparations containing bentonite (for example some aminosalicylic acid preparations). Daily doses of rifampicin should be given at least 1 hour before ingestion of one of these medicines.

Other medicine interactions with rifampicin:

When given concomitantly, decreased concentrations of atovaquone and increased concentrations of rifampicin were observed.

Interference with laboratory and diagnostic tests:

Therapeutic levels of rifampicin have been shown to inhibit standard microbiological assays for serum folate and Vitamin B_{12}. Thus, alternative assay methods should be considered.

Transient elevation of serum bilirubin has also been observed.

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RIFINAH may impair biliary excretion of contrast media used for visualisation of the gallbladder, due to competition for biliary excretion. Therefore, these tests should be performed before the morning dose of RIFINAH.

Applies to Isoniazid:

Isoniazid can inhibit the hepatic metabolism of a number of medicines, in some cases leading to increased toxicity. These include the antiepileptics carbamazepine, ethosuximide primidone and phenytoin, the benzodiazepines diazepam and triazolam, disulfiram and theophylline. Isoniazid has been associated with increased concentrations or toxicity of, cicloserine and warfarin.

Daily ingestion of alcohol may be associated with higher incidence of isoniazid hepatitis.

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

Food interactions:

Applies to Isoniazid:

Because isoniazid has some monoamine oxidase inhibiting activity, an interaction with tyramine-containing foods (cheese, red wine) may occur. Diamine oxidase may also be inhibited, causing exaggerated response (e.g. headache, sweating, palpitations, flushing, hypotension) to foods containing histamine (e.g. skipjack, tuna, other tropical fish). Tyramine- and histamine-containing foods should be avoided by patients receiving RIFINAH.

4.6 Fertility, pregnancy and lactation

Pregnancy

The safety of RIFINAH tablets in pregnant and lactating women has not been established.

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

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Breastfeeding

Rifampicin and isoniazid are known to pass into maternal breast milk.

4.7 Effects on ability to drive or use machines

RIFINAH may cause undesirable effects, e.g. dizziness and visual disturbances which may reduce the capacity for the completion of certain tasks (see section 4.8). Patients should be informed of the potential for these undesirable effects that may occur and if they experience these symptoms, consideration should be given not to drive or operate machinery.

4.8 Undesirable effects

Applies to Rifampicin:

Infections and infestations:

Frequency unknown: pseudomembranous colitis, “flu syndrome” consisting of episodes of pyrexia, chills, headache, dizziness and bone pain

Blood and lymphatic system disorders:

Frequent: thrombocytopenia with or without purpura, usually associated with intermittent therapy, but is reversible if medicine is discontinued as soon as purpura occurs

Less frequent: leukopenia

Frequency unknown: disseminated intravascular coagulation, eosinophilia, agranulocytosis, haemolytic anaemia, vitamin K dependent coagulation disorders

Immune system disorders:

Frequency unknown: anaphylactic reaction

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Endocrine disorders:

Frequency unknown: adrenal insufficiency in patients with compromised adrenal function

Metabolism and nutritional disorders:

Frequency unknown: decreased appetite

Psychiatric disorders:

Frequency unknown: psychotic disorder

Nervous system disorders:

Frequent: headache, dizziness

Frequency unknown: drowsiness, ataxia, numbness, cerebral hemorrhage and fatalities have been reported when RIFANAH administration has been continued or resumed after the appearance of purpura (see section 4.3)

Eye disorders:

Less frequent: eye irritation, visual disturbances

Frequency unknown: tear discolouration. Soft contact lenses worn by patients receiving RIFINAH may become permanently stained (see section 4.4)

Vascular disorders:

Frequency unknown: shock, flushing, vasculitis, bleeding

Respiratory, thoracic and mediastinal disorders:

Frequency unknown: dyspnoea, wheezing, discoloured sputum

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Gastrointestinal disorders:

Frequent: nausea, vomiting

Less frequent: diarrhoea

Frequency unknown: gastrointestinal disorder, abdominal discomfort, tooth discolouration (which may be permanent)

Hepato-biliary disorders:

Frequency unknown: hepatitis, hyperbilirubinemia, cholestasis (see section 4.4)

Skin and subcutaneous tissue disorders:

Frequency unknown: erythema multiforme acute generalised 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, pruritic rash, urticaria, allergic dermatitis, pemphigoid, sweat discolouration

Musculoskeletal and connective tissue disorders:

Frequency unknown: muscle weakness, myopathy, bone pain

Renal and urinary disorders:

Frequency unknown: acute kidney injury usually due to renal tubular necrosis or tubulointerstitial nephritis, chromaturia

Pregnancy, puerperium and perinatal conditions

Frequency unknown: post-partum haemorrhage, foetal-maternal haemorrhage (see section 4.6)

Reproductive system and breast disorders:

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Frequency unknown: menstrual disorder

Congenital, familial and genetic disorders:

Frequency unknown: porphyria exacerbation (see section 4.3 and 4.4)

General disorders and administration site conditions:

Frequent: pyrexia, chills

Frequency unknown: oedema

Investigations:

Frequent: increased blood bilirubin, increased aspartate aminotransferase (AST), increased alanine aminotransferase (ALT) (see section 4.4)

Frequency unknown: decreased blood pressure, increased blood creatinine, increased hepatic enzyme (see section 4.5)

Applies to Isoniazid:

Blood and lymphatic system disorders:

Less frequent: eosinophilia, agranulocytosis, thrombocytopenia, anaemia

Immune system disorders:

Less frequent: hypersensitivity reactions (including erythema multiforme)

Frequency unknown: anaphylactic reactions

Endocrine disorders:

Frequency unknown: gynecomastia

Metabolism and nutrition disorders:

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Frequency unknown: pellagra

Psychiatric disorders:

Frequency unknown: psychotic reactions

Nervous system disorders:

Frequent: peripheral neuropathy (Pyridoxine supplementation prevents the development of peripheral neuritis (see section 4.4))

Frequency unknown: polyneuritis, presenting as paraesthesia, muscle weakness, loss of tendon reflexes. Other neurotoxic effects which are uncommon with conventional doses are convulsions, toxic encephalopathy, optic neuritis and atrophy, memory impairment and toxic psychosis.

Ear and labyrinth disorders:

Frequency unknown: vertigo

Vascular disorders:

Frequency unknown: vasculitis

Gastrointestinal disorders:

*Frequent***:** nausea, vomiting, dry mouth, constipation, epigastric distress

Less frequent: pancreatitis

Hepato-biliary disorders:

Less frequent: severe and sometimes fatal hepatitis

Skin and subcutaneous tissue disorders:

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Less frequent: rash, acne, exfoliative dermatitis

Frequency unknown: Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) syndrome, Toxic Epidermal Necrolysis (TEN), Stevens-Johnson syndrome, (SJS) (see section 4.4), pemphigus, purpura, alopecia

Musculoskeletal and connective tissue disorders:

Less frequent: systemic lupus erythematosus-like syndrome

General disorders and administration site conditions:

Less frequent: fever

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8, or to the Pharmacovigilance Unit at Sanofi at za.drugsafety@sanofi.com (email) or 011 256 3700 (tel).

4.9 Overdose

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

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. Cases of skin pigmentation

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induced by rifampicin overdosage have been reviewed. Brownish-red or orange discolouration of the skin appeared within a few hours of medicine administration; urine, mucous membranes and sclera were also discoloured. Periorbital or facial oedema, pruritus and gastrointestinal intolerance occurred in most patients. Fatalities occurred with doses over 14 g.

Isoniazid:

Isoniazid doses of 6 g or more are associated with severe toxicity and doses above 15 g may be fatal without appropriate treatment. Symptoms may not occur until 2 hours after ingestion. Symptoms include: nausea, vomiting, dizziness, slurring of speech, blurring of vision, and visual hallucinations and CNS depression (see section 4.8).

Management:

In cases of overdosage with RIFINAH tablets, activated charcoal slurry may be used to reduce the absorption of the medicine from the gastrointestinal tract.

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

If acute RIFINAH overdose is suspected, even in asymptomatic patients, the administration of intravenous pyridoxine (vitamin B_6) should be considered. An initial dose of pyridoxine hydrochloride 5 g (even if the amount of isoniazid ingested is unknown), given intravenously over 3 to 5 minutes, has been recommended. This dose is repeated at 5 to 20 minute intervals, until the dose greatly exceeds that of the ingested isoniazid, seizures cease, or consciousness is regained. 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.

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5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties:

Rifampicin and isoniazid belong to the medicine class A 20.2.3 Tuberculostatics.

Rifampicin and isoniazid are active bactericidal antituberculosis medicines. Rifampicin and isoniazid are particularly active against rapidly growing extracellular organisms and have bactericidal activity intracellularly.

Rifampicin inhibits DNA-dependant 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:

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 tablets.

Rifampicin:

Rifampicin is readily absorbed from the gastrointestinal tract. Peak blood levels in normal adults and children vary widely from individual to individual. Peak serum concentrations of the order of 10 μg/ml occur about 2 to 4 hours after a dose of 600 mg. Absorption of rifampicin is reduced when it is ingested with food.

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The half-life for rifampicin ranges initially from 2 to 5 hours, the longest elimination times occurring after the largest doses. However, as rifampicin induces its own metabolism, elimination time may decrease by up to 40 % during the first 2 weeks, resulting in a half-life of about 1 to 3 hours. The half-life is prolonged in patients with liver disease. 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.

After absorption, rifampicin is rapidly eliminated in bile and an enterohepatic circulation ensues. During this process, rifampicin undergoes progressive deacetylation, so that nearly all the medicine in the bile is in this form in about 6 hours. This metabolite retains 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 medicine.

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.

Isoniazid:

Isoniazid is readily absorbed from the gastrointestinal tract. Peak concentration of about 3 to 8 μg per ml appear in blood 1 to 2 hours after a fasting dose of 300 mg by mouth. 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 medicine also passes through the placental barrier and into milk in concentrations comparable to those in plasma. In patients with normal renal function, over 75 % of a dose appears in the urine in 24 hours, mainly as metabolites.

Isoniazid is metabolised primarily by acetylation and dehydrazination. The rate of acetylation is genetically determined.

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6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Each film-coated tablet contains:

Polyvinylpyrrolidone, sodium lauryl sulphate, croscarmellose sodium, microcrystalline cellulose, starch, glyceryl behenate, magnesium stearate.

The film-coating contains the following excipients:

RIFINAH150/75: Aluminium lake pigments (Sunset Yellow FCF, Ponceau 4R and Indigo carmine), macrogol, partly hydrolysed polyvinyl alcohol, talc, titanium dioxide, iron oxide yellow and iron oxide red.

RIFINAH 300 FC: Aluminium lake pigments (Allura red AC and Sunset Yellow FCF), macrogol, partly hydrolysed polyvinyl alcohol, talc, titanium dioxide.

6.2 Incompatibilities

None known.

6.3 Shelf life

RIFINAH 150/75: 24 months

RIFINAH 300 FC: 24 months

6.4 Special precautions for storage

Store at or below 25 °C in a dry place.

6.5 Nature and contents of container

RIFINAH 150/75: Packs of 56 and 84 tablets in foil-foil blisters.

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RIFINAH 300 FC: Packs of 56 tablets in foil-foil blisters.

6.6 Special precautions for disposal and other handling

No special requirements.

7 HOLDER OF THE CERTIFICATE OF REGISTRATION

Sanofi-Aventis South Africa (Pty) Ltd.

2 Bond Street, Midrand, 1685

South Africa

Telephone number: 011 256 3700

8 REGISTRATION NUMBERS:

RIFINAH 150/75: A40/20.2.3/0534

RIFINAH 300 FC: A40/20.2.3/0535

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

RIFINAH 150/75: 01/12/2006

RIFINAH 300 FC: 13/04/2007

10 DATE OF REVISION OF THE TEXT

24 August 2022

Monica Botha: