NEW ZEALAND DATA SHEET

1 RIFINAH TABLETS

Rifinah 150/100mg tablets

Rifinah 300/150mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Rifinah 150/100mg:

Active ingredients: rifampicin 150 mg and isoniazid 100 mg tablets

Rifinah 300/150mg:

Active ingredients: rifampicin 300 mg and isoniazid 150 mg tablets

Excipient with known effect: Sucrose 181.03 mg

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Rifinah 150/100mg tablets are cyclamen biconvex, round, smooth, sugar coated tablets.

Rifinah 300/150mg tablets are orange capsule shaped, sugar-coated tablets, 18.7 mm in length and 8.5 mm in width.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Rifinah 150/100mg and Rifinah 300/150mg are indicated in the treatment of all forms of tuberculosis.

4.2 DOSE AND METHOD OF ADMINISTRATION

Another anti-tuberculosis drug may be given concurrently until the susceptibility of the infecting organism to rifampicin and isoniazid has been confirmed.

Patients should be given the following single daily dose on an empty stomach at least 30 minutes before a meal or 2 hours after a meal.

Concomitant administration of pyridoxine (B6) is recommended in the elderly, malnourished, in those predisposed to neuropathy (e.g. diabetics) and in adolescents.

Rifinah 150/100mg
Patients weighing less than 50 kg
3 tablets

Rifinah 300/150mg
Patients weighing 50 kg or greater
2 tablets

The ratio of rifampicin and isoniazid present in Rifinah make it difficult for both components to be administered in a dosage suitable for children. Rifinah is therefore not recommended for paediatric use.

4.3 CONTRAINDICATIONS

Rifinah is contraindicated in patients with a history of sensitivity to rifamycins, isoniazid, or any of the components.

Rifinah is contraindicated in the presence of jaundice.

Rifinah use is contraindicated when given concurrently with the combination of saquinavir / ritonavir (see Section 4.5 Interaction with other medicines and other forms of interaction).

Concomitant administration with lurasidone as it markedly decreases the exposure of lurasidone compared to the use of lurasidone alone (see Section 4.5 Interaction with other medicines and other forms of interaction).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Rifinah is a combination of 2 drugs, each of which has been associated with liver dysfunction.

Liver

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

Cases of drug-induced liver injury, including fatal cases (especially when used in combination with other anti-tuberculosis drugs), have been reported in patients treated with rifampicin with an onset of a few days to a few months following treatment initiation. Signs and symptoms include elevated serum hepatic enzymes, cholestatic jaundice, hepatitis, hepatotoxicity, hepatocellular injury, and mixed liver injury. Most patients recovered on discontinuation of rifampicin treatment; nevertheless, progression to acute liver failure requiring liver transplantation can occur. The mechanism of rifampicin-induced liver injury is not clearly elucidated, but data indicate either an immuno-allergic mechanism or direct toxicity of metabolic products. Patients should be instructed to contact their physician in case symptoms suggestive of liver injury occur. In such patients rifampicin should be discontinued and liver function should be assessed. Rifampicin should not be re-introduced in patients with an episode of hepatic injury during treatment with rifampicin for which no other cause of liver injury has been determined.

Immunological reactions/ anaphylaxis

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

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) syndrome

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 Undesirable effects).

It is important to note that early manifestations of hypersensitivity, such as fever, lymphadenopathy or biological abnormalities, (including eosinophilia, liver abnormalities), may be present even though rash is not evident. If such signs or symptoms are present, the patient should be advised to consult their physician immediately.

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.

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 Adverse Effects (Undesirable Effects)).

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.

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). 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.

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

Rifinah 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.

Rifinah is a well characterised and potent inducer of drug metabolising enzymes and transporters and might therefore decrease or increase concomitant drug exposure, safety and efficacy (see

Section 4.5 Interaction with other medicines and other forms of interaction). 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 Undesirable effects). 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. 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.

Cerebellar syndrome (including cerebellar ataxia, ataxia, dysdiadochokinesis, balance disorders, nystagmus, dysmetria) has been reported with the use of isoniazid mainly in patients with chronic kidney disease (see Section 4.8 Undesirable effects).

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 Undesirable effects). 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 their physician immediately. 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.

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.

Thrombotic microangiopathy

Cases of thrombotic microangiopathy (TMA), manifested as thrombotic thrombocytopenic purpura (TTP) or haemolytic uremic syndrome (HUS), including fatal cases, have been reported with Rifinah use. If laboratory or clinical findings associated with TMA occur in a patient receiving Rifinah, treatment should be discontinued and thorough evaluation for TMA performed, including platelet levels, renal function, serum lactate dehydrogenase (LDH) and a blood film for schistocytes (erythrocyte fragmentation). ADAMTS13 activity and anti-ADAMTS13-antibody determination should be completed. If anti-ADAMTS13-antibody is elevated in conjunction with low ADAMTS13 activity, treatment with Rifinah should not be resumed and patients should be treated accordingly (consider plasma exchange).

Contraception in males and females

Males should be warned not to father a child and to use effective contraceptive measures during treatment with Rifinah and for 3 months following completion of treatment.

Females of childbearing potential should be warned not to become pregnant and to use effective contraceptive measures during treatment with Rifinah and for 6 months following completion of treatment. (See Section 5.3 Preclinical Safety Data and Section 4.5 Interactions with Other Medicines and Other Forms of Interactions).

Excipients

Sucrose: If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrose-isomaltose insufficiency should not take this medicine.

4.5 INTERACTION WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTION

Food Interactions

Isoniazid

As 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 (eg headache, sweating, palpitations, flushing, and hypotension) to foods containing histamine (eg skipjack, tuna, and other tropical fish). Tyramine and histamine containing foods should be avoided.

Drug Interactions

Rifampicin and Isoniazid

Cytochrome P-450 enzyme interaction

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

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

Rifinah is a well characterised and potent inducer of drug 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 drugs are substrates for one or more of these enzyme or transporter pathways, and these pathways may be induced by rifampicin simultaneously. Therefore, rifampicin 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. To maintain optimum therapeutic blood levels dosages of drugs may require adjustment when starting or stopping concomitantly administered rifampicin.

Rifampicin may accelerate the metabolism and may reduce activity of medicines such as:

- Anticonvulsants (eg phenytoin)
- Antiarrhythmics (eg disopyramide, mexiletine, quinidine, propafenone, tocainide)
- Antiestrogens (eg tamoxifen, toremifene)
- Antipsychotics (eg haloperidol)
- Oral anticoagulants (eg warfarin)
- Antifungals (eg fluconazole, itraconazole, ketoconazole)
- Antiretroviral drugs (eg zidovudine, saquinavir, indinavir, efavirenz)
- Barbiturates
- Beta-blockers
- Caspofungin

- Calcium channel blockers (eg diltiazem, nifedipine, verapamil)
- Chloramphenicol
- Clarithromycin
- Corticosteroids
- Cyclosporin
- Cardiac glycoside preparations
- Clofibrate
- Systemic hormonal contraceptives including estrogens and progestins
- Dapsone
- Benzodiazepines (eg diazepam)
- Benzodiazepine-related drugs (eg zopiclone)
- Doxycycline
- Enalapril
- Estrogens
- Fluoroquinolones
- Oral hypoglycemic agents (sulfonylureas)
- Immunosuppressive agents (eg tacrolimus, cyclosporin)
- Irinotecan
- Levothyroxine
- Losartan
- Narcotic analgesics
- Mifepristone
- Methadone
- Praziquantel
- Progestins
- Quinine
- Riluzole
- Selective 5-HT3 receptor antagonists (eg ondansetron)
- Statin metabolised by CYP 3A4 (eg simvastatin)
- Telithromycin
- Tacrolimus

- Thiazolidinediones (eg rosiglitazone)
- Theophylline
- Tricyclic antidepressants (eg amitriptyline, nortriptyline).
- Hepatitis-C antiviral drugs (e.g. daclatasvir, simeprevir, sofosbuvir, telaprevir)

It may be necessary to adjust the dosages of these drugs if they are given concurrently with rifampicin.

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.

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

Concurrent use of ketoconazole and rifampicin has resulted in decreased serum concentrations of both medicines.

After two weeks of repeated administration of rifampicin, trough levels of caspofungin were 30% lower than in adult subjects who received caspofungin alone.

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

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 a potent CYP inducer such as rifampicin.

Concurrent use of treatment of hepatitis-C antiviral drugs and rifampicin should be avoided.

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

Concomitant use of paracetamol with rifampicin may increase the known risk of hepatotoxicity seen in relation to each drug.

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 Contraindications).

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

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

Rifampicin was shown *in vivo* to be a strong inducer of CYP2C9, CYP2C19 and CYP3A4 and a moderate inducer of CYP2B6. Rifampicin has also been shown to increase the clearance of dapsone and the production of the hydroxylamine metabolite of dapsone which could increase the risk of methemoglobinemia. It may be necessary to adjust dapsone dosage if it is given concurrently with rifampicin.

Rifampicin 600mg was shown to decrease lurasidone AUC by 81%. Therefore, markedly reduced exposure of lurasidone can be expected when lurasidone is given concomitantly with a CYP3A4 inducer such as rifampicin (see Section 4.3 Contraindications).

Isoniazid

Isoniazid has been reported to inhibit the metabolism of the following drugs: anticonvulsants (eg. carbamazepine, phenytoin, primidone, valproic acid), benzodiazepines (eg. diazepam), haloperidol, ketoconazole, theophylline and warfarin.

Corticosteroids may decrease the serum concentration of isoniazid by increasing acetylation rate and/or renal clearance.

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

Laboratory Test Interactions

Therapeutic levels of rifampicin have been known to inhibit standard microbiological assays for serum folate and vitamin B12. Therefore, alternative assay methods should be considered. Transient elevation of BSP and serum bilirubin have been reported. 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 rifampicin.

4.6 FERTILITY, PREGNANCY AND LACTATION

Contraception in males and females

Due to the genotoxic potential of rifampicin (see section 5.3 Preclinical Safety Data), males should be warned not to father a child and to use effective contraceptive measures for the duration of treatment and for 3 months following completion of treatment.

Females of childbearing potential should be warned not to become pregnant and to use effective contraceptive measures (using non-hormonal methods of birth control, see section 4.5 Interactions

with Other Medicines and Other Forms of Interactions) during treatment and for 6 months following completion of treatment.

Pregnancy

Category C.

Rifampicin has been shown to be teratogenic in rodents when given in large doses. There are no well-controlled studies with Rifinah in pregnant women. Therefore, Rifinah should be used in pregnant women or in women of childbearing potential only if the potential benefit justifies the potential risk to the foetus.

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 can cause post-natal haemorrhages in the mother and infant, for which treatment with vitamin K may be indicated.

Use in lactation

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

Fertility

There is no known human data for Rifinah on the long-term potential for impairment of fertility. Rifampicin has a genotoxic potential in animals, which is a risk factor for impairment of human fertility (see section 5.3 Preclinical Safety Data).

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Rifinah may cause undesirable effects which may reduce the capacity for the completion of certain tasks. Patients should be informed of the potential for these undesirable effects and if they experience these symptoms, consideration should be given not to drive or operate machinery.

4.8 UNDESIRABLE EFFECTS

Rifampicin and isoniazid, the component drugs in Rifinah, are usually well tolerated at the recommended dosage.

General disorders and administration site conditions:

Paradoxical drug reaction: Recurrence or appearance of fresh symptoms, 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.

Rifampicin

Hepatitis can be caused by rifampicin and liver function tests should be monitored monthly and alternative antituberculosis treatment considered if appropriate (see Section 4.4 Special warnings and precautions for use).

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).

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.
Disseminated intravascular coagulation, eosinophilia, agranulocytosis, haemolytic anaemia, vitamin K dependent coagulation disorders and thrombotic microangiopathy including thrombotic thrombocytopenic purpura/haemolytic uremic syndrome have been reported.

Congenital, familial and genetic disorders: Cases of porphyria have been reported.

Endocrine disorders: Rare reports of adrenal insufficiency in patients with compromised adrenal function have been observed.

Eye disorders: Tear discolouration has been reported.

Gastrointestinal disorders:
Common: Nausea, vomiting.
Uncommon: Diarrhoea.
Gastrointestinal disorders, such as anorexia and abdominal discomfort have been reported. Tooth discolouration (which may be permanent) has also been reported.

General disorders and administration site conditions:
Very common: Pyrexia, chills
Oedema has been reported.

Hepatobiliary disorders: Hepatitis may be caused by rifampicin and liver function tests should be monitored. Drug-induced liver injury (including fatal cases especially when used in combination with other anti-tuberculosis drugs), hyperbilirubinaemia, and cholestasis has been reported (see Section 4.4 Special warnings and precautions for use).

Immune system disorders: Anaphylactic reactions have been reported.

Infections and infestations: Pseudomembranous colitis, influenza consisting of episodes of pyrexia, chills, headache and dizziness has been reported with rifampicin therapy.

Investigations:
Common: Increases in blood bilirubin, aspartate aminotransferase and alanine aminotransferase. An increase in hepatic enzymes and blood creatinine has also been reported. Blood pressure decrease has been observed.

Metabolism and nutrition disorders:
Decreased appetite has been reported.

Musculoskeletal and connective tissue disorders: Muscle weakness and myopathy have been reported to occur in a small percentage of patients treated with rifampicin. Bone pain has been reported.

Nervous system disorders:
Common: Headache, dizziness.
Cerebral haemorrhage and fatalities have been reported when rifampicin administration has been continued or resumed after the appearance of purpura.

Pregnancy, puerperium and perinatal conditions: Post-partum haemorrhage and fetal-maternal haemorrhage have been reported.

Psychiatric disorders: Psychoses (psychotic disorder) has been rarely reported.

Renal and urinary disorders: Acute kidney injury usually due to renal tubular necrosis or tubulointerstitial nephritis and chromaturia (discolouration of urine), have been reported.

Reproductive system and breast disorders: Occasional disturbances of the menstrual cycle have been reported in women receiving long-term antituberculosis therapy with regimens containing rifampicin.

Respiratory, thoracic and mediastinal disorders: Interstitial lung disease (including pneumonitis), dyspnoea, wheezing and discoloured sputum have been observed.

Skin and subcutaneous tissue disorders: Cutaneous reactions, which are mild and self-limiting, may occur and do not appear to be hypersensitivity reactions. Typically they consist of flushing and itching with (pruritic rash) or without a rash (pruritus). Urticaria and more serious hypersensitivity cutaneous reactions (allergic dermatitis), have occurred but are uncommon. Pemphigoid, erythema multiforme including Stevens-Johnson syndrome, toxic epidermal necrolysis, Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) syndrome and acute generalized exanthematous pustulosis (AGEP) (see Section 4.4 Special warnings and precautions for use) have been reported rarely. Rifampicin can cause certain bodily fluids such as sputum, urine, sweat and tears to become red-orange in colour (see Section 4.4 Special warnings and precautions for use).

Vascular disorders: Shock, flushing, vasculitis and bleeding have been reported.

Reactions usually occurring with intermittent dosage regimens and most probably of immunological origin include:

- "Flu Syndrome" consisting of episodes of fever, chills, headache, dizziness, and bone pain appearing most commonly during the 3rd to the 6th month of therapy. The frequency of the syndrome varies but may occur in up to 50% of patients given once weekly regimens with a dose of rifampicin of 25 mg/kg or more.
- Shortness of breath and wheezing.
- Decrease in blood pressure and shock.
- Anaphylaxis.
- Haemolytic anaemia.
- Acute kidney injury usually due to renal tubular necrosis or to tubulo interstitial nephritis.

Isoniazid

Blood and lymphatic system disorders: Various haematological disturbances have been identified during treatment with isoniazid including thrombotic microangiopathy including thrombotic thrombocytopenic purpura/haemolytic uremic syndrome, eosinophilia, agranulocytosis, thrombocytopenia, anaemia (including aplastic, haemolytic and sideroblastic anemia) and lymphadenopathy.

Endocrine disorders: Gynaecomastia has been reported.

Gastrointestinal disorders: Pancreatitis, nausea, vomiting and epigastric distress.

General disorders and administration site conditions: Fever has been reported.

Hepatobiliary disorders: Severe and sometimes fatal hepatitis may occur with isoniazid therapy.

Immune system disorders: Anaphylactic reactions have been reported.

Metabolism and nutrition disorders: Pellagra has been reported.

Musculoskeletal and connective tissue disorders: Systemic lupus erythematosus-like syndrome and rheumatic syndrome have been reported.

Nervous system disorders: Peripheral neuropathy is the most common toxic effect and is dose related. Polyneuritis associated with isoniazid, presenting as paraesthesia, muscle weakness, loss of tendon reflexes, etc. Other neurotoxic effects, which are uncommon with conventional doses, are convulsions, toxic encephalopathy, optic neuritis and atrophy, memory impairment and toxic psychosis. Cerebellar syndrome (including cerebellar ataxia, ataxia, dysdiadochokinesis, balance disorders, nystagmus, dysmetria) mainly in patients with chronic kidney disease.

Skin and subcutaneous tissue disorders: Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) syndrome, (see Section 4.4 Special warnings and precautions for use), rash,

acne, Toxic Epidermal Necrolysis (TEN), Stevens-Johnson syndrome (SJS) (see Section 4.4 Special warnings and precautions for use), exfoliative dermatitis, pemphigus, alopecia.

Vascular disorders: Vasculitis has been reported.

Rifampicin + Isoniazid

Blood and lymphatic system disorders: Not known: Thrombotic microangiopathy including thrombotic thrombocytopenic purpura/hemolytic uremic syndrome.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions at https://pophealth.my.site.com/carmreportnz/s/.

4.9 OVERDOSE

Symptoms

Nausea, vomiting, abdominal pain, pruritus, headache, and increasing lethargy will probably occur within a short time after acute ingestion; unconsciousness may occur when there is severe hepatic disease. Transient increases in liver enzymes and/or bilirubin may occur. Brownish-red or orange discoloration of the skin, urine, sweat, saliva, tears and faeces will occur, and its intensity is proportional to the amount ingested. Facial or periorbital oedema has also been reported in paediatric patients. Hypotension, sinus tachycardia, ventricular arrhythmias, seizures and cardiac arrest were reported in some fatal cases.

The minimum acute lethal or toxic dose is not well established. However, nonfatal acute overdoses in adults have been reported with doses ranging from 9 to 12 g rifampicin. Fatal acute overdoses in adults have been reported with doses ranging from 14 to 60 g. Alcohol or a history of alcohol abuse was involved in some of the fatal and nonfatal reports. Nonfatal overdoses in paediatric patients ages 1 to 4 years old of 100 mg/kg for one to two doses has been reported.

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.

Treatment

In cases of overdosage with Rifinah, following evacuation of the gastric contents, the instillation of activated charcoal slurry into the stomach may help absorb any remaining drug from the

gastrointestinal tract. Antiemetic medication may be required to control severe nausea and vomiting.

Intensive supportive measures should be instituted and individual symptoms treated as they arise. If acute 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 alone with forced diuresis.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Site and Mode of Action

Rifampicin and isoniazid are active bactericidal anti-tuberculosis drugs. Rifampicin and isoniazid are particularly active against the rapidly growing extracellular organisms and have bactericidal activity intracellularly. 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

Pharmacokinetics 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.

Rifampicin

Rifampicin is readily absorbed from the stomach and duodenum. Peak serum concentrations of the order of 10 microgram/mL occur about 2-4 hours after a dose of 10 mg/kg body weight on an empty stomach. Absorption of rifampicin is reduced when the drug is ingested with food.

In normal subjects the biological half-life of rifampicin in serum averages about 3 hours after a 600 mg dose and increases to 5.1 hours after a 900 mg dose. With repeated administration, the

half-life decreases and reaches average values of approximately 2-3 hours. It does not differ in patients with renal failure at doses up to 600 mg/day and, consequently, no dosage adjustment is required.

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 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.

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 ionised 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 all body fluids (cerebrospinal, pleural; and ascitic fluids), tissues, organs, and excreta (saliva, sputum, and faeces). The drug also passes through the placental barrier and into the milk in concentrations comparable to those in the plasma. From 50 to 70% of a dose of isoniazid is excreted in the urine in 24 hours.

Isoniazid is metabolized primarily by acetylation and dehydrazination. The rate of acetylation is genetically determined. Approximately 50% of Blacks 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.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

There is insufficient human data on the long-term potential for genotoxicity of Rifinah.

Rifampicin

Data from literature report that rifampicin possesses a mutagenic potential in the Ames test and is considered to be aneugenic as well as clastogenic in mice after oral administration.

Isoniazid

Data from literature report that isoniazid possesses mutagenic potential in the Ames test and weak clastogenic effect from studies in mice after oral administration.

Carcinogenicity and mutagenicity

Rifampicin

There is insufficient human data on long-term potential for carcinogenicity or mutagenicity.

A few cases of accelerated growth of lung carcinoma have been reported in man, but a causal relationship with the medicine has not been established. An increase in the incidence of hepatomas in female mice (of a strain known to be particularly susceptible to the spontaneous development of hepatomas) was observed when rifampicin was administered in doses 2 to 10 times the average daily human dose for 60 weeks followed by an observation period of 46 weeks. No evidence of carcinogenicity was found in male mice of the same strain, mice of a different strain, or rats, under similar experimental conditions.

Rifampicin has been reported to possess immunosuppressive potential in rabbits, mice, rats, guinea pigs, human lymphocytes in vitro, and humans.

Isoniazid

Isoniazid has been shown to induce pulmonary tumours in a number of strains of mice.
There is no known human data on the long-term potential for mutagenicity of Rifinah. There was no evidence of mutagenicity in bacteria*, Drosophila melanogaster*, or mice. However, an increase in chromatid breaks was noted when whole-blood cell cultures were treated with rifampicin.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Microcrystalline cellulose, magnesium stearate, calcium stearate, sodium lauryl sulfate, carmellose sodium, acacia, gelatin, magnesium carbonate, titanium dioxide, kaolin, purified talc, sucrose, colloidal anhydrous silica, povidone, erythrosine (150mg tablets), sunset yellow aluminium lake (300mg tablets), Carnauba wax, Colophony, hard paraffin, and white beeswax.

6.2 INCOMPATIBILITIES

Not applicable.

6.3 SHELF LIFE

4 years.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C.

6.5 NATURE AND CONTENTS OF CONTAINER

Rifinah 150/100mg and 300/150mg are packed in blister packs of 100 tablets.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7 MEDICINE SCHEDULE

Prescription Medicine

8 SPONSOR

Pharmacy Retailing (NZ) Ltd t/a Healthcare Logistics
PO Box 62027
Sylvia Park Auckland 1644
Freecall: 0800 283 684
Email: medinfo.australia@sanofi.com

9 DATE OF FIRST APPROVAL

8 May 1975

10 DATE OF REVISION OF THE TEXT

10 June 2025

SUMMARY OF CHANGES

Section heading	Summary of new information
2	Declaration of quantity of excipient with known effect
4.4	Inclusion of warning statements regarding contraception for males and females Addition of cross-referencing to Sections 4.5 and 5.3 Addition of **"**Excipients" subsection and warning statement for sucrose
4.6	Addition of statements pertaining to contraception for males and females Updated Fertility section to include genotoxic potential in animals and cross-linking to Section 5.3
5.3	Addition of genotoxicity data for rifampicin and isoniazid Revision of wording for carcinogenicity section regarding availability of human data