

DATA SHEET

1 PRODUCT NAME

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

For the full list of excipients, see section 6.1.

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 ratios 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 CONTRAINDICATION

Rifinah is contraindicated in patients with a history of sensitivity to rifampicin or isoniazid or any of its components.

Rifinah is contraindicated in the presence of jaundice.

Rifinah use is contraindicated when given concurrently with the combination of saquinavir / ritonavir (refer to Section 4.5).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

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

Rifampicin

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 glutamic pyruvic transaminase (SGPT) and serum glutamic oxaloacetic transaminase (SGOT) should be carried out prior to therapy and then every two to four weeks during therapy. If signs of hepatocellular damage occur, Rifinah should be withdrawn.

In some cases of hyperbilirubinaemia resulting from, competition between rifampicin and bilirubin for excretory pathways of the liver at the cell level can occur in the early days of treatment. An isolated report showing a moderate rise in bilirubin and/or transaminase level is not

in itself an indication for interrupting treatment, rather, the decision should be made after repeating the tests, noting trends in the levels and considering them in conjunction with the patient's clinical condition.

Because of the possibility of immunological reactions, including anaphylaxis, (see Section 4.9) 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.

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.

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.

Rifampicin is a well characterised and potent inducer of drug metabolizing enzymes and transporters and might therefore decrease concomitant drug exposure and efficacy (see Section 4.5). Therefore patients should be advised not to take any other medication without medical advice.

Isoniazid

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

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

Cases of severe cutaneous reactions including Stevens-Johnson syndrome (SJS) and Toxic Epidermal Necrolysis (TEN), some with a fatal outcome, have been reported with the use of isoniazid (see Adverse 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.

Rifampicin and Isoniazid alone or in combination

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 their physician immediately.

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

Rifinah

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, chronic liver disease, intravenous drug use, and being a black or hispanic woman.

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

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.

Rifampicin

Rifampicin is a well characterised and potent inducer of drug metabolising enzymes and transporters. Enzymes and transporters reported to be affected by rifampicin 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 reduce the activity of certain co-administered drugs, 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
- Calcium channel blockers (eg diltiazem, nifedipine, verapamil)
- Chloramphenicol
- Clarithromycin
- Corticosteroids
- Cyclosporin
- Cardiac glycoside preparations
- Clofibrate
- Systemic hormonal contraceptives
- Dapsone
- Benzodiazepines (eg diazepam)

- Benzodiazepine-related drugs (eg zopiclone)
- Doxycycline
- Estrogens
- Fluoroquinolones
- Oral hypoglycemic agents (sulfonylureas)
- Immunosuppressive agents (eg tacrolimus, cyclosporin)
- Irinotecan
- Levothyroxine
- Losartan
- Narcotic analgesics
- 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.

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.

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.

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).

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.

Isoniazid

Isoniazid has been reported to inhibit the metabolism of the following drugs: anticonvulsants (eg. carbamazepine, phenytoin, promidone, 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 competition of 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

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 affect 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.

There are no known human data for Rifinah on the long term potential for impairment of fertility.

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.

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.

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).

The following CIOMS frequency rating is used, when applicable:

Very common ($\geq 1/10$); Common ($\geq 1/100$ to $< 1/10$); Uncommon ($\geq 1/1,000$ to $< 1/100$); Rare ($\geq 1/10,000$ 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 and haemolytic anaemia 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. Hyperbilirubinaemia has been reported (see Section 4.4).

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: 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) 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).

Vascular disorders: Shock, flushing and vasculitis 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 eosinophilia, agranulocytosis, thrombocytopenia and anaemia. Lymphadenopathy has been reported.

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.

Skin and subcutaneous tissue disorders: Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) syndrome, (see Section 4.4), rash, acne, Toxic Epidermal Necrolysis (TEN), Stevens-Johnson syndrome (SJS) (see Section 4.4), exfoliative dermatitis, pemphigus.

Vascular disorders: Vasculitis has been reported.

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 <https://nzphvc.otago.ac.nz/reporting/>.

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 symptomatic 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 ketoacidosis. Haemodialysis is advised for refractory cases; if this is not available, peritoneal dialysis can be used alone with forced dialysis. Symptoms are more likely to be related to isoniazid, including coma respiratory distress, hyperglycaemia and metabolic ketoacidosis.

Contact the Poisons Information Centre (telephone 0800 POISON or 0800 764 766) for advice on management of overdosage.

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. 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 rifampicins.

Isoniazid acts against actively growing tubercule 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 mcg/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 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.

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

CARCINOGENICITY AND MUTAGENICITY

Rifampicin

There are no known 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 sulphate, 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).

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

sanofi-aventis new zealand Limited
Level 8,
56 Cawley St
Ellerslie
Auckland, New Zealand
Toll Free Number (medical information): 0800 283 684

9 DATE OF FIRST APPROVAL

8 May 1975

10 DATE OF REVISION OF THE TEXT

28 February 2018

SUMMARY OF CHANGES

Section heading	Summary of new information
4.4	Addition of precaution statement about induction of metabolising enzymes and transporters Addition of Severe bullous reactions Reference heading Adverse Effects changed to Section 4.8
4.5	Addition of interactions due to induction of

	metabolising enzymes and transporters Addition of Hepatitis-C antiviral drugs Addition of reduction in exposure to oral contraceptives
4.6	Addition, rifampicin crossing the placental barrier
4.8	Addition of AGEP Spelling correction antituberculosis