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SCHEDULING STATUS: S4

PROPRIETARY NAME (and dosage form):
RIFINAH® 150/75 Tablets

COMPOSITION:
RIFINAH® 150/75 contains 150 mg rifampicin and 75 mg isoniazid

PHARMACOLOGICAL CLASSIFICATION:
A 20.2.3 Tuberculostatics

PHARMACOLOGICAL ACTION:
Pharmacodynamics:
Rifampicin and isoniazid are active bacterial 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.
Pharmacokinetics:
Pharmacokinetic studies in normal volunteers have shown that the two ingredients in RIFINAH have comparable bioavailability, whether they are given together as individual dose form 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 the medicine is ingested with food.
Half-lives for rifampicin have been reported to range 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 half-lives 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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INDICATIONS:
Continuation phase treatment of pulmonary and extra-pulmonary tuberculosis in newly diagnosed patients and re-treatment of adult cases.

CONTRA-INDICATIONS:
Contra-indicated 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 contra-indicated.
RIFINAH is contraindicated when given concurrently with the combination of saquinavir/ritonavir (see interactions).

WARNINGS:
RIFINAH 150/75 is a combination of two medicines, each of which has been associated with liver dysfunction.
Rifampicin:
Patients with impaired liver function should only be given rifampicin in cases of necessity and then with caution and under strict medical supervision. In these patients, careful monitoring of 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 withdrawn.
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.
Because of the possibility of immunological reactions, including anaphylaxis, 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.
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 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.

Patients who are at risk of neuropathy or pyridoxine deficiency including those who are diabetic, alcoholic, elderly, malnourished, uraemic or pregnant should receive pyridoxine usually in a dose of 10 mg daily.

INTERACTIONS:
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.

Rifampicin:

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Enzyme induction:
Examples of medicines metabolised by cytochrome P-450 enzyme are: Anticonvulsants (e.g. phenytoin), antiarrhythmics such as disopyramide, lorcainide, mexiletine, propafenone, quinidine, tocainide, antiestrogens (e.g. tamoxifen, toremifen), antipsychotic (e.g. haloperidol), oral anticoagulants (e.g. warfarin), antifungals (e.g. fluconazole, itraconazole, ketoconazole), antiretroviral medicines (e.g. zidovudine, saquinavir, indinavir, efavirenz), barbiturates, beta-blockers, benzodiazepines (e.g. diazepam), benzodiazepine-related medicines (e.g. zopiclone, zolpidem), calcium channel blockers (e.g. diltiazem, nifedipine, verapamil), chloramphenicol, clarithromycin, corticosteroids, cardiac glycoside preparations, clofibrate, systemic hormonal contraceptives, dapsone, doxycycline, estrogens, fluoroquinolones, gestrinone, oral hypoglycaemic agents (sulfonylureas), immunosuppressive agents (e.g. tacrolimus, cyclosporine), irinotecan, levothyroxine, losartan, narcotic analgesics, methadone, praziquantel, progestins, quinine, riluzole, selective 5-HT_3 receptor antagonists (e.g. ondasetron), statins metabolised by CYP 3A4, telithromycin, theophylline, thiazolidinediones (e.g. rosiglitazone), tricyclic antidepressants. It may be necessary to adjust the dosages of these medicines if they are given concurrently with rifampicin.

Other interactions:
The absorption of rifampicin may be reduced by concomitant administration with antacids, medicines that reduce gastric motility (anticholinergics and opoids), 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.

The prothrombin time of patients receiving concurrent anticoagulant therapy may be decreased. Frequent monitoring of the prothrombin level in such patients with subsequent adjustment in anticoagulant dosage, is recommended.
Patients using oral contraceptives should be advised to change to non-hormonal methods of birth control during rifampicin therapy as rifampicin reduces the efficacy of oral contraceptives.

Diabetes may become more difficult to control.
Halothane has been reported to increase the hepatotoxicity of both compounds.

Ketoconazole has been reported to diminish serum concentrations of both compounds. The concentration of enalaprilat, the active metabolite of enalapril may be decreased. Dosage should be adjusted if indicated by the patient's clinical condition.
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.

Therapeutic levels of RIFINAH 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. RIFINAH may impair biliary excretion of contrast media used for visualisation of the gallbladder, due to competition for biliary excretion.

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 and phenytoin, the benzodiazepines diazepam and triazolam, chlorzoxazone, and theophylline. The metabolism of enflurane may be increased in patients receiving isoniazid, resulting in potentially nephrotoxic levels of fluoride. Isoniazid has been associated with increased concentrations or toxicity of clofazimine, cycloserine and warfarin.

Daily ingestion of alcohol may be associated with higher incidence of isoniazid hepatitis. Isoniazid inhibits the metabolism of primidone and increases the toxicity of disulfiram. Para-aminosalisylic acid may increase the plasma concentration and elimination half-life of isoniazid.

Food interactions:
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.

PREGNANCY AND LACTATION:
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.
RIFINAH Tablets should be used in pregnant women or in women of childbearing potential only if the potential benefit justifies the potential risk to the foetus.
Rifampicin and isoniazid are known to pass into maternal breast milk. Therefore, RIFINAH Tablets should be used in a nursing mother only if the potential benefit to the patient outweighs the potential risk to the infant.

DOSAGE AND DIRECTIONS FOR USE:
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
30 – 37	2
38 – 54	3

Rifinah tablets are unsuitable for children under 12 years.

SIDE EFFECTS AND SPECIAL PRECAUTIONS:
Rifampicin:
Body as a Whole: Less Frequent - 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; shock; anaphylaxis; acute renal failure usually due to acute tubular necrosis or to acute interstitial nephritis occur.
Urogenital System: Less frequent - Disturbances of the menstrual cycle have been reported in women receiving long-term antituberculosis therapy with regimens containing rifampicin.
Skin and Appendages: Frequent - Some patients may experience a cutaneous syndrome, which presents 2 to 3 hours after a daily or intermittent dose as facial flushing, itching, rash, or rarely, eye irritation.
Less frequent - Urticaria and more serious hypersensitivity cutaneous reactions have occurred, but are uncommon.
Haemic and Lymphatic System: Frequent - Thrombocytopenia with or without purpura may occur, usually associated with intermittent therapy, but is reversible if the medicine is discontinued as soon as purpura occurs. Cerebral haemorrhage and fatalities have been reported when rifampicin administration has been continued or resumed after the appearance of purpura.
Less frequent - Disseminated intravascular coagulation has also been rarely reported.
Eosinophilia, leukopenia, haemolytic anaemia, oedema, muscle weakness and myopathy have been reported to occur in patients treated with rifampicin.
Agranulocytosis has been reported very rarely.
Rare reports of adrenal insufficiency in patients with compromised adrenal function have been observed.
Digestive system: Frequent - Gastrointestinal reactions consist of anorexia, nausea, vomiting, abdominal discomfort and diarrhoea have been reported.
Less frequent - Pseudomembranous colitis has been reported with rifampicin therapy.
Hepatic reactions: Frequent - Hepatitis may be caused by rifampicin and liver function tests should be monitored (see Warnings).
Other: Frequent **-** Patients should be advised that rifampicin may colour faeces, saliva, sputum, sweat, tears, urine and other body-fluids orange-red. Soft contact lenses worn by patients receiving rifampicin may become permanently stained.

Isoniazid:
Body as a whole: Frequent - Pellagra. Less frequent - Systemic lupus erythematosus-like syndrome.
Digestive system: Frequent - Pancreatitis, nausea, vomiting, epigastric distress.
Haemic and Lymphatic System: Less frequent - Eosinophilia, agranulocytosis, thrombocytopaenia, anaemia.
Skin and Appendages: Less frequent - Rash, acne, Stevens-Johnson syndrome, exfoliative dermatitis.
Hepatic reactions: Less frequent - Severe and sometimes fatal hepatitis.
Hypersensitivity reactions: Frequently - Neurotoxic effects with conventional doses are psychotic reactions, convulsions, toxic encephalopathy, optic neuritis and atrophy, memory impairment and toxic psychosis.
Less frequently - Fever, skin reactions (including eryhtema multiforme).

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:
There is limited overdose information involving isoniazid and rifampicin in combination.
Rifampicin:
Cases of skin pigmentation induced by rifampicin overdosage have been reviewed. Reddish-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.
Management

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In cases of overdosage with RIFINAH Tablets, gastric lavage should be performed as soon as possible. Following evacuation of the gastric contents, the instillation of activated charcoal slurry into the stomach may help absorb any remaining 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.

IDENTIFICATION:
RIFINAH 150/75: Rust brown, round, biconvex, film coated tablets.

PRESENTATION:
RIFINAH 150/75: Packs of 56 and 84 tablets in foil-foil blisters.
RIFINAH 300 FC: Packs of 56 in foil-foil blisters.

STORAGE INSTRUCTIONS:
Store below 25°C in a dry place.
Keep out of reach of children.

REGISTRATION NUMBERS:
RIFINAH 150/75: A/20.2.3/400534

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:
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