Rifafour e-275

SCHEDULING STATUS: S4

PROPRIETARY NAME (and dosage form):
RIFAFOUR e-275 (tablets)

COMPOSITION:

Each tablet contains:	Rifampicin	150 mg
	Isoniazid	75 mg
	Pyrazinamide	400 mg
	Ethambutol HCl	275 mg

Contains sodium ascorbate as anti-oxidant.

Excipients:

Core tablet: croscarmellose sodium, glyceryl behenate, lactose monohydrate, magnesium stearate, maize starch, polyvinylpyrrolidone and sodium lauryl sulphate and sodium ascorbate as anti-oxidant.

Film coating: polyvinyl alcohol, titanium dioxide, macrogol 3350, talc, Carmine FD&C Blue Indigo, Carmine Aluminium Lake and iron oxide black.

The tablets contain lactose monohydrate.

PHARMACOLOGICAL CLASSIFICATION:

A 20.2.3 Tuberculostatic combinations

PHARMACOLOGICAL ACTION:

Rifafour e-275 Tablets is a combination of four first line agents used in the treatment of tuberculosis. Rifampicin is a semi-synthetic, broad-spectrum bactericidal antibiotic. Isoniazid is a synthetic, antitubercular agent which is bacteriostatic against semi-dormant bacilli and bactericidal against actively dividing mycobacteria. Pyrazinamide may be bactericidal or bacteriostatic, depending on its concentration and the susceptibility of the organism. Ethambutol is a synthetic, bacteriostatic antitubercular agent. All agents are readily absorbed following oral administration, with wide distribution to most tissues and fluids including cerebrospinal fluid.

INDICATIONS:

Initial phase treatment of pulmonary and extrapulmonary tuberculosis in new adult patients and re-treatment of adult cases.

CONTRA-INDICATIONS:

Rifafour e-275 Tablets are contra-indicated in:

- patients with hypersensitivity to rifamycins, isoniazid, pyrazinamide, ethambutol or other chemically related medication;
- the presence of jaundice or active hepatic disease;
- patients with optic neuritis;
- children under 13 years of age.

Rifafour e-275 is contra-indicated when given concurrently with the combination of saquinavir/ritonavir (See Interactions).

Rifampicin very markedly reduces ketoconazole levels. Rifampicin levels are halved by ketoconazole. (See Interactions).

WARNINGS:

Liver function should be checked before and during treatment and special care should be exercised in alcoholic patients, the elderly or those with pre-existing liver disease.

Caution should be observed with the use of Rifafour e-275 Tablets in the following patients:

- Impaired kidney function: dosage adjustment may be required according to the serum concentration of ethambutol;
- Patients with visual defects: should visual disturbances occur during treatment, these must be reported immediately and Rifafour e-275 discontinued pending visual evaluation;
- Patients at risk of neuropathy or pyridoxine deficiency, including those who are diabetic, alcoholic, malnourished, uraemic or pregnant: pyridoxine supplementation (in a 10 mg to 50 mg daily dose) is usually required in these instances;
- Patients with a history of gout;
- Patients with porphyria;
- Patients with epilepsy, as convulsions may be precipitated;
- Patients with a history of psychosis;
- Patients with diabetes: pyrazinamide may cause interference with urine ketone determinations;
- Rifampicin may decrease the effect of oral contraceptives and patients are advised to change to non-hormonal methods of birth control;
- Treatment with Rifafour e-275 Tablets may produce reddish colouration of urine, tears and saliva. Contact lenses may be irreversibly stained.
- Concomitant antacid administration may reduce the absorption of rifampicin by up to about one-third. Daily doses of rifampicin should be given at least 1 hour before the ingestion of antacids.

INTERACTIONS:

Rifampicin and isoniazid:

When Rifafour e-275 is given concomitantly with the combination saquinavir/ritonavir, the potential for hepatotoxicity is increased. Therefore, concomitant use of Rifafour e-275 with saquinavir/ritonavir is contra-indicated. (See Contra-Indications).

Cytochrome P-450 Enzyme interaction:

Rifampicin is known to induce and isoniazid is known to inhibit certain cytochrome P-450 enzymes. Caution should be used when prescribing Rifafour e-275 Tablets 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 concomitantly administered Rifafour e-275 Tablets.

Rifampicin:

Enzyme Induction: Rifampicin accelerates the metabolism of certain medicines by inducing microsomal enzymes, leading to decreases in plasma concentration of such medicines.

Examples of medicines metabolised by cytochrome P-450 enzymes are: anticonvulsants (e.g. phenytoin), antidysrhythmics (e.g. disopyramide, mexiletine, quinidine, propafenone, tocainide, verapamil), antioestrogens (e.g. tamoxifen, toremifen) antipsychotics (e.g. haloperidol), oral anticoagulants (e.g. warfarin), antifungals (e.g. fluconazole, itraconazole, ketoconazole), antiretroviral medicines (e.g. zidovudine, saquinavir, indinavir, efavirenz), atovaquone, barbiturates (e.g. hexobarbitone), beta-blockers, benzodiazepines (e.g. diazepam), benzodiazepine-related medicines (e.g. zopiclone, zolpidem), calcium channel blockers (e.g. diltiazem, nifedipine, verapamil), chloramphenicol, cimetidine, clarithromycin, corticosteroids, cardiac glycosides (e.g. digoxin), clofibrate, systemic hormonal contraceptives, dapsone, doxycycline, oestrogens, fluoroquinolones, gestrinone, oral hypoglycaemic agents (sulfonylureas), immunosuppressive agents (e.g. azathioprine, cyclosporine, tacrolimus) irinotecan, levothyroxine, losartan, narcotic analgesics, methadone, phenytoin, praziquantel, progestins, quinine, selective 5-HT_3 receptor antagonists (e.g. ondansetron) statins metabolized by CYP 3A4, sulphasalazine, telithromycin, theophylline, thiazolidinediones tricyclic antidepressants (e.g. amitryptyline, nortryptyline).

Patients using systemic hormonal contraceptives should be advised to change to non-hormonal methods of birth control during rifampicin therapy. (Refer to "Warnings").

When the two medicines were taken concomitantly, decreased concentrations of atovaquone and increased concentrations of rifampicin were observed. Rifampicin reduces serum atovaquone levels by about 50 %, whereas atovaquone modestly raises serum rifampicin levels.

Concurrent use of itraconazole, ketoconazole, voriconazole 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.

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

Concurrent use of alcohol, paracetamol and other hepatotoxic medication may increase the incidence of rifampicin-induced hepatotoxicity. The effectiveness of oestrogen-containing oral preparations is reduced.

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.

Rifafour e-275 Tablets 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.

Isoniazid:

Chronic use of isoniazid may decrease the plasma clearance and prolong the duration of action of alfentanil, coumarin anticoagulants, benzodiazepines, carbamazepine, phenytoin, ethosuximide, chlorzoxazone, and theophylline. Appropriate adjustment of the anticonvulsant dose may be required.

Concurrent use of paracetamol, alcohol, rifampicin and other hepatotoxic medication, may increase the potential for isoniazid-induced hepatotoxicity. Aluminium-containing antacids may delay absorption and decrease serum concentrations of isoniazid.

Ingestion of certain types of cheese e.g. Swiss or Cheshire, or fish e.g. tuna, may result in itching of the skin, rapid or pounding heart, chills or headache. Glucocorticoid corticosteroids may increase hepatic metabolism and/or excretion of isoniazid.

Concurrent use of cycloserine, disulfiram and other neurotoxic medicines may increase the potential for CNS toxicity. Isoniazid may increase the formation of potentially nephrotoxic inorganic fluoride metabolites when used concurrently with enflurane.

Interactions with ketoconazole and miconazole have been reported. False positive reactions with copper sulphate urine glucose tests may occur.

Pyrazinamide:

Pyrazinamide may decrease the efficacy of gout therapy (e.g. allopurinol, colchicine, probenecid or sulphinpyrazone) and dosage adjustments of this medication may be necessary.

Ethambutol:

Concurrent administration of neurotoxic medication with ethambutol may potentiate neurotoxic effects such as optic and peripheral neuritis.

PREGNANCY AND LACTATION:

Safety in pregnancy has not been established.

All agents of Rifafour e-275 Tablets are excreted in breast milk. Safety during lactation has not been established.

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

DOSAGE AND DIRECTIONS FOR USE:

Take Rifafour e-275 Tablets with a full glass of water 1 hour before, or 2 hours after a meal. However, if gastrointestinal irritation occurs, the Tablets may be taken with food. If aluminium-containing antacids are taken, administer one hour after the tablet dose.

The recommended treatment dosages, based on the patient's body weight, given daily for the 2 month initial-phase treatment in adults and children over 13 years of age are as follows:

30 – 37 kg	2 Tablets
38 – 54 kg	3 Tablets
55 – 70 kg	4 Tablets
71 kg and over	5 Tablets

SIDE-EFFECTS AND SPECIAL PRECAUTIONS:

Side-effects associated with rifampicin:

Infections and infestations

The following side effects have been reported and the frequencies are not known:

Pseudomembranous colitis has been reported with rifampicin therapy.

Skin and subcutaneous tissue disorders

The following side effects have been reported and the frequencies are not known:

Some patients may experience a cutaneous syndrome which presents 2 to 3 hours after a daily or intermittent dose i.e. facial flushing, urticaria, pruritus, erythema, rash, eye irritation.

More serious hypersensitivity cutaneous reactions may also occur, but are uncommon.

Pemphigoid reactions, erythema multiforme including Stevens-Johnson syndrome, toxic epidermal necrolysis and vasculitis have been reported.

Immune system disorders

The following side effects have been reported and the frequencies are not known:

Lupus-like syndrome.

A 12 hour "flu" syndrome, usually occurring after 3 to 6 months of intermittent treatment and usually with doses of 20 mg/kg or more, may present as fever, chills, bone pain and malaise, shortness of breath and wheezing; decrease in blood pressure and shock; acute haemolytic anaemia; acute renal failure usually due to acute tubular necrosis or to acute interstitial nephritis; anaphylaxis.

Gastrointestinal disorders

The following side effects have been reported and the frequencies are unknown:

Nausea, vomiting, anorexia, abdominal discomfort, diarrhoea and epigastric distress, which may be alleviated by administration with food.

Hepato-biliary disorders

The following side effects have been reported and the frequencies are unknown:

Hepatitis and the prodromal symptoms of hepatitis may occur (nausea, vomiting, unusual tiredness / fatigue). Liver function should be monitored. (See Warnings).

Blood and the lymphatic system disorders

The following side effects have been reported and the frequencies are unknown:

Rifampicin can cause thrombocytopenia and purpura usually with intermittent regimens, 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.

Disseminated intravascular coagulation has also been reported.

Other haematological adverse effects include eosinophilia, leucopoenia and haemolytic anaemia. Agranulocytosis has been reported. Oedema and haemolysis have been reported.

Vascular disorders

The following side effects have been reported and the frequencies are unknown:

Disseminated intravascular coagulation has also been reported.

Nervous system disorders

The following side effects have been reported and the frequencies are unknown:

Headache, drowsiness, dizziness, ataxia, numbness, visual disturbances. Confusion and generalised numbness. Psychosis has been reported.

Musculoskeletal, connective tissue and bone disorders

The following side effects have been reported and the frequencies are unknown:

Myopathy and muscular weakness.

Renal and urinary disorders

The following side effects have been reported and the frequencies are unknown:

Alterations in kidney function and renal failure have occurred. Reports of adrenal insufficiency in patients with compromised adrenal function have been observed.

Reproductive system and breast disorders

The following side effects have been reported and the frequencies are unknown:

Menstrual disturbances have been reported.

General disorders:

Rifampicin may produce reddish colouration of urine, sputum and tears and the patient should be warned of this. Soft contact lenses may be permanently stained. Blurred vision has been reported.

Side-effects associated with isoniazid:

Hepato-biliary disorders

The following side effects have been reported and the frequencies are unknown:

Elevated liver enzymes associated with clinical signs of hepatitis such as nausea, vomiting or fatigue may indicate hepatic damage. The incidence of liver damage is highest in patients over 35 years of age, those who are slow acetylators and those who consume alcohol on a daily basis. Severe and sometimes fatal hepatitis can occur.

Gastrointestinal disorders

The following side effects have been reported and the frequencies are unknown:

Nausea and vomiting, pancreatitis and epigastric distress.

Metabolism and nutrition disorders

The following side effects have been reported and the frequencies are unknown:

Hyperglycaemia, metabolic acidosis. Pellagra.

Immune system disorders

The following side effects have been reported and the frequencies are unknown:

Hypersensitivity reactions (skin eruptions including erythema multiforme, fever, lymphadenopathy, vasculitis and anaphylaxis) may occur.

Blood and the lymphatic system disorders
The following side effects have been reported and the frequencies are unknown:
Various haematological disturbances including anaemia, eosinophilia, sideroblastic anaemia, agranulocytosis, haemolytic anaemia, thrombocytopenia, neutropoenia, and less frequently, aplastic anaemia.
Nervous system disorders
The following side effects have been reported and the frequencies are unknown:
Neurological effects include psychotic reactions and convulsions. The frequency of seizures may be increased in patients with epilepsy.
Polyneuritis associated with isoniazid presenting as paraesthesia, muscle weakness, loss of tendon reflexes, etc. may occur.
Peripheral neuropathy has also been associated with isoniazid administration. Pyridoxine supplementation prevents the development of peripheral neuritis, as well as most other nervous system dysfunctions. Optic neuritis and atrophy, memory impairment, toxic psychosis and toxic encephalopathy have also been reported.
Musculoskeletal, connective tissue and bone disorders
The following side effects have been reported and the frequencies are unknown:
Rheumatoid syndrome. Systemic lupus erythematosus-like syndrome.
Renal and urinary disorders
The following side effects have been reported and the frequencies are unknown:
Urinary retention.
Reproductive system and breast disorders
The following side effects have been reported and the frequencies are unknown:
Gynaecomastia.
Skin and subcutaneous tissue disorders
Cutaneous reactions include rash, acne, Stevens Johnson syndrome, exfoliative dermatitis, pemphigus, lupus-like erythematosus-like reactions.
Side-effects associated with pyrazinamide:
Hepato-biliary disorders
The following side effects have been reported and the frequencies are unknown:
The most serious side effect is hepatotoxicity and its frequency appears to be dose-related. It varies from a symptomless abnormality of hepatic cell function through a mild syndrome of fever, malaise and liver tenderness, to more serious reactions such as clinical jaundice and rare cases of acute yellow atrophy and death.
Musculoskeletal, connective tissue and bone disorders
Common: Hyperuricaemia, occasionally accompanied by arthralgia and may lead to attacks of gout.
Skin and subcutaneous tissue disorder
The following side effects have been reported and the frequencies are unknown:
Photosensitivity, pruritus, erythema and skin rash have been reported.
Rare: angioedema has been reported.
Gastrointestinal disorders
The following side effects have been reported and the frequencies are unknown:
Anorexia, nausea and vomiting and aggravation of peptic ulcer.
General disorders
The following side effects have been reported and the frequencies are unknown:
Malaise, fever.
Blood and the lymphatic system disorders
The following side effects have been reported and the frequencies are unknown:
Sideroblastic anaemia, thrombocytopaenia with or without purpura.
Renal and urinary disorders
The following side effects have been reported and the frequencies are unknown:
Dysuria.
Side-effects associated with ethambutol:
Nervous system disorders
The following side effects have been reported and the frequencies are unknown:
Retrobulbar neuritis with a reduction in visual acuity, constriction of visual field, central or peripheral scotoma, and green-red colour blindness may occur, affecting one or both eyes. The degree of visual impairment appears to depend on the dose and duration of therapy. Retinal haemorrhage has occurred less frequently.
Peripheral neuritis, confusion, disorientation, hallucinations, headache, dizziness and malaise.
Renal and urinary disorders
The following side effects have been reported and the frequencies are unknown:
Renal clearance of urate may be reduced and acute gout has been precipitated.
General disorders
The following side effects have been reported and the frequencies are unknown:
Hypersensitivity reactions include skin rash, pruritus, fever and joint pains.
Blood and the lymphatic system disorders
Leucopoenia.
Gastrointestinal disorders
The following side effects have been reported and the frequencies are unknown:
Gastrointestinal disturbances include metallic taste, nausea, vomiting, anorexia and abdominal pain.
Hepato-biliary disorders
The following side effects have been reported and the frequencies are unknown:
Jaundice or transient liver dysfunction.

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SPECIAL PRECAUTIONS:
In the following cases, treatment with Rifafour e-275 Tablets should be stopped immediately and the patient evaluated: jaundice, rash and fever, elevated liver enzymes associated with the clinical signs of hepatitis, visual impairment. If liver damage is confirmed, the medicine should not be recommenced.
Treatment should be discontinued permanently should thrombocytopenia, purpura, shock or renal failure occur.
Periodic eye examinations during treatment are suggested.
As Rifafour e-275 Tablets contain lactose, patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.
Isoniazid has been associated with vertigo, visual disorders and psychotic reactions. (See Side-effects). Patients should be informed of these, and advised that if affected, they should not drive, operate machinery or take part in any activities where these symptoms may put either themselves or others at risk.
KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:
There is limited overdose information involving rifampicin, isoniazid, pyrazinamide and ethambutol 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. 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 dysrhythmias, seizures and cardiac arrest were reported in some fatal cases.
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. Nonfatal overdoses in paediatric patients ages 1 to 4 years old of 100 mg/kg for one or two doses have been reported.
Isoniazid:
Isoniazid overdosage produces signs and symptoms within 30 minutes to 3 hours after ingestion. Nausea, vomiting, dizziness, slurring of speech, blurring of vision and visual hallucinations are among the early manifestations. With marked overdosage, respiratory distress and CNS depression, progressing rapidly from stupor to profound coma are to be expected, along with severe, intractable seizures. Severe metabolic acidosis, acetonuria and hyperglycaemia are typical laboratory findings.
Pyrazinamide:
There is limited information related to pyrazinamide overdosage. Liver toxicity and hyperuricaemia may occur with overdosage.
Ethambutol:
There is limited information related to ethambutol overdose. Loss of appetite, gastro-intestinal disturbances, fever, headache, dizziness, confusion and hallucinations may occur.
Management:
In case of overdosage with Rifafour e-275, gastric lavage should be performed as soon as possible. Following evacuation of the gastric contents, the installation of activated charcoal slurry into the stomach may help absorb any remaining medicine from the gastrointestinal tract. Antiemetic medication may be required to control severe nausea and vomiting.
Intensive support measures should be instituted, including airway patency and individual symptoms treated as they arise.
IDENTIFICATION
Purple, round, film coated Tablets.
PRESENTATION
Packs of 28, 56, 84, 100 and 112 Tablets in foil-foil blisters. Not all pack sizes are marketed.
STORAGE INSTRUCTIONS:
Store in a cool place, below 25 °C in well-closed containers, protected from light.
KEEP OUT OF REACH OF CHILDREN.
REGISTRATION NUMBER:
34/20.2.3/0187
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