PROFESSIONAL INFORMATION (CLEAN COPY), FOR RIFAFOUR e-275 TABLETS, DATED 12 APRIL 2018

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: carmine, FD&C blue indigo carmine aluminium lake, iron oxide black, macrogol 3350, polyvinyl alcohol, talc and titanium dioxide.

Contains sugar (54,66 mg lactose monohydrate per tablet).

CATEGORY AND CLASS:

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.

CONTRAINDICATIONS:

RIFAFOUR e-275 tablets are contraindicated in:

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

RIFAFOUR e-275 is contraindicated 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 AND SPECIAL PRECAUTIONS:

RIFAFOUR e-275 tablets is a combination of four medicines, each of which has been associated with liver dysfunction.

Applies to rifampicin:

Liver:

Patients with impaired liver function should only be given rifampicin in cases of necessity and then with caution and under strict medical supervision. In these patients, careful monitoring of liver function, especially serum alanine aminotransferase (ALT) and serum aspartate aminotransferase (AST) should be carried out prior to therapy and then every 2 to 4 weeks during therapy. If signs of hepatocellular damage occur, rifampicin should be withdrawn.
In some cases, hyperbilirubinaemia resulting from competition between rifampicin and bilirubin for excretory pathways of the liver at cell level can occur in the early days of treatment. An isolated report showing a moderate rise in bilirubin and/or transaminase level is not in itself an indication for interrupting treatment; rather, the decision should be made after repeating the tests, noting the trends in the levels and considering them in conjunction with the patient's clinical condition.

Immunological reactions/anaphylaxis:

Because of the possibility of immunological reactions, including anaphylaxis (see SIDE EFFECTS), 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.

Applies to isoniazid:

Liver:

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.

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN):

Cases of severe cutaneous reactions including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), some with a fatal outcome, have been reported with the use of isoniazid (see SIDE 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) develop, the patient should be advised to consult their doctor immediately. RIFAFOUR e-275 should be permanently discontinued if an alternative aetiology for the signs and symptoms cannot be established.

Applies to pyrazinamide:

Gout:

RIFAFOUR e-275 should be used with caution in patients with a history of gout. If hyperuricaemia accompanied by an acute gouty arthritis occurs, the patient should be transferred to a regimen not containing pyrazinamide.

Applies to rifampicin, isoniazid, pyrazinamide and ethambutol:

Medicine reaction with eosinophilia and systemic symptoms ("DRESS"):

Severe, systemic hypersensitivity reactions, including fatal cases, such as medicine reaction with eosinophilia and systemic symptoms (DRESS) syndrome have been observed during treatment with anti-tuberculosis therapy (see SIDE 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 doctor immediately. RIFAFOUR e-275 should be discontinued if an alternative aetiology for the signs and symptoms cannot be established.

Special precautions:

Applies to RIFAFOUR e-275 tablets:

Monitoring:

Adults treated for tuberculosis with RIFAFOUR e-275 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 with patients older than 35 years of age, liver function tests should be performed periodically in older persons. Other factors associated with an increased risk of hepatitis include daily use of alcohol, those who are slow acetylators and with chronic liver disease.

Periodic eye examinations during treatment are suggested. Patients with visual defects: should visual disturbances occur during treatment, these must be reported immediately and RIFAFOUR e-275 discontinued pending visual evaluation.

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.

Applies to rifampicin:

Porphyria exacerbation:

Reports have associated porphyria exacerbation with rifampicin administration as a result of induction of delta amino levulinic acid synthetase (see CONTRAINDICATIONS).

Metabolism of endogenous substrates:

Rifampicin has enzyme induction properties that can enhance the metabolism of endogenous substrates including adrenal hormones, thyroid hormones and vitamin D.

Oral contraceptives:

Rifampicin may decrease the effect of oral contraceptives and patients are advised to change to non-hormonal methods of birth control.

Antacid:

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 (see INTERACTIONS for rifampicin).

Discolouration of teeth, body fluids and contact lenses:

Rifampicin may produce a discolouration (yellow, orange, red, brown) of the teeth, urine, sweat, sputum and tears and the patient should be forewarned of this. Soft contact lenses have been permanently stained (see SIDE EFFECTS).

Applies to isoniazid:

Pyridoxine supplementation:

Patients at risk of neuropathy or pyridoxine deficiency, including those who are diabetic, alcoholic, elderly, malnourished, uraemic, have HIV infection or are pregnant: pyridoxine (vitamin B_6) supplementation (in a 10 mg to 50 mg daily dose) is usually required.

Caution should be observed with the use of RIFAFOUR e-275 tablets in patients:

- with epilepsy, as convulsions may be precipitated, and
- with a history of psychosis (see SIDE EFFECTS of isoniazid).

Applies to pyrazinamide:

Caution should be observed with the use of RIFAFOUR e-275 tablets in patients with diabetes. Pyrazinamide may cause interference with urine ketone determinations.

Applies to ethambutol:

Caution should be observed with the use of RIFAFOUR e-275 tablets in patients with impaired kidney function: dosage adjustment may be required according to the serum concentration of ethambutol.

Applies to RIFAFOUR e-275 tablets:

Hyperglycaemia and lactose intolerance:

RIFAFOUR e-275 tablets contain lactose, which may have an effect on the glycaemic control of patients with diabetes mellitus. Each tablet contains 54,66 mg lactose monohydrate. Patients with the rare hereditary conditions of galactose intolerance e.g. galactosaemia, Lapp lactase deficiency or glucose-galactose malabsorption should not take RIFAFOUR e-275.

Effects on ability to drive and use machines:

RIFAFOUR e-275 may cause undesirable effects, e.g. vertigo, dizziness, psychotic reactions and visual disturbances, which may reduce the capacity for the completion of certain tasks (see SIDE EFFECTS). Patients should be informed of the potential for these undesirable effects that may occur and if they experience these symptoms, consideration should be given not to drive or operate machinery.

INTERACTIONS:

Applies to 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 contraindicated (see CONTRAINDICATIONS).

***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.

Applies to 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, flecainide, quinidine, propafenone, 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. atazanavir, lopinavir, nevirapine, zidovudine, saquinavir, indinavir, efavirenz), 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 (e.g. ciprofloxacin, levofloxacin), gestrinone, oral hypoglycaemic agents (sulfonylureas), immunosuppressive agents (e.g. azathioprine, ciclosporin, sirolimus, tacrolimus), irinotecan, levothyroxine, losartan, narcotic analgesics, methadone, phenytoin, praziquantel, progestins, quinine, riluzole, selective 5-HT_3 receptor antagonists (e.g. ondansetron) statins metabolised by CYP3A4 (e.g. atorvastatin, simvastatin), sulfasalazine, telithromycin, theophylline, thiazolidinediones (e.g. pioglitazone), tricyclic antidepressants (e.g. amitriptyline, nortriptyline).
It may be necessary to adjust the dosages of these medicines if they are given concurrently with rifampicin.

The effectiveness of oestrogen-containing oral preparations is reduced. Patients using systemic hormonal contraceptives should be advised to change to non-hormonal methods of birth control during rifampicin therapy (see WARNINGS AND SPECIAL PRECAUTIONS).

Other interactions:

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.

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 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.

Interference with laboratory and diagnostic tests:

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

Transient elevation of serum bilirubin has also been observed. 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.

Applies to isoniazid:

Chronic use of isoniazid may decrease the plasma clearance and prolong the duration of action of alfentanil, the benzodiazepines diazepam and triazolam, the antiepileptics carbamazepine, phenytoin, ethosuximide and primidone, disulfiram and theophylline. Appropriate adjustment of the anticonvulsant dose may be required. Isoniazid has been associated with increased concentrations or toxicity of cycloserine and warfarin.
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.
Glucocorticoid corticosteroids may increase hepatic metabolism and/or excretion of isoniazid.
para-Aminosalicylic acid may increase the plasma concentration and elimination half-life of isoniazid.
Concurrent use of ciclosporin, disulfiram and other neurotoxic medicines may increase the potential for CNS toxicity. Interactions with ketoconazole and miconazole have been reported.
False positive reactions with copper sulphate urine glucose tests may occur.

Food interactions:

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 RIFAFOUR-e-275.

Applies to 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.

Applies to ethambutol:

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

HUMAN REPRODUCTION:

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.

Rifampicin has been reported to cross the placental barrier. 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:

Side effects associated with rifampicin:

Infections and infestations

Frequency unknown: pseudomembranous colitis; 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.

Blood and the lymphatic system disorders

Frequent: thrombocytopenia with or without purpura is usually associated with intermittent regimens but is reversible if the medicine is discontinued as soon as purpura occurs.

Less frequent: leucopenia

Frequency unknown: disseminated intravascular coagulation, eosinophilia, agranulocytosis, haemolytic anaemia, haemolysis

Immune system disorders

Frequency unknown: anaphylactic reaction, lupus-like syndrome

Endocrine disorders

Frequency unknown: adrenal insufficiency in patients with compromised adrenal function

Metabolism and nutritional disorders

Frequency unknown: decreased appetite

Psychiatric disorders

Frequency unknown: psychotic disorder

Nervous system disorders

Frequency unknown: headache, dizziness, drowsiness, ataxia, numbness, confusion, generalised numbness; cerebral haemorrhage and fatalities have been reported when rifampicin administration has been continued or resumed after the appearance of purpura.

Eye disorders

Less frequent: eye irritation visual disturbances

Frequency unknown: tear discolouration, blurred vision, soft contact lenses may be permanently stained (see WARNINGS AND SPECIAL PRECAUTIONS)

Vascular disorders

Frequency unknown: shock, flushing, vasculitis

Respiratory, thoracic and mediastinal disorders

Frequency unknown: dyspnoea, wheezing, discoloured sputum

Gastrointestinal disorders

Frequency: nausea, vomiting

Less frequent: diarrhoea

Frequency unknown: gastrointestinal disorder, abdominal discomfort, epigastric distress (which may be alleviated by administration with food), tooth discolouration (which may be permanent)

Hepatobiliary disorders

Frequency unknown: hepatitis and the prodromal symptoms of hepatitis may occur (nausea, vomiting, unusual tiredness/fatigue); hyperbilirubinaemia. Liver function should be monitored (see WARNINGS AND SPECIAL PRECAUTIONS)

Skin and subcutaneous tissue disorders

Frequency unknown: erythema multiforme including Stevens-Johnson syndrome and toxic epidermal necrolysis, medicine reaction with eosinophilia and systemic symptoms (DRESS) syndrome (see WARNINGS AND SPECIAL PRECAUTIONS); skin reaction, pruritus, pruritic rash, urticaria, erythema, allergic dermatitis, pemphigoid, sweat discolouration

Musculoskeletal, connective tissue and bone disorders

Frequency unknown: muscular weakness, myopathy, bone pain

Renal and urinary disorders

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

Pregnancy, puerperium and perinatal conditions

Frequency unknown: post-partum haemorrhage, fetal-maternal haemorrhage (see HUMAN REPRODUCTION)

Reproductive system and breast disorders

Frequency unknown: menstrual disorder

Congenital, familial and genetic disorders

Frequency unknown: porphyria exacerbation (see CONTRAINDICATIONS and WARNINGS AND SPECIAL PRECAUTIONS)

General disorders and administration side conditions

Frequent: pyrexia, chills

Frequency unknown: oedema

Investigations

Frequent: increased blood bilirubin, increased aspartate aminotransferase (AST), increased alanine aminotransferase (ALT) (see WARNINGS AND SPECIAL PRECAUTIONS)

Frequency unknown: decreased blood pressure, increased blood creatinine, increased hepatic enzyme (see WARNINGS AND SPECIAL PRECAUTIONS)

Side effects associated with isoniazid:

Blood and the lymphatic system disorders

Frequency unknown: eosinophilia, agranulocytosis, thrombocytopenia, anaemia (sideroblastic anaemia, haemolytic anaemia, neutropenia, and less frequently, aplastic anaemia)

Immune system disorders

Less frequent: hypersensitivity reactions (skin eruptions including erythema multiforme, lymphadenopathy), systemic lupus erythematosus-like syndrome

Frequency unknown: anaphylactic reactions

Endocrine disorders

Frequency unknown: gynecomastia

Metabolism and nutrition disorders

Frequency unknown: pellagra, hyperglycaemia, metabolic acidosis

Psychiatric disorders

Frequency unknown: psychotic reactions

Nervous system disorders

Frequent: peripheral neuropathy (pyridoxine supplementation prevents the development of peripheral neuritis as well as most other nervous system dysfunctions (see WARNINGS AND SPECIAL PRECAUTIONS).

Frequency unknown: polyneuritis presenting as paraesthesia, muscle weakness, loss of tendon reflexes, etc., convulsions (frequency of seizures may be increased in patients with epilepsy), toxic encephalopathy, optic neuritis and atrophy, memory impairment, toxic psychosis

Ear and labyrinth disorders

Frequency unknown: vertigo

Vascular disorders

Frequency unknown: vasculitis

Gastrointestinal disorders

Less frequent: pancreatitis

Frequency unknown: nausea, vomiting, dry mouth, constipation, epigastric distress

Hepatobiliary disorders

Frequency unknown: severe and sometimes fatal hepatitis. 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.

Skin and subcutaneous tissue disorders

Frequency unknown: rash, acne, exfoliative dermatitis, medicine reaction with eosinophilia and systemic symptoms (DRESS) syndrome, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN), (see WARNINGS AND SPECIAL PRECAUTIONS), pemphigus, lupus erythematosus-like reactions, purpura, alopecia

Musculoskeletal, connective tissue and bone disorders

Frequency unknown: rheumatoid syndrome

Renal and urinary disorders

Frequency unknown: urinary retention

General disorders and administration site conditions

Frequency unknown: fever

Side effects associated with pyrazinamide:

Blood and the lymphatic system disorders

Frequency unknown: sideroblastic anaemia, thrombocytopenia with or without purpura

Metabolism and nutrition disorders

Frequent: hyperuricaemia (may lead to attacks of gout)

Frequency unknown: gout, anorexia

Gastrointestinal disorders

Frequency unknown: nausea, vomiting, aggravation of peptic ulcer

Hepatobiliary disorders

Frequency unknown: hepatitis. 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.

Skin and subcutaneous tissue disorder

Less frequent: angioedema

Frequency unknown: medicine reaction with eosinophilia and systemic symptoms (DRESS) syndrome (see WARNINGS AND SPECIAL PRECAUTIONS), photosensitivity, pruritus, erythema, rash

Musculoskeletal, connective tissue and bone disorders

Less frequent: arthralgia

Renal and urinary disorders

Frequency unknown: dysuria

General disorders and administration site conditions

Frequency unknown: malaise, fever

Side effects associated with ethambutol:

Blood and the lymphatic system disorders

Frequency unknown: leucopenia, thrombocytopenia

Metabolism and nutrition disorders

Frequency unknown: hyperuricaemia

Psychiatric disorders

Frequency unknown: confusion, disorientation, hallucinations

Nervous system disorders

Frequency unknown: peripheral neuritis, headache, dizziness

Eye disorders

Less frequent: retinal haemorrhage

Frequency 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.

Gastrointestinal disorders

Frequency unknown: metallic taste, nausea, vomiting, anorexia, abdominal pain

Hepatobiliary disorders

Frequency unknown: jaundice or transient liver dysfunction

Skin and subcutaneous tissue disorders

Frequency unknown: medicine reaction with eosinophilia and systemic symptoms (DRESS) syndrome (see WARNINGS AND SPECIAL PRECAUTIONS), hypersensitivity reactions include skin rash, pruritus

Musculoskeletal, connective tissue and bone disorders

Frequency unknown: arthralgia

Renal and urinary disorders

Frequency unknown: renal clearance of urate may be reduced and acute gout has been precipitated

General disorders and administration site conditions

Frequency unknown: malaise, fever

Investigations

Frequency unknown: pulmonary infiltrates.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

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

Symptoms:

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 discolouration 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 g to 12 g rifampicin. Fatal acute overdoses in adults have been reported with doses ranging from 14 g 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. Anti-emetic 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 20, 28, 40, 56, 60, 80, 84, 100, 112 and 500 tablets in foil-foil blisters or white polypropylene securitainers.

STORAGE INSTRUCTIONS:

Store in a cool place, at or below 25 °C in well-closed containers, protected from light.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER:

34/20.2.3/0187

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

sanofi-aventis south africa (pty) ltd.

2 Bond Street

Midrand

South Africa

1685

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