Natrapharm

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RIFAMPICIN / ISONIAZID

Fixcom 2®

150mg / 75mg
Film coated tablet

FORMULATION:
Each tablet contains:
Rifampicin..... 150mg
Isoniazid..... 75mg

INDICATIONS:
For the treatment of pulmonary and extrapulmonary tuberculosis.

DOSAGE AND ADMINISTRATION:
Anti-tuberculosis short course chemotherapy recommended by World Health Organization (WHO) involves an intensive phase followed by a continuation phase for 4 months.

The dosage schedule will follow the recommended WHO TB treatment regimens. The number of tablets of fixed-dose combination tablets per patient will depend on the body weight. Hence, all patients must be weighed (using kilogram as a unit) before treatment is started.

Patient Body weight (kg)	Number of tablets per day Continuation Phase (4 months) (HR) Isoniazid 150mg + Rifampicin 150mg)
30 - 37	2
38 - 54	3
55 - 70	4
Over 71	5

The tablets should be taken one hour before or two hours after meals.

PHARMACODYNAMICS:
There are three main properties of antituberculosis drugs: bactericidal activity; sterilizing activity and the ability to prevent resistance. The essential antituberculosis drugs possess these properties to different extents. Isoniazid and rifampicin are the most powerful bactericidal drugs, active against all populations to TB bacilli. Rifampicin is the most potent sterilizing drug available.

PHARMACOKINETICS:
Rifampicin: Rifampicin is readily absorbed from the gastrointestinal tract and peak plasma concentrations of about 7 to 10 ug per ml have been reported 2 to 4 hours after a dose of 600mg, although there may be considerable interindividual variation. Food may reduce and delay absorption. Rifampicin is approximately 80% bound to plasma proteins. It is widely distributed in body tissues and fluids and diffusion into the CSF is increased when the meninges are inflamed. Rifampicin crosses the placenta and is distributed into breast milk. 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.

Rifampicin is rapidly metabolized in the liver mainly to active 25-0-deacetyrifampicin; rifampicin and deacetylrifampicin are excreted in the bile. Deacetylation diminishes intestinal reabsorption and increases faecal excretion, although significant enterohepatic circulation still takes place. About 60% of a dose eventually appears in the feces. The amount excreted in the urine increases with increasing doses and up to 30% of a dose of 900 mg may be excreted in the urine, about half of it within 24 hours. The metabolite formylrifampicin is also excreted in the urine. In patients with impaired renal function the half-life of rifampicin is not prolonged at doses of 600mg or less.

Isoniazid is readily absorbed from the gastrointestinal tract. Peak concentrations of about 3 to 8 ug per ml appear in blood 1 to 2 hours after a fasting dose of 300mg by mouth. The rate and extent of absorption of isoniazid is reduced by food. Isoniazid is not considered to be bound appreciably to plasma proteins and diffuses into all body tissues and fluids, including the CSF. The plasma half-life for Isoniazid ranges from about 1 to 6 hours, those who are fast acetylators having shorter half-lives. The primary metabolic route is the acetylation of isoniazid to acetylisoniazid by N-acetyltransferase found in the liver and small intestine.

In patients with normal renal function, over 75% of a dose appears in the urine in 24 hours, mainly as metabolites. Small amounts of drug are also excreted in the feces. Isoniazid is removed by dialysis.

TREATMENT REGIMENS IN SPECIAL SITUATIONS

Pregnancy

A woman should be asked before starting TB treatment it she is pregnant. Most antituberculosis drugs are safe for use in pregnancy. A pregnant woman should be advised that successful treatment of TB with the recommended standardized regimen is important for successful outcome of pregnancy.

Breastfeeding

A breastfeeding woman who has TB should receive a full course of TB treatment. Timely and properly applied chemotherapy is the best way to prevent transmission of tubercle bacilli to her baby. All tuberculosis are compatible with breastfeeding; a woman taking them can safely continue to breastfeed. Mother and baby should stay together and the baby continue to be breastfed in the normal way, but be given prophylactic isoniazid for at least 3 months beyond the time the mother is considered to be non-infectious. BCG vaccination of the newborn should be postponed until the end ot isoniazid prophylaxis.

Oral Contraception

Rifampicin interacts with oral contraceptive medications with a risk of deceased protective efficacy against pregnancy. A woman receiving oral contraception may choose between two options while receiving treatment with rifampicin: following consultation with a clinician, an oral contraceptive pill containing a higher dose ot estrogen (50ug) may be taken, or another form of contraception used.

Liver disorders

Isoniazid and rifampicin are all associated with hepatitis. Of the two drugs, rifampicin is least likely to cause hepatocellular damage, although it is associated with cholestatic jaundice.

Patients with the following conditions can receive the usual short — course chemotherapy regimens provided there is no clinical evidence of chronic liver disease: However, hepatotoxic reactions to antituberculosis drugs may be more common among these patients and should therefore be anticipated.

Established chronic liver disease

Isoniazid plus rifampicin plus one or two non-hepatotoxic drugs such as streptomycin and ethambutol can be used for a total treatment duration of 8 months. Alternative regimens are 9 Rifampicin/ Ethambutol (RE) or Streptomycin / isoniazid / Ethambutol (SHE) in the initial phase followed by Isoniazid / Ethambutol (HE) in the continuation phase, with a total treatment duration of 12 months. Recommended regimens are therefore 2SHRE/6HR. 9 RE or 2SHE/10HE.

Acute hepatitis (e.g. acute viral hepatitis)

Uncommonly, a patient has TB and concurrently acute hepatitis unrelated to TB or TB treatment. Clinical judgement is necessary. In some cases, it is possible to defer TB treatment until the acute hepatitis has resolved. In other cases, when it is necessary to treat TB during acute hepatitis, the combination of Streptomycin/Ethambutol for 3 months is the safest option. If the hepatitis has resolved, the patient can then receive a continuation phase of 6 months isoniazid and rifampicin 6(HR). If the hepatitis has not resolved, Streptomycin /ethambutol should be continued tor a total ot 12 months.

Renal failure

Isoniazid and ritampicin are either eliminated almost entirely by biliary excretion or metabolized into non-toxic compounds. These drugs can therefore be given in normal dosage to patients with renal failure. Patients with severe renal failure should receive pyridoxine with isoniazid in order to prevent peripheral neuropathy.

MONITORING OF ADVERSE EFFECTS
Most TB patients complete their treatment without any significant adverse effects of drugs. However, a few patients do experience adverse effects. It is therefore important that patients be clinically monitored during treatment so that adverse effects can be detected promptly and managed properly. Routine laboratory monitoring is not necessary.

Health personnel can monitor adverse effects of drugs by teaching patients how to recognize symptoms of common adverse effects and to report if they develop such symptoms, and by asking about symptoms when patients report to collect drugs. In general, a patient who develops minor adverse effects should continue the TB treatment, sometimes at a reduced dose. The patient also receives symptomatic treatment. If a patient develops a major side effect, the treatment or the offending drug is stopped. Further management depends on the nature of the adverse reaction. Patients with major adverse reactions should be managed in a hospital.

SIDE-EFFECTS	DRUG(S) PROBABLY RESPONSIBLE	MANAGEMENT
Minor		Continue anti-TB drugs Check drug doses
Anorexia, nausea Abdominal pain	Rifampicin	Give drugs with small meals or last thing at night
Burning sensation in the feet	Isoniazid	Pyridoxine 100mg daily
Orange/red urine	Rifampicin	Reassurance: Patients should be told when starting treatment that this commonly happens and is normal

SIDE-EFFECTS	DRUG(S) PROBABLY RESPONSIBLE	MANAGEMENT
Major		Stop responsible drug(s)
Itching, skin rash	Isoniazid, Rifampicin	Stop anti-TB drugs
Jaundice (other causes excluded); hepatitis	Isoniazid Rifampicin	Stop anti-TB drugs
Confusion (suspect drug-induced acute liver failure if jaundice present)	Most anti-TB drugs	Stop anti-TB drugs Urgent liver functions tests and prothrombin time
Shock, purpura, acute renal failure	Rifampicin	Stop rifampicin

DRUG INTERACTIONS
Isoniazid tends to raise plasma concentrations of phenytoin and carbamazepine by inhibiting their metabolism in the liver. The absorption of isoniazid is impaired by aluminium hydroxide

Rifampicin induces hepatic enzymes, and may increase the dosage requirements of drugs metabolized in the liver. These include corticosteroids, steroid contraceptives, oral hypoglycaemic agents, oral anticoagulants, phenytoin, cimetidine, cyclosporine and digitalis glycosides. Since rifampicin reduces the effectives of oral contraceptives, women should be advised to choose between one of the following options for contraception. Following consultation with a clinician, the patient may use an oral contraceptive pill containing a higher dose of estrogen (50ug). Alternatively, a nonhormonal method of contraception may be used throughout rifampicin treatment and for at least one month subsequently.

Current antiretroviral drugs interact with rifampicin. This may result ineffectiveness of antiretroviral drugs, ineffective treatment of TB or an increased risk of drug toxicity. Biliary excretion of radiocontrast media and sulfobromophthalein sodium may be reduced and microbiological assays for folic acid and vitamin B_{12} disturbed.

PREACUTIONS
Isoniazid — Monitoring of serum concentrations of hepatic transaminases, where possible, is useful in patients with pre-existing chronic liver disease. Patients at risk of peripheral neuropathy, as a result of malnutrition, chronic alcohol dependence or diabetes, should additionally receive pyridoxine, 10mg daily. Where the standard of health in the community is low, this should be offered routinely.
Since isoniazid interacts with anticonvulsants used for epilepsy, it may be necessary to reduce the dosage of these drugs during treatment with isoniazid.

Rifampicin — Serious immunological reactions resulting in renal impairment, haemolysis or thrombocytopenia are on record in patients who resume taking rifampicin after a prolonged lapse of treatment. In this rare situation, it should be immediately and definitely withdrawn
Careful monitoring of liver function is required in the elderly and in patients who are alcohol-dependent or have hepatic disease. Patients should be warned that treatment may produce reddish coloration ot urine, tears, saliva and sputum and that contact lenses may be irreversibly stained.

OVERDOSE AND TREATMENT:
Symptoms: Overdose of Fixcom 2 produces signs and symptoms within 30 min to 3 hrs after ingestion. Nausea, vomiting, lethargy, dizziness, slurring of speech, blurring of vision and visual hallucinations are among the early manifestations. Actual unconsciousness may occur with severe hepatic involvement. Brownish-red or orange discoloration of the skin, urine, sweat, saliva, tears and feces may be proportional to the amount ingested. Liver enlargement possibly with tenderness can develop within a few hours after severe overdose and jaundice may develop rapidly. Hepatic involvement may be more marked in patients with prior impairment of hepatic function. With marked overdose, 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 finding.

Treatment: Discontinue Fixcom 2. Secure the airway and establish adequate respiratory exchange. Pyridoxine should be administered in a dose of 1g for each gram of isoniazid apparently ingested. Gastric lavage within the first 2-3 hrs is advised, but should not be attempted until convulsions are under control. Gastric lavage with activated charcoal slurry instilled into the stomach following evacuation of gastric contents could help and absorb any remaining drug in the gastrointestinal tract. Antiemetic medication may be required to control severe nausea and/or vomiting. Forced osmotic diuresis (with measured intake and output) will help to promote excretion of the drug. Extracorporal hemodialysis may be required.

CAUTION:
Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription

AVAILABILITY:
Blister pack x 10's (Box of 80's)
Blister pack x 28's (Box of 336's)

For suspected adverse drug reaction, report to the FDA: www.fda.gov.ph

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STORE AT TEMPERATURES NOT EXCEEDING 30°C

Manufactured for
Natrapharm, Inc.
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