**Products: 4 FDC-B and 4 FDC**

**RIFAMPICIN 150mg, ISONIAZID 75 mg, PYRAZINAMIDE 400 mg and ETHAMBUTOL 275 mg in a fixed dose combination tablet**

**Uses:**
An optional component of several anti-TB chemotherapeutic regimens currently recommended by WHO.

**Contraindications and Precautions:**
- •Preparation not suitable for use in children
- •Not appropriate for intermittent therapy in these drug strengths
- •Known hypersensitivity to the drugs

See also individual monographs for Rifampicin, Isoniazid, Pyrazinamide and Ethambutol below

**Dose:**
Use for initial (intensive) phase of treatment in place of the single tablets: *By mouth*, **ADULT**
- •30-37 kg 2 tablets daily for 2 months
- •38-54 kg 3 tablets daily for 2 months
- •55-70 kg 4 tablets daily for 2 months
- •71 kg or more 5 tablets daily for 2 months

# RIFAMPICIN

**General information**

A semisynthetic derivative of rifamycin, a complex macrocyclic antibiotic that inhibits ribonucleic acid synthesis in a broad range of microbial pathogens. It has bactericidal action and a potent sterilizing effect against tubercle bacilli in both cellular and extracellular locations. Rifampicin is lipid-soluble. Following oral administration, it is rapidly absorbed and distributed throughout the cellular tissues and body fluids; if the meninges are inflamed, significant amounts enter the cerebrospinal fluid. A single dose of 600 mg produces a peak serum concentration of about 10 micrograms/ml in two to four hours, which subsequently decays with a half-life of two to three hours. It is extensively recycled in the enterohepatic circulation, and metabolites formed by deacetylation in the liver are eventually excreted in the faeces. Since resistance readily develops, rifampicin must always be administered in combination with other effective antimycobacterial agents.

**Clinical information**

**Uses**

A component of all six and eight month anti-TB chemotherapeutic regimens currently recommended by WHO; Leprosy

**Dosage and administration**

Rifampicin should preferably be given at least 30 minutes before meals, since absorption is reduced when it is taken with food. Rifampicin should be given as combination therapy
Adults and children: 10 mg/kg daily, *or* 2 or 3 times weekly (maximum dose, 600 mg daily)

**Contraindications**

· Known hypersensitivity to rifamycins · Jaundice

**Precautions**

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, have hepatic disease or are on prolonged therapy.

Reduce dose in renal impairment.

Patients should be warned that treatment may produce reddish coloration of urine, tears, saliva and sputum, and that contact lenses may be irreversibly stained.

Patients or their care-givers should be told how to recognise signs of liver disorders and advised to discontinue treatment and seek immediate medical attention if symptoms such as poersistent nausea, vomiting, malaise or jaundice develop

**Use in pregnancy**

Whenever possible, the six month regimen based upon isoniazid, rifampicin and pyrazinamide should be used. Vitamin K should be administered to the infant at birth because of the risk of postnatal haemorrhage.

**Adverse effects**

Rifampicin is well tolerated by most patients at currently recommended doses, although gastrointestinal tolerance can be unacceptably severe. Other adverse effects (skin rashes, fever, influenza-like syndrome and thrombocytopenia) are more likely to occur with intermittent administration. Exfoliative dermatitis is more frequent in HIV-positive TB patients. Temporary oliguria, dyspnoea and haemolytic anaemia have also been reported in patients taking the drug three times weekly. These reactions usually subside if the regimen is changed to one with daily dosage. Moderate rises in serum concentrations of bilirubin

and transaminases, which are common at the outset of treatment, are often transient and without clinical significance. However, dose-related hepatitis can occur which is potentially fatal. It is consequently important not to exceed the maximum recommended daily dose of 10 mg/kg (600 mg).

**Drug interactions**

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, cyclosporin and digitalis glycosides. Since rifampicin reduces the effectiveness of the oral contraceptive pill, women should consequently be advised to choose between one of the following two options for contraception. Following consultation with a physician, she could take an oral contraceptive pill containing a higher dose of oestrogen (50mcg). Alternatively she could use a nonhormonal method of contraception throughout rifampicin treatment and for at least one month subsequently.

## ISONIAZID

**General information**

Isoniazid, the hydrazide of isonicotinic acid is highly bactericidal against replicating tubercle bacilli. It is rapidly absorbed and diffuses readily into all fluids and tissues. The plasma half-life, which is genetically determined, varies from less than one hour in fast acetylators to more than three hours in slow acetylators. It is largely excreted in the urine within 24 hours, mostly as inactive metabolites.

**Clinical information**

**Uses**

Tuberculosis treatment, in combination with other drugs

Tuberculosis prophylaxis and occasionally to prevent:

. • transmission to close contacts at high risk of disease

. • progression of infection to primary complex in recently infected, asymptomatic individuals

. • recrudescence of infection in immunodeficient individuals.

**Dosage and administration**

*By mouth*, ADULT and CHILD

•5 mg/kg (4–6 mg/kg) daily (maximum, 300 mg daily)

•*or* 10 mg/kg 3 times weekly

•*or* 15 mg/kg twice weekly

Tuberculosis, treatment in critically ill patients unable to take oral therapy (combination

therapy), *use intramuscular injection* , **ADULT** 200–300 mg as single daily dose; **CHILD** 10– 20 mg/kg daily

Tuberculosis, prophylaxis, *by mouth*

- **ADULT** 300 mg daily for at least 6 months
- **CHILD** 5 mg/kg daily for at least 6 months

Note: Isoniazid should be taken on an empty stomach; if taken with food to reduce gastrointestinal irritation, oral absorption and bioavailability may be impaired

**Contraindications**

- Known hypersensitivity
- Drug induced hepatic disease

**Precautions**

- Hepatic impairment (monitor hepatic function)
- Malnutrition
- Chronic alcohol dependence
- Chronic renal failure
- Diabetes mellitus
- HIV infection—prophylactic pyridoxine 10 mg daily required because risk of peripheral neuritis
- Epilepsy (isoniazid may provoke attacks)
- Slow acetylator status (increased risk of adverse effects)
- History of psychosis
- Pregnancy
- Breast-feeding
- Porphyria

Note: Patients at risk of peripheral neuropathy as a result of malnutrition, chronic alcohol dependence or diabetes should additionally receive pyridoxine, 10 mg daily.

Note: For liver disorders, patients or their care-givers should be told how to recognise signs of liver disorder, and advised to discontinue treatment and seek immediate medical attention if symptoms such as nausea, vomiting, malaise or jaundice develop

**Adverse effects**

Isoniazid is generally well tolerated at recommended doses. Systemic or cutaneous hypersensitivity reactions occasionally occur during the first weeks of treatment. The risk of peripheral neuropathy is excluded if vulnerable patients receive daily supplements of pyridoxine. Other less common forms of neurological disturbance, including optic neuritis, toxic psychosis and generalized convulsions, can develop in susceptible individuals, particularly in the later stages of treatment and occasionally necessitate the withdrawal of

isoniazid. Hepatitis is an uncommon but potentially serious reaction that can usually be averted by prompt withdrawal of treatment. More often, however, a sharp rise in serum concentrations of hepatic transaminases at the outset of treatment is not of clinical significance, and usually resolves spontaneously during continuation of treatment.

**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.

**Overdosage**

Nausea, vomiting, dizziness, blurred vision and slurring of speech occur within 30 minutes to three hours of overdosage. Massive poisoning results in coma preceded by respiratory depression and stupor. Severe intractable seizures may occur. Emesis and gastric lavage can be of value if instituted within a few hours of ingestion. Subsequently, haemodialysis may be of value. Administration of high doses of pyridoxine is necessary to prevent peripheral neuritis.

**Storage**

Tablets should be kept in well-closed containers, protected from light. Solution of injection should be stored in ampoules protected from light.

## PYRAZINAMIDE

**General information**

A synthetic analogue of nicotinamide that is only weakly bactericidal against M.tuberculosis, but has potent sterilizing activity, particularly in the relatively acidic intracellular environment of macrophages and in areas of acute inflammation. It is highly effective during the first two months of treatment while acute inflammatory changes persist and its use has enabled treatment regimens to be shortened and the risk of relapse to be reduced.

It is readily absorbed from the gastrointestinal tract and is rapidly distributed throughout all tissues and fluids. Peak plasma concentrations are attained in two hours and the plasma half-life is about 10 hours. It is metabolised mainly in the liver and is excreted largely in the urine.

**Clinical information**

**Uses**

A component of all six and eight month anti-TB chemotherapeutic regimens currently recommended by WHO.

**Dosage and administration**

*By mouth:*

Adults and children (for the first two or three months) 25 mg/kg daily 35 mg/kg three times weekly 50 mg/kg two times weekly

**Contraindications**

· Known hypersensitivity · Severe hepatic impairment
·Porphyria

**Precautions**

. ·Hepatic impairment (monitor hepatic function)
. ·Patients with diabetes mellitus (monitored blood glucose--concentrations may change suddenly
. ·Gout may be exacerbated.

**Use in pregnancy**

Although the safety of pyrazinamide in pregnancy has not been established, the six month regimen based upon isoniazid, rifampicin and pyrazinamide should be used whenever possible.

**Adverse effects**

Pyrazinamide in usually well tolerated. Hypersensitivity reactions are rare, but some patients complain of slight flushing of the skin.

Moderate rises in serum transaminase concentrations are common during the early phases of treatment. Severe hepatotoxicity is rare.
As a result of inhibition of renal tubular secretion, a degree of hyperuricaemia usually occurs, but this is often asymptomatic. Gout requiring treatment with allopurinol occasionally develops. Arthralgia, particularly of the shoulders, commonly occurs and is responsive to simple analgesics. Both hyperuricaemia and arthralgia may be reduced by prescribing regimens with intermittent administration of pyrazinamide.

Note: Patients and their care-givers should be told how to recognise signs of liver disorder, and advised to discontinue treatment and seek immediate medical attention if symptoms such as persistent nausea, vomiting, malaise or jaundice develop.

**Overdosage**

Little had been recorded on the management of pyrazinamide overdose. Acute liver damage and hyperuricaemia have been reported. Treatment is essentially symptomatic. Emesis and gastric lavage may be of value if undertaken within a few hours of ingestion. There is no specific antidote and treatment is supportive.

**Storage**

Tablets should be stored in tightly closed containers, protected from light.

# ETHAMBUTOL

## General information

A synthetic congener of 1,2-ethanediamine that is active against M. tuberculosis, M. bovis and some non-specific mycobacteria. It is used in combination with other anti-TB drugs to prevent or delay the emergence of resistant strains.

It is readily absorbed from the gastrointestinal tract. Plasma concentrations peak in 2-four hours and decay with a half-life of three to four hours. Ethambutol is excreted in the urine both unchanged and as inactive hepatic metabolites.

About 20% is excreted in the faeces as unchanged drug.

## Clinical information

### Uses

An optional component of several anti-TB chemotherapeutic regimens currently recommended by WHO.

### Dosage and administration

By mouth: Adults: 15 mg/kg daily 30 mg/kg three times weekly, or 45 mg/kg (40-50 mg/kg) twice a week

Children: 15 mg/kg daily

Dosage must always be carefully calculated on a weight basis to avoid toxicity, and should be reduced in patients with impaired renal function.

### Contraindications

. • Known hypersensitivity
. • Pre-existing optic neuritis from any cause
. • Inability to report symptomatic visual disturbances—children under 5 years)
. • Severe renal impairment

### Precautions

. • Visual disturbances—ocular examination recommended before and during treatment (see note below)
. • Reduce dose in renal impairment and monitor plasma concentration
. • Use in the elderly

Note: Patients should report visual disturbances immediately and discontinue treatment; children who are incapable of reporting symptomatic visual changes accurately should be given alternative therapy, as should, if possible, any patient who cannot understand

warnings about visual adverse effects

Whenever possible, renal function should assessed before treatment.

**Use in pregnancy**

The six month regimen based upon isoniazid, rifampicin and pyrazinamide should be used. If a fourth drug is needed during the initial phase, ethambutol should be preferred to streptomycin.

**Adverse effects**

Dose-dependent optic neuritis can readily result in impairment of visual acuity and colour vision. Early changes are usually reversible, but blindness can occur if treatment is not discontinued promptly.

Signs of peripheral neuritis occasionally develop in the legs.

**Overdosage**

Emesis and gastric lavage may be of value if undertaken within a few hours of ingestion. Subsequently, dialysis may be of value. There is no specific antidote and treatment is supportive.

**Storage**

Tablets should be stored in well-closed containers.