DAILY DOSAGE RANGE:

Rifampicin	8-12 mg/Kg maximum 600mg/day.
Isoniazid	4-6 mg/Kg maximum 300mg/day.
Ethambutol HCl	15-25 mg/Kg/day.
Pyrazinamide	20-35 mg/Kg maximum 3g/day.

PROPOSED DOSAGE :

The patients should be given 1 tablet/15 Kg body weight of **Rifa 4+**, according to the following chart one to two hours before meal or as directed by the physician

Rifa 4+ *For initial phase of T.B. treatment*	
WEIGHT	
30-37 Kg	2
38-54-Kg	3
55-70 Kg	4

OVER DOSAGE :

Because of the potential toxicity **Rifa 4+** *should be used with extreme caution in elderly patients. The sign and symptoms of overdosage toxicity include;*

Rifampicin nausea, vomiting, lethargy, acute unconsciousness, liver enlargement with tenderness leading to jaundice. Brownish-red to orange discoloration of the skin, urine, sweat, saliva, tears and feces.

Isoniazid slurring of speech, blurred vision, hallucination, respiratory distress, CNS depression progressing to profound coma alongwith severe intractable seizure, metabolic acidosis, acetonuria, & hyperglycemia are the typical clinical findings.

Ethambutol HCl loss of visual acuity.

Pyrazinamide hepatic abnormalities may progress to severe damage.

TREATMENT :

Gastric lavage with activated charcoal slurry alongwith anti-emetic therapy to control nausea/vomiting and supportive measures to establish adequate ventilation. Forced osmotic diuresis with measured intake and output will help to promote the elimination of the drug. Bile drainage may be indicated in the presence of serious impairment of hepatic function lasting more than 24-48 hrs. Under these circumstances, extracorporeal hemodialysis may be required.

STORAGE CONDITIONS :

* Store in a cool and dry place.
* Protect from heat, light and moisture.
* Store at 20 ºC to 25 ºC (68 ºF to 77 ºF), excursions permitted between 15 ºC and 30 ºC (between 59 ºF and 86 ºF).
* Keep all medicines out of the reach of children.

PRESENTATION:

Rifa 4+ film coated tablets are available in (10 x 10) blister pack tablets.

Manufactured by :
Schazoo Zaka (Pvt) Ltd.
Kalalwala, 20-Km Lahore-Jaranwala Road,
Distt: Sheikhupura, Pakistan.

For initial intensive phase of T.B. treatment

Rifa 4+® Tablets

COMPOSITION:

Each film coated tablet contains:

Rifampicin U.S.P.....150 mg Isoniazid U.S.P. ..... 75 mg
Ethambutol HCl U.S.P. 275 mg Pyrazinamide U.S.P. 400 mg

Ref.: *"In the developing nations which harbor the majority of the world's tuberculosis patients, a standard regimen including a 4-drug initial phase followed by a 3-drug continuation phase should be administered to avoid resistance.*
(SBARBARO, M. D. & ISEMAN, J.A.; "Approaching tuberculosis treatment in the 1990's." University of Colorado School of Medicine, Denver Colorado, USA.)

CLINICAL PHARMACOLOGY:

Rifampicin

First-line primary anti-tuberculosis agent given in combination with other anti-TB drugs. In susceptible bacteria at comparable concentrations Rifampicin inhibits highly sensitive DNA-dependent RNA- polymerase , thus preventing the synthesis of m-RNA and consequently of any other protein without interfering mammalian enzyme even at much higher concentrations. It has powerful bactericidal activity particularly against rapidly multiplying both extra-cellular as well as intra-cellular populations with added advantage of high concentrations attainable in lung tissues , lower relapse rate and good patient acceptability. Rifampicin is rapidly absorbed from the upper part of the gastro-intestinal tract with a peak plasma level occuring within 1.5-3 hrs., following oral administration. The biological half-life is approximately 3 hrs., with wide spread distribution, crosses blood-brain and placental barrier and protein binding is 80%. Rifampicin is rapidly eliminated via bile and undergoes enterohepatic circulation. About 30% of the drug is excreted in urine with 15% being unchanged drug. Food can delay the absorption of Rifampicin nevertheless, to ensure that the absorption of the drug is not impaired , it is recommended that the **Rifa 4+** is taken on an empty stomach at least 30 minutes before meal.

Isoniazid

Isoniazid is a first-line primary anti-tuberculostatic agent with highly bactericidal and sterilizing action in killing of "persisters" on both intra-cellular and extra-cellular populations. The GIT absorption is fast and well with high tissue and body fluid penetration with peak plasma level reached within 1-2 hrs. Isoniazid is very rapidly metabolized primarily by N-acetylation and dehydrazination with 50-70% eliminated in urine during 24 hrs.

Ethambutol HCl

Ethambutol HCl is a first-line primary anti-tuberculosis drug with bacteriostatic action on both intracellular and extracellular populations. It penetrates into rapidly proliferating mycobacterium cell and inhibits the synthesis of metabolites leading to metabolic disturbances, multiplication arrest and ultimately death of the cell. No cross resistance with other anti-tuberculostatic agents has been demonstrated so far. Simultaneous administration of Ethambutol HCl with other antituberculostatic agent minimized the incidence of emergence of mycobacterial resistance to Isoniazid. After administration of single oral dose, a peak plasma level is attained within 2-4 hrs. which drops to undetectable by 24 hrs., except in patients with impaired renal function and maintains

similar profiles even after long-term therapy. Approximately half of the initial dose is excreted as such alongwith 8-15% in the form of metabolites in urine and 20-22% is excreted in feces as unchanged drug. No drug accumulation has been observed with consecutive single daily dose in patients with normal kidney function.

Pyrazinamide

It is also a first-line primary anti-tuberculosis drug bacteriostatic on intra-cellular population with action mechanism similar to Isoniazid and is the most active drug in sterilizing tuberculous lesions. Following oral administration GIT absorption is very good with a peak plasma concentration achieved within 24 hrs. Pyrazinamide is widely distributed into body tissues and fluids including liver, lungs and cerebrospinal fluid. The plasma protein binding is approximately 10% with a half-life of 9-10 hrs., in normal hepatic and renal functions. Pyrazinamide is detoxified in liver, excreted approximately 70% in urine by glomerular filtration within 24 hrs., & about 4-14% of the drug is eliminated unchanged.

INDICATIONS:

Rifa 4 + is recommended during the initial intensive phase of pulmonary and extra-pulmonary tuberculosis administered on a daily continuous basis. When required, other anti-tuberculosis drugs i.e. Streptomycin may be added.

CONTRA-INDICATIONS:

Rifa 4 + *is not recommended in patients with*

1- Hypersensitivity to Rifampicin, Isoniazid, Ethambutol HCl, & Pyrazinamide including drug related hepatitis.
2- Visual defects
3- Acute hepatic disorders
4- Renal dysfunction which requires dosage adjustment determined by the blood levels of Ethambutol HCl since main excretory path is by kidney.
5- Epileptic seizure or psychotic states characterized by mania or hypomania.

PRECAUTIONS:

* Regular monitoring of organ system functioning should be assessed during long-term treatment.
* Acute gout or *diabetes mellitus* leads to management problems with Pyrazinamide.
* High doses of Isoniazid may cause Pyridoxine deficiency therefore, simultaneous supplementation of the vitamin is advised.
* Ethambutol HCl is not recommended in children under 13 years of age since safety has not yet been established.
* Urine, feces, saliva, sputum, sweat and tears may be colored reddish-orange by the excretion of Rifampicin and its metabolites. Therefore, avoid wearing soft contact lenses as these may be discolored by Rifampicin excreted via lacrimation.

DRUG INTERACTIONS:

* Rifampicin increases the requirement for coumarin type anticoagulants therefore, daily monitoring of *prothrombin time* is needed to maintain the effective dose.
* Simultaneous administration may hinder the pharmacological activity of Methadone, oral Hypoglycemics, Digoxin, Quinidine, Disopyramide, Dapsone & Corticosteroids thus requiring *dosage adjustment* of these drugs.
* The reliability of the oral contraceptives may be affected by Rifampicin hence, *alternative contraceptive* measures may be considered.
* Isoniazid may reduce the excretion of anti-convulsant agent phenytoin leading to *potentiation effect.*

USE IN PREGNANCY & LACTATION:

No well-controlled study data is available on **Rifa 4 +** or its active contents in pregnancy. Rifampicin have been shown to be teratogenic in animals in very high doses. When administered during the last few weeks of pregnancy it can cross the placental barrier and appear in umbilical cord blood of neonates and can cause post-natal bleeding in mothers and infants which may be controlled with vitamin-K therapy. Isoniazid may exert embryocidal effect in animals when administered during pregnancy. Although no congenital abnormalities have been found in reproduction studies. Ethambutol HCl have shown to possess some teratogenic potential whereas reproduction investigations with Pyrazinamide have not been conducted so far. Rifampicin, Isoniazid & Pyrazinamide are excreted in the breast milk therefore, infants should not be breast fed during therapy. Therefore, these drugs should be used in pregnancy only if the potential benefit justifies the potential risk to fetus.

SIDE EFFECTS :

Vision

RIFAMPICIN: visual disturbances.
ISONIAZID : optic neuritis & atrophy.
ETHAMBUTOL HCl : decrease in visual acuity due to optic neuritis.

CNS

RIFAMPICIN : headache, drowsiness, dizziness, fatigue, ataxia, inability to concentrate and mental confusion.
ISONIAZID : headache, mental confusion, insomnia, tinitis, restlessness, increased reflexes, muscle twitching , paresthesias and convulsions only in large doses particularly in alcoholic and diabetics.
ETHAMBUTOL HCl : headache, dizziness, mental confusion, disorientation, hallucination, malaise, numbness and tingling of extremities and fever.

CVS

RIFAMPICIN : thrombocytopenia, eosinophilia, transient leukopenia, hemolytic anemia and reduced hemoglobin level.
ISONIAZID: thrombocytopenia, eosinophilia, agranulocytosis, anemia, methemoglobinemia, vasculitis & arthralgia.
PYRAZINAMIDE: rarely thrombocytopenia and sidroblastic anemia with erythroid hyperplasia, vacuolation of erythrocytes and increased iron concentration and disturbances in clotting mechanism.

GIT

RIFAMPICIN : heartburn, gastric distress, nausea, vomiting, anorexia, muscle cramps & diarrhoea. ISONIAZID : epigastric distress, constipation & dryness of the mouth.
ETHAMBUTOL HCl : heartburn, epigastric distress, nausea, vomiting, abdominal pain, cramps, anorexia and diarrhoea.
PYRAZINAMIDE : nausea, vomiting and diarrhoea.

Liver

RIFAMPICIN :rarely hepatitis or a shock like syndromes with jaundice alongwith elevated serum bilirubin, BSPP, alkaline phosphatase and transaminase activity when given with isoniazid.
ISONIAZID: severe to fatal hepatitis occurring frequently in old age patients enhanced by use of alcohol.
ETHAMBUTOL HCl : transient impairment of liver resulting in hyperuricemia alongwith elevated serum uric acid level and precipitation of acute gout.
PYRAZINAMIDE : dose related hepatotoxicity.

Kidney

RIFAMPICIN : elevation in BUN and serum uric acid level, rarely hemoglobinuria, hematuria and renal insufficiency usually occur in intermittent therapy.
ISONIAZID : prostatic obstruction and urinary retention.

Allergy

RIFAMPICIN : rash, urticaria, pruritis, pemphigoid reactions and soreness of the buccal cavity. ISONIAZID : rash, urticaria, skin eruption, morbilliform, maculopaulor & purpuria.
ETHAMBUTOL HCl : anaphylactoid reactions, dermatitis & pruritis.
PYRAZINAMIDE: rash, urticaria, pruritis, acne, photosensitivity, prophyria and dysuria.