occurs with concomitant administration of rifampicin and ethambutol-HCl.
Isoniazid-thrombocytopenia, eosinophilia, agranulocytosis, anemia, methemoglobinemia, vasculitis and arthralgia.
Pyrazinamide-rarely thrombocytopenia and sidroblastic anemia with erythroid hyperplasia, vacuolation of erythrocytes and increased iron concentration and disturbances in clotting mechanism.

Rifampicin-heartburn, gastric distress, nausea, vomiting, anorexia, muscle cramps and diarrhoea.
Isoniazid-epigastric distress, constipation and dryness of the mouth.
Ethambutol-HCl-heartburn, epigastric distress, nausea, vomiting, abdominal pain, cramps, anorexia and diarrhoea.
Pyrazinamide-nausea, vomiting and diarrhoea.

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.

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.

Rifampicin-rash, urticaria, pruritis, pemphigoid reactions and soreness of the buccal cavity.
Isoniazid-rash, urticaria, skin eruption, morbilliform, maculopaulor and purpuria.
Ethambutol-HCl-anaphylactoid reactions, dermatitis and pruritis.
Pyrazinamide-rash, urticaria, pruritis, acne, photosensitivity, prophyria and dysuria.

DAILY DOSAGE RANGE
WHO-RECOMMENDATIONS

Rifampicin	08-12 mg/Kg maximum 600mg/day.
Isoniazid	05-10 mg/Kg maximum 300mg/day.
Ethambutol-HCl	15-25 mg/Kg.
Pyrazinamide	20-35 mg/Kg maximum 3g/day.

The patients should be given 1 tablet/10 Kg body weight for RIFA-4 and 1 tablet/15 Kg body weight for RIFATOL according to the following chart one to two hours before meal or as directed by the physician.

Rifa-4 *For initial intensive phase*		Rifatol *For continuation phase*	
Weight	**TABLETS**	**Weight**	**TABLETS**
30-39 Kg	3	30-39 Kg	2
40-49 Kg	4	40-49 Kg	3
50 Kg & Above	5	50 Kg & Above	4

Because of the potential toxicity RIFA-4 and RIFATOL 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, and 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.
Protect from heat and sunlight.
Store in a dry place.
Keep all medicines out of the reach of children.
Use on prescription only.

PRESENTATION:
RIFA-4 *film coated tablets are available in* (10 x 10) blister pack tablets.
RIFATOL *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.

Rifa-4® TABLETS

For initial intensive phase of tuberculosis

COMPOSITION :
Each film coated tablet contains;
Rifampicin U.S.P. ..... 120 mg.
Isoniazid U.S.P. ..... 60 mg.
Ethambutol HCl U.S.P. ... 225 mg.
Pyrazinamide U.S.P. ..... 300 mg.

Rifatol® TABLETS

For continuation phase of tuberculosis

COMPOSITION :
Each film coated tablet contains;
Rifampicin U.S.P. ..... 150 mg.
Isoniazid U.S.P. ..... 75 mg.
Ethambutol HCl U.S.P. ..... 300 mg.

"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.
(Approaching tuberculosis treatment in the 1990's. J.A. Sbarbaro, M.D. Iseman " University of Colorado School of Medicine, Denver Colorado, USA.)

CLINICAL PHARMACOLOGY
RIFAMPICIN
First-line primary anti-tuberculosis agent given in combination with other anti-turberculosis 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 attained 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** and **RIFATOL** are taken on an empty stomach at least 30 min. 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 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 has 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 drugs 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. and about 4-14% of the drug is eliminated unchanged.

INDICATIONS
RIFA-4 is recommended during the initial intensive phase for two to three months of pulmonary and extra-pulmonary tuberculosis administered on a daily continuous basis. When required other anti-tuberculosis drugs i.e. streptomycin may be added.
RIFATOL is recommended for the continuation phase for four to six months administered on a daily continuous basis. RIFATOL can also be used for initial intensive phase in combination with other anti-tuberculosis drugs i.e. pyrazinamide or streptomycin.

CONTRA-INDICATIONS
RIFA-4 and RIFATOL is not recommended in patients with ;
- hypersensitivity to rifampicin, isoniazid, ethambutol-HCl, and pyrazinamide including drug related hepatitis.
- visual defects such as cataracts, recurrent inflammatory conditions of the eyes, optic neuritis and diabetic retinopathy require full ophthalmic examination including visual acuity, colorvision, perimetry and ophthalmoscopy before the start and periodically thereafter during the treatment if clinical judgment demands its use. Snellen eye charts are recommended for testing of visual acuity. All patients receiving ethambutol-HCl should be inquired periodically about blurred vision and other subjective eye symptoms.
- acute hepatic disorders since an increased risk may exist for individuals with liver disease, benefits must be weighed carefully against further liver damage.
- renal dysfunction which require dosage adjustment determined by the blood levels of ethambutol-HCl since main excretory path is by kidney.
- epileptic seizure or psychotic states characterized by mania or hypomania.

PRECAUTIONS
* Regular monitoring of organ system functioning including renal, hepatic and hematopoietic should be assessed during long-term treatment.
* Acute gout or *diabetes mellitus* leads to management problems with pyrazinamide.
* Intermittent therapy is not recommended to avoid rifampicin mediated renal hypersensitivity.
* 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.
* The metabolism of the drug is racial determined occurring rapidly in the majority of Eskimos and Orientals whereas slowly in about 50% of Blacks and Caucasians. The rate of inactivation does not significantly alter the effectiveness of isoniazid. However, slow detoxification may lead to high blood levels of the drug resulting in INH-toxicity.

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, digitoxin, quinidine, disopyramide, dapsone and 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.
- Due to interference in the microbiological estimation of serum folate and cyanocobalamine by rifampicin at therapeutic levels therefore, alternative methods may be considered.

USE IN PREGNANCY AND LACTATION
- No well-controlled study data is available on RIFA-4, RIFATOL or their 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 and 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 foetus.

SIDE EFFECTS

Rifampicin-visual disturbances.
Isoniazid-optic neuritis and atrophy.
Ethambutol-HCl-decrease in visual acuity due to optic neuritis.

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.

Rifampicin-thrombocytopenia, eosinophilia, transient leukopenia, hemolytic anemia and reduced haemoglobin level. Thrombocytopenia