RIFAMPICIN + ISONIAZID + PYRAZINAMIDE + ETHAMBUT OL HCI

QUADTAB™

150 mg / 75 mg / 400 mg / 2 75 mg FILM-C OATED TABLET

ANTITUBER CULOSIS

FORMULATION
Each film-coated tablet contains:
Rifampicin ..... 150 mg
Isoniazid ..... 75 mg
Pyrazinamide ..... 400 mg
Ethambutol HCl ..... 275 mg

℞

PRODUCT DESCRIPTION
Rifampicin + Isoniazid + Pyrazinamide + Ethambutol HCl (Quadtab™) Tablet is a red, elliptical, film-coated tablet, bisected on one side and plain on the other side.

PHARMACODYNAMICS
Rifampicin
Rifampicin, a semisynthetic antibiotic derivative of Rifamycin, suppresses bacterial ribonucleic acid (RNA) synthesis by binding to the ß subunit of deoxyribonucleic acid (DNA)-dependent RNA polymerase, thus inhibiting the attachment of the enzyme to DNA, blocking RNA transcription, elongation, and subsequent translation to protein. It does not inhibit the counterpart mammalian enzyme.

Rifampicin has bactericidal action and potent sterilizing effect against both intracellular and extracellular tubercle bacilli. Cross resistance has been shown only with other Rifamycin derivatives.

Isoniazid
Isoniazid kills actively growing tubercle bacilli by inhibiting the biosynthesis of mycolic acid which is the major component of the cell wall of *Mycobacterium tuberculosis*. It is active against susceptible bacteria only when they are undergoing cell division.

Pyrazinamide
Pyrazinamide is the pyrazine analog of nicotinamide. The precise mechanism of action of Pyrazinamide is unknown. Its metabolite, pyrazinoic acid, which is less active *in vitro*, may possibly be involved in Pyrazinamide's *in vivo* activity.

Pyrazinamide is an effective bactericidal antituberculosis drug, and has a specific sterilizing action against *Mycobacterium tuberculosis* in the intracellular environment of macrophages. The acid environment presumably in some way makes *Mycobacterium tuberculosis* more susceptible to Pyrazinamide, but this does not occur with *Mycobacterium bovis* which is resistant to the drug. As with other antituberculosis drugs, resistance to Pyrazinamide develops rapidly if it is used alone to treat human tuberculosis.

Ethambutol HCl
Ethambutol HCl diffuses into actively growing Mycobacteria cells such as tubercle bacilli. It inhibits the synthesis of one or more metabolites resulting in impaired cellular metabolism, arrested cell multiplication and cell death. It is active against susceptible bacteria only when they are undergoing cell division. No cross-resistance with other agents has been demonstrated.

PHARMACOKINETICS
Rifampicin
Rifampicin is completely absorbed from the gastrointestinal tract. Following a single oral dose of 600 mg rifampicin in healthy fasting adults, peak plasma concentrations averaged 7 mcg/mL and were attained within 2 to 4 hours. However, there is considerable interpatient variation, and peak plasma concentrations of rifampicin may range from 4 to 32 mcg/mL. If rifampicin is administered with food, peak plasma concentrations may be slightly reduced and delayed.

Rifampicin is widely distributed in most body tissues and fluids. Its diffusion into the cerebrospinal fluid (CSF) is increased when the meninges are inflamed. It crosses the placenta and is distributed into milk. Rifampicin has a half-life of 2 to 5 hours, the longest elimination time occurring after large doses. Its half-life is prolonged in patients with liver disease.

Rifampicin is metabolized in the liver by deacetylation. It undergoes enterohepatic circulation and is largely reabsorbed, but the metabolite is not. Excretion is mainly via the biliary tract; 3 to 30% of Rifampicin 600 mg single oral dose is excreted in the urine as unchanged drug and active metabolite within 24 hours. Approximately 60% of Rifampicin is excreted in the feces.

Isoniazid
Isoniazid is readily absorbed from the gastrointestinal tract. Peak concentrations of about 3 to 7 mcg/mL appear in blood 1 to 2 hours following an oral fasting dose of 300 mg isoniazid. When administered orally with food, the extent of absorption and peak plasma concentrations may be reduced.
Isoniazid is distributed into all body tissues and fluids. Cerebrospinal fluid (CSF) concentrations of Isoniazid are reported to be 90% to 100% of concurrent plasma concentrations. Isoniazid is not substantially bound to plasma proteins. It passes through the placental barrier and into breast milk in concentrations comparable to those in plasma.

The plasma half-life of Isoniazid in patients with normal renal and hepatic function ranges from 1 to 4 hours depending on the rate of metabolism. The plasma half-life may be prolonged in patients with impaired hepatic function or severe renal impairment.

Isoniazid is inactivated in the liver, mainly by acetylation and dehydrazination. Metabolites of the drug include acetylisoniazid, isonicotinic acid, monoacetylhydrazine, diacetylhydrazine, and isonicotinyl glycine. The rate of acetylation is genetically determined and is subject to individual variation. About 50% of Africans, Americans and Caucasians are slow acetylators; the majority of native Alaskans and Orientals are rapid acetylators. The rate of acetylation does not significantly alter the effectiveness of Isoniazid. However, slow acetylation may lead to higher blood levels of the drug, and thus to an increase in toxic reactions.
Approximately 75 to 96% of a 5 mg/kg oral dose of Isoniazid is excreted as unchanged drug and metabolites in the urine within 24 hours.

Pyrazinamide
Pyrazinamide is well absorbed from the gastrointestinal tract and attains peak plasma concentrations within 2 hours. Plasma concentrations generally range from 30 to 50 mcg/mL with doses of 20 to 25 mg/kg. When administered orally with food, the extent of absorption and peak plasma concentrations of the drug may be reduced.
Pyrazinamide is widely distributed in body tissues and fluids including the liver, lungs and cerebrospinal fluid (CSF). The CSF concentration is approximately equal to concurrent steady-state plasma concentrations in patients with inflamed meninges. Pyrazinamide's half-life is 9 to 10 hours in patients with normal renal and hepatic function and may be prolonged in patients with impaired renal and hepatic function. Pyrazinamide is hydrolyzed in the liver to its major active metabolite, pyrazinoic acid. Pyrazinoic acid is hydrolyzed to the main excretory product, 5-hydroxy-pyrazinoic acid which is excreted through the kidneys. Approximately 70% of an oral dose is excreted in the urine within 24 hours mainly by glomerular filtration.

Ethambutol HCl
About 80% of an oral Ethambutol dose is absorbed from the gastrointestinal tract and the remainder appears in the feces unchanged. Absorption is not significantly impaired by food. After a single dose of 25 mg/kg body weight, peak plasma Ethambutol concentrations of up to 5 mg/L appear within 4 hours and are less than 1 mg/L by 24 hours.
Ethambutol is distributed to most tissues, including the lungs, kidneys and erythrocytes. It diffuses into the CSF when the meninges are inflamed. The elimination half-life after oral administration is about 3 to 4 hours.
Ethambutol is partially metabolized in the liver. Most of a dose appears in the urine within 24 hours as unchanged drug and 8 to 15% as the inactive metabolites. About 20% of the dose is excreted unchanged in the feces. Marked accumulation may occur with renal insufficiency.

INDICATIONS
For the initial phase treatment of all forms of pulmonary and extrapulmonary tuberculosis.

DOSAGE AND ADMINISTRATION
The recommended anti-TB treatment regimen is based on the TB Diagnostic Category
Rifampicin + Isoniazid + Pyrazinamide + Ethambutol HCl (Quadtab) Tablet is for a 2-month initial phase treatment and should be followed by a 3-drug (e.g., Rifampicin + Isoniazid + Ethambutol HCl) or 2-drug (e.g., Rifampicin + Isoniazid), 4-month or longer continuation phase for the treatment of tuberculosis. Continue treatment if patient is still sputum or culture positive, or if resistant organisms are present.

Usual Adult Dose: Orally, once daily, either one hour before or two hours after a meal.

Patient's Body Weight (kg)	Once Daily Dose
30 to 39	2 tablets
40 to 54	3 tablets
55 to 70	4 tablets
71 and higher	5 tablets

Recommended Dosing for Essential Antituberculosis Drugs

Drugs	Dosage (mg/kg body weight)	
	Daily	3 times weekly
Isoniazid (H)	5 (range: 4 to 6) Daily maximum: 300 mg	10 (range: 8 to 12)
Rifampicin (R)	10 (range: 8 to 12) Daily maximum: 600 mg	10 (range: 8 to 12) Daily maximum: 600 mg
Pyrazinamide (Z)	25 (range: 20 to 30)	35 (range: 30 to 40)
Ethambutol HCl (E)	15 (range: 15 to 25)	30 (range: 20 to 35)
Streptomycin (S)	15 (range: 12 to 18)	15 (range: 12 to 18)

Recommended Treatment Regimens for each Diagnostic Category
(adapted from the WHO Treatment of Tuberculosis: Guidelines for National Programmes, 3rd Edition, revised Chapter 4 June 2004)

TB Diagnostic Category	TB Patients	TB Treatment regimens[i]	
		Initial Phase	Continuation Phase
I	New smear-positive patients; New smear-negative PTB with extensive parenchymal involvement; Concomitant HIV disease or severe forms of EPTB[ii]	**Preferred** 2 HRZE [iii]	**Preferred** 4 HR 4 $(HR)_3$
		Optional 2 $(HRZE)_3$ or 2 HRZE [iv]	**Optional** 4 $(HR)_3$ or 6 HE [v]
II	Previously treated sputum smear-positive PTB: • Relapse; • Treatment after default	**Preferred** 2 HRZES / 1 HRZE [vi]	**Preferred** 5 HRE [vi]
		Optional 2 $(HRZES)_3$/ 1 $HRZE_3$	**Optional** **5** $(HRE)_3$
	• Treatment failure category I [vii] In settings with: • Adequate program performance; • Representative DRS data showing high rates of MDR TB and/or capacity for DST of cases; • Availability of Category IV regimens	Specially designed standardized or individualized regimens are often needed for these patients	
	In settings where • Representative DRS data show low rates of MDR TB or individualized DST shows drug-susceptible disease or In settings of • Poor program performance; • Absence of representative DRS data; • Insufficient resources to implement Category IV treatment	**Preferred** 2 HRZES / 1 HRZE	**Preferred** 5 HRE [vi]
		Optional 2 $(HRZES)_3$/ 1 $HRZE_3$	**Optional** 5 $(HRE)_5$
III	New smear-negative PTB (other than Category I) and less severe form of EPTB	**Preferred** 2 HRZE [viii]	**Preferred** 4 HR 4 $(HR)_3$
		Optional 2 $(HRZES)_3$ or 2 HRZE	**Optional** 4 $(HR)_3$ or 6 HE
IV	Chronic (still sputum-positive after supervised re-treatment); proven or suspected MDR TB cases [ix]	Specially designed standardized or individualized regimens	

i Numbers preceding regimens indicate length of treatment (months). Subscripts following regimens indicate frequency of administration (days per week). When no subscripts are given, the regimen is daily. Direct observation of drug intake is always required during the initial phase of treatment and strongly recommended when Rifampicin is used in the continuation phase and required when treatment is given intermittently. FDCs are highly recommended for use in both the initial and continuation phases of treatment.
ii Severe forms of EPTB are the following: meningeal, pericardial, peritoneal, bilateral or extensive pleural effusive, spinal, intestinal, and genitourinary.
iii Streptomycin may be used instead of Ethambutol. In tuberculous meningitis, Ethambutol should be replaced by streptomycin.
iv Intermittent initial phase therapy is not recommended when the continuation phase of Isoniazid and Ethambutol is used.
v This regimen may be considered in situations where the preferred regimen cannot be applied as recommended. However, it is associated with a higher rate of treatment failure and relapse compared with the 4 HR continuation phase regimen. Intermittent initial phase treatment is not recommended when followed by the 6 HE continuation phase regimen.
vi Daily treatment is preferred. However, thrice weekly treatment during the continuation phase or during both phases is an acceptable option.
vii Treatment failures may be at risk of MDR TB, particularly if Rifampicin was used in the continuation phase. Drug susceptibility testing is recommended for these cases if available. Treatment failures with known or suspected MDR TB should be treated with a Category IV regimen.
viii Ethambutol in the initial phase may be omitted for patients with limited, non-cavitary, smear-negative pulmonary TB who are known to be HIV-negative, patients with less severe forms of extrapulmonary TB, and young children with primary TB.
ix Drug susceptibility testing is recommended for patients who are contacts of MDR TB patients.

Legend:
PTB - Pulmonary Tuberculosis
EPTB - Extrapulmonary Tuberculosis
MDR-TB - Multidrug-resistant Tuberculosis
FDC - Fixed-Dose Combination
HIV - Human Immunodeficiency Virus
DRS - Drug-Resistance Surveillance
DST - Individualized Susceptibility Testing

Patient Information
- Take medication on regular basis; avoid missing doses. Do not discontinue therapy except on advice of physician.
- Medication may cause a reddish-orange discoloration of the urine, stools, saliva, tears, sweat and sputum. This is to be expected and is not harmful. Soft contact lenses may be permanently stained.
- Notify physician promptly if any of the following symptoms are experienced: fever, loss of appetite, malaise, nausea and vomiting, darkened urine, yellowish discoloration of the skin and eyes, pain or swelling of the joints.

CONTRAINDICATIONS
· Hypersensitivity to rifampicin, isoniazid, pyrazinamide, and ethambutol, or to any ingredient of the product
· Jaundice or severe liver disease
· Concurrent administration of saquinavir and ritonavir
· Acute liver disease
· History of previous isoniazid-associated liver injury
· History of severe adverse reactions to Isoniazid, including severe hypersensitivity reactions or drug fever, chills, and arthritis
· Acute gout
· Pre-existing optic neuritis from any cause

WARNINGS AND PRECAUTIONS
Rifampicin, Isoniazid and Pyrazinamide have been associated with liver dysfunction. Use with caution and under strict medical supervision in patients with impaired liver function. Carefully monitor liver function [i.e., alanine aminotransferase (ALT) and aspartate aminotransferase (AST)] prior to therapy and then every 2 to 4 weeks during therapy. Discontinue product if signs of hepatocellular damage occur.

Discontinue product and evaluate at the first sign of hypersensitivity reaction. If the product must be reinstituted, give only after symptoms have cleared and only under the supervision of a physician.

Rifampicin
Rifampicin should be used with caution in patients with a history of diabetes mellitus, as diabetes management may be more difficult. Hyperbilirubinemia may occur in the first 2 or 3 weeks of treatment. Moderate increases in bilirubin and/or transaminase levels are not indications to discontinue Rifampicin.
Thrombocytopenia has been reported with high dose Rifampicin intermittent therapy and after resumption of interrupted treatment. This effect is reversible if the drug is discontinued as soon as purpura occurs. However, the continuation of Rifampicin administration after the appearance of purpura may lead to cerebral hemorrhage and fatalities.
Rifampicin has been associated with porphyria exacerbation and is considered unsafe in porphyric patients.
As with any potent drug, periodic assessment of organ system functions, including renal, hepatic, and hematopoietic, should be made during long-term therapy.

Isoniazid
Isoniazid should be used with caution in patients with convulsive disorders, history of psychosis, chronic liver disease or severe renal impairment, daily users of alcohol, individuals who inject illicit drugs, and those with a history of prior therapy in whom isoniazid was discontinued because of adverse effects related to the drug.
Periodic ophthalmologic examinations should be performed in patients who develop visual symptoms while receiving Isoniazid, and periodically thereafter, even without the occurrence of visual symptoms.
Isoniazid should be used with caution in patients who are at risk of neuropathy or pyridoxine deficiency, including those who are diabetic, alcoholic, malnourished, uremic, pregnant, or infected with HIV. Prophylactic doses of 10 to 50 mg pyridoxine a day have been recommended.

Pyrazinamide
Caution should be observed in patients with renal impairment. Pyrazinamide inhibits renal excretion of urates frequently resulting in hyperuricemia, which is usually asymptomatic. If hyperuricemia is accompanied by acute gouty arthritis, Pyrazinamide should be discontinued.
Pyrazinamide should be used with caution in patients with a history of diabetes mellitus, as diabetes management may be more difficult.

Ethambutol HCl
Ethambutol HCl may damage vision. Test vision before and regularly during administration. Ethambutol may cause optic neuritis, which causes eye pain, decreased visual acuity, general loss of vision, central and peripheral constriction of visual fields, and loss of red/green color perception.
If the patient has any indication that the perception of color or sight is deteriorating, treatment must be stopped immediately and a physician consulted. Do not give Ethambutol to any patient too young to understand this warning or who cannot communicate any visual problems (usually < 6 years old).
Whenever possible, assess renal function before and regularly during treatment. Patients with renal impairment may have increased serum concentration and prolonged half-life of ethambutol. In patients with renal impairment, reduce Ethambutol dose according to the drug serum concentration.
Ethambutol may precipitate attacks of gout.

INTERACTIONS WITH OTHER MEDICAMENTS
Rifampicin
Agents that decrease the effects of Rifampicin: Drugs that reduce gastric motility (e.g., anticholinergics, opioids), aminosalicylic acid preparations, and clofazimine.
Rifampicin decreases the effects of the following: Anti-arrhythmic agents: disopyramide, mexiletine, quinidine; Antibacterials: chloramphenicol, clarithromycin, dapsone, doxycycline, fluoroquinolones (ciprofloxacin); Anticonvulsants: phenytoin; Antifungal agents: ketoconazole, fluconazole, itraconazole; Antipsychotic agents: clozapine, haloperidol; Antiretroviral agents: saquinavir, ritonavir, delavirdine, zidovudine; Barbiturates; Benzodiazepines: diazepam, midazolam, triazolam; Beta-blockers: propranolol, bisoprolol; Calcium-channel blockers: diltiazem, nifedipine, verapamil; Cardiac glycosides: digitoxin, digoxin; Corticosteroids; Estrogens; Immunosuppressive agents: ciclosporin, tacrolimus; Narcotic analgesics: methadone; Oral anticoagulants: coumarins; Oral antidiabetic agents: sulfonylureas, chlorpropamide, rosiglitazone; Oral or other systemic hormonal contraceptives; Progestins; Quinine; Theophyllines; Tricyclic anti-depressants: amitriptyline, nortriptyline

Other Drug Interactions:
Halothane or Isoniazid when co-administered with Rifampicin may result in a higher rate of hepatotoxicity than with either agent alone. If alterations in liver function tests occur, consider discontinuation of one or both drugs.

Concurrent administration with antacids may decrease Rifampicin absorption. Therefore, administer Rifampicin at least 1 hour before ingestion of antacid.

A drug-induced lupus-like syndrome consisting of malaise, myalgia, arthritis, peripheral edema, and positive antinuclear antibody (ANA) test results have been noted in patients receiving Rifampicin concomitantly with Clarithromycin and/or Ciprofloxacin.

Antiretroviral drugs, i.e., HIV protease inhibitors and nonnucleoside reverse transcriptase inhibitors (NNRTIs), interact with Rifampicin leading to ineffectiveness of either drug or increased risk of toxicity.

Rifampicin increases the requirements for anticoagulants of the coumarin type. Prothrombin time must be performed frequently or as often as necessary in patients receiving Rifampicin and anticoagulants concurrently to maintain the required dose of the anticoagulant.

Rifampicin decreases plasma concentrations of 25-hydroxy vitamin D (the major circulating vitamin D metabolite) and 1α,25-dihydroxy vitamin D. There have been reports of decreased plasma concentrations of vitamin D metabolites accompanied by decreased plasma calcium and phosphate concentrations and increased parathyroid hormone concentrations.

Drug/Laboratory Interactions:
Rifampicin interferes with standard microbiological assays for serum folate and vitamin B_{12}. Therefore, consider alternate assay methods in patients taking Rifampicin.

Abnormalities in liver function tests (e.g., elevation in serum bilirubin, alkaline phosphatase and serum transaminases) and decreases in biliary excretion of contrast media used for gallbladder visualization have been observed. These tests should be performed before taking Rifampicin in the morning.

Isoniazid
Isoniazid inhibits the metabolism of the following drugs: anticonvulsants (e.g., Carbamazepine, Phenytoin), benzodiazepines (e.g., Diazepam, Triazolam), Haloperidol, Ketoconazole, and Theophylline.

Isoniazid has been associated with increased concentrations or toxicity of Clofazimine and Warfarin.

Concomitant antacid administration may reduce Isoniazid absorption. Isoniazid should be administered at least 1 hour before the antacid.

Corticosteroids may decrease the serum concentration of Isoniazid by increasing acetylation rate and/or renal clearance. Para-aminosalicylic acid may competitively inhibit N-acetylation of Isoniazid, thus, increasing Isoniazid serum concentrations and elimination half-life.

The central nervous system (CNS) effects of Meperidine (drowsiness), Cycloserine (dizziness and drowsiness), and Disulfiram (acute behavioral and coordination changes) may be exaggerated when concomitantly administered with Isoniazid. Concurrent administration with Levodopa may produce symptoms of excess catecholamine stimulation (agitation, flushing, and palpitations) or lack of Levodopa effect.

Isoniazid may produce hypoglycemia and lead to loss of glucose control in patients on oral hypoglycemics.

Fast acetylation of Isoniazid may produce high concentrations of hydrazine which facilitates defluorination of Enflurane resulting in nephrotoxicity.

Drug/Laboratory Interaction:
Isoniazid may cause false-positive results with cupric sulfate solution for urine glucose determinations.

Pyrazinamide
Pyrazinamide interferes with oral antidiabetics or with medicines taken for the treatment of gout.

Probenecid blocks the excretion of Pyrazinamide. Pyrazinamide decreases the effects of probenecid.

Drug/Laboratory Interactions:
Pyrazinamide may interfere with acetest and ketostix qualitative urine tests for ketones, producing a pinky-brown color.

Ethambutol HCl
Aluminum salts found in antacids may delay and reduce the absorption of Ethambutol HCl. Separate their administration by several hours.

STATEMENT ON USAGE FOR HIGH RISK GROUPS
PREGNANCY AND LACTATION
Pregnancy: **Pregnancy Category C.**
The effect of Rifampicin on the human fetus is not known. Rifampicin crosses the placental barrier and appears in cord blood. An increase in congenital malformations, primarily spina bifida and cleft palate, has been reported in the offspring of rodents given oral doses of 150 to 250 mg/kg/day of Rifampicin during pregnancy. Rifampicin can cause postnatal hemorrhages in the mother and infant, for which treatment with Vitamin K may be indicated. Isoniazid exerts an embryocidal effect in both rats and rabbits, but no Isoniazid-related congenital anomalies have been found in reproduction studies in mammalian species. If Isoniazid is administered during pregnancy, concomitant administration of Pyridoxine 25 mg daily is recommended. The use of Pyrazinamide and Ethambutol HCl in pregnancy has not been established. The product should be used in pregnancy only if the potential benefit justifies the potential risk to the fetus.

Lactation: Rifampicin, Isoniazid, Pyrazinamide, and Ethambutol HCl appear in breast milk. Therefore, do not administer to breastfeeding women unless, in the opinion of a physician, the potential benefit of the drug justifies the possible risk to the baby.

GERIATRICS
Rifampicin
Dose adjustment is necessary in elderly patients with impaired liver function.

Isoniazid
The risk of toxic liver damage from Isoniazid treatment increases with age in both sexes. Achievement of safe and effective therapy in patients with acute and chronic liver disease may require adjustment of Isoniazid dosage and if possible, monitoring of serum Isoniazid concentrations.

Pyrazinamide
Dosage of Pyrazinamide should be selected carefully starting at the low end of the dosage range because the elderly frequently have decreased liver and/or renal function and concomitant disease and drug therapy.

Ethambutol HCl
Ethambutol should be used with caution in the elderly because of the special risk of toxicity, as they may have impaired renal function and impaired vision.

UNDESIRABLE EFFECTS
Rifampicin
Hepatic: Elevations in serum concentrations of alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin, and alkaline phosphatase, asymptomatic jaundice, and hepatitis. Rarely, hepatitis or shock-like syndrome with liver involvement and abnormal liver function test results.
Local, Sensitivity and Dermatologic: Hypersensitivity reactions characterized by a flu-like syndrome (i.e., fever, chills, sometimes with headache, dizziness, and bone pain, shortness of breath, and malaise), edema of face and extremities, hypotension, shock, dyspnea, wheezing, rash, pruritus, urticaria, acneiform eruptions, pemphigoid reaction, erythema multiforme including Stevens-Johnson syndrome, Lyells syndrome, toxic epidermal necrolysis, vasculitis, exfoliative dermatitis, flushing, and rarely, anaphylaxis.
Nervous system: Headache, drowsiness, fatigue, dizziness, inability to concentrate, mental confusion, behavioral changes, psychosis, and generalized numbness.
Gastrointestinal: Heartburn, epigastric distress, nausea, vomiting, anorexia, abdominal cramps, flatulence, diarrhea, sore mouth and tongue, pseudomembranous colitis, and pancreatic insufficiency.
Musculoskeletal: Ataxia, muscular weakness, myopathy, and pain in muscles, joints and extremities.
Hematologic: Thrombocytopenia, eosinophilia, leukopenia, purpura, hemolytic anemia, hemolysis, hemoglobinuria, decreased hemoglobin concentrations, disseminated intravascular coagulation, agranulocytosis, and cerebral hemorrhage.
Renal: Increased blood urea nitrogen (BUN) and serum uric acid concentrations, hemoglobinuria, light chain proteinuria, hematuria, renal insufficiency, interstitial nephritis, acute tubular necrosis, and acute renal failure.
Endocrine: Precipitation of adrenocortical insufficiency and menstrual disturbances.
Ophthalmologic: Visual disturbances, eye irritation, and exudative conjunctivitis.

Isoniazid
Hepatic: Mild liver dysfunction, as evidenced by mild and transient elevations in serum concentrations of alanine aminotransferase (ALT), aspartate aminotransferase (AST) and bilirubin concentrations. Rarely, progressive liver dysfunction, bilirubinuria, jaundice, and severe and sometimes fatal hepatitis.
Hypersensitivity: Fever, skin eruptions (morbilliform, maculopapular, purpuric, or exfoliative), lymphadenopathy, vasculitis, and, rarely, hypotension.
Nervous system: Seizures, toxic encephalopathy, stupor, euphoria, memory impairment, separation of ideas and reality, loss of self-control, dizziness, vertigo, and toxic psychosis.
Gastrointestinal: Nausea, vomiting, constipation, and epigastric distress.
Musculoskeletal: Ataxia and muscle twitching.
Hematologic: Agranulocytosis, eosinophilia, thrombocytopenia, methemoglobinemia, and hemolytic, sideroblastic, or aplastic anemia.
Endocrine: Hyperglycemia and metabolic acidosis.
Ophthalmologic: Optic neuritis and atrophy.
Others: Tinnitus, peripheral neuritis usually preceded by paresthesia of the feet and hands, dryness of the mouth, Pyridoxine deficiency, pellagra, hyperreflexia, urinary retention, gynecomastia, systemic lupus erythematosus-like syndrome, and rheumatic syndrome with arthralgia.

Pyrazinamide
Hepatic: Hepatotoxicity appears to be dose-related, and may appear at any time during therapy. Transient increases in serum concentrations of alanine aminotransferase (ALT) and aspartate aminotransferase (AST), jaundice, hepatitis, liver tenderness, and hepatomegaly have been reported.
Dermatologic: Hypersensitivity reactions, including rash, urticaria, and pruritus have been reported. Rarely, maculopapular rash, acne and photosensitivity with reddish-brown discoloration of exposed skin.
Gastrointestinal: Nausea, vomiting, anorexia, and aggravation of peptic ulcer.
Hematologic: Rarely, porphyria, thrombocytopenia and sideroblastic anemia with erythroid hyperplasia, vacuolation of erythrocytes, increased serum iron concentration, and adverse effects on blood clotting mechanisms.
Renal: Dysuria and interstitial nephritis.
Others: Fever, splenomegaly, malaise, and frequently mild arthralgia and myalgia
Hyperuricemia commonly occurs and may lead to attacks of gout.

Ethambutol HCl
Hepatic: Cholestatic jaundice, which appeared to be caused by Ethambutol, has been reported in at least one patient who received the drug both alone and in combination with Streptomycin. Transient impairment of liver function, as indicated by abnormal liver function tests, and jaundice have been observed.
Dermatologic and Hypersensitivity: Dermatitis, erythema multiforme, skin rashes, and pruritus have been reported. Rarely, anaphylactoid reactions, Stevens-Johnson syndrome, and toxic epidermal necrolysis.
Nervous system: Headache, dizziness, mental confusion, disorientation, possible hallucinations.
Gastrointestinal: Gastrointestinal upset, abdominal pain, nausea, vomiting, and anorexia have occurred occasionally.
Hematologic: Thrombocytopenia, leukopenia and eosinophilia.
Ophthalmologic: Optic neuritis with decreases in visual acuity, constriction of visual fields, central and peripheral scotomas, and loss of red-green color discrimination. The extent of ocular toxicity appears to be related to the dose and duration of treatment.
Others: Fever, malaise, joint pain, pulmonary infiltrates, elevated serum uric acid levels, precipitation of acute gout, and rarely, numbness and tingling of the extremities due to peripheral neuritis.

OVERDOSE AND TREATMENT
Signs and Symptoms of Overdose
Rifampicin
Symptoms of Rifampicin overdose include extensions of the common undesirable effects (e.g., nausea, vomiting, abdominal pain, pruritus, headache, increasing lethargy, brownish-red or orange discoloration of skin, urine, sweat, saliva, tears, and feces, and transient elevations in liver enzymes and/or bilirubin). Liver enlargement (possibly with tenderness), jaundice, rapid increases in total and direct serum bilirubin and liver enzymes, and loss of consciousness may develop after massive Rifampicin overdose. Patients with known liver disease may experience marked liver toxicity. In children, facial or periorbital edema has been reported. There have been reports of hypotension, sinus tachycardia, ventricular arrhythmias, seizures, and cardiac arrest in some cases of fatalities resulting from Rifampicin overdose. It is unlikely that Rifampicin will cause undesirable effects on the body's hematopoietic system, electrolyte concentration or acid-base balance.
Isoniazid
Overdosage of Isoniazid has produced nausea, vomiting, dizziness, slurred speech, blurred vision, and visual hallucinations. Symptoms usually occur within 30 minutes to 3 hours after ingestion of the drug. After marked overdosage, respiratory distress and CNS depression, progressing rapidly from stupor to coma, severe intractable seizures, metabolic acidosis, acetonuria, and hyperglycemia have occurred. If untreated or treated inadequately, Isoniazid overdosage may be fatal. Isoniazid-induced seizures are associated with decreased γ-aminobutyric acid (GABA) concentrations in the CNS resulting from inhibition by Isoniazid of brain pyridoxal-5-phosphate activity.
Pyrazinamide
Signs and symptoms of Pyrazinamide overdose include gastrointestinal disturbances, central nervous system (CNS) stimulation, acute liver damage, hyperuricemia, and, in severe cases, respiratory failure and coma.
Ethambutol HCl
Symptoms of Ethambutol overdosage include gastrointestinal disturbances, vomiting, anorexia, fever, headache, dizziness, hallucinations and/ or visual disturbances. No deaths caused by deliberate overdosage have been reported.
Treatment
Institute supportive and symptomatic therapy in cases of overdose. Emesis and gastric lavage may be appropriate if undertaken within a few hours of ingestion. After removing the gastric contents, activated charcoal slurry instilled into the stomach may help adsorb any drug remaining in the gastrointestinal tract. Hemodialysis can be beneficial.
In the management of Rifampicin overdosage, an antiemetic may be given to control nausea and vomiting. Active diuresis with measured intake and output may promote Rifampicin excretion. Bile drainage or hemodialysis may be initiated in patients with serious liver impairment lasting more than 24 to 48 hours. Improvement of impaired liver function and reversal of liver enlargement in patients with previously adequate liver function may occur within 72 hours.
In the management of Isoniazid overdosage, an airway should be secured and adequate respiratory exchange established immediately. Seizures may be controlled with intravenous administration of Diazepam or short-acting barbiturates and a dosage of Pyridoxine HCl equal to the amount of Isoniazid ingested. Generally, 1 to 4 g of Pyridoxine HCl is given intravenously followed by 1 g intramuscular administration every 30 minutes until the entire dose has been given. Intravenous Sodium bicarbonate may be administered to control metabolic acidosis and repeated as needed.
Forced osmotic diuresis should be initiated as soon as possible following Isoniazid overdosage to increase renal clearance of Isoniazid and should be continued several hours after clinical improvement to ensure complete clearance and prevent relapse.
In the management of Pyrazinamide overdosage, short acting barbiturates may be given for manifestations of CNS stimulation, artificial respiration and oxygen for respiratory failure, and analeptics for coma.

STORAGE CONDITIONS
Keep the product out of reach and sight of children. Store at temperatures not exceeding 30°C.

AVAILABILITY
Box of 100 tablets (in flex foil)

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

ADVERSE DRUG REACTION REPORTING STATEMENT
For suspected adverse drug reaction, seek medical attention immediately and report to the FDA at www.fda.gov.ph. **AND** Unilab at (+632) 858-1000 or productsafety@unilab.com.ph. By reporting undesirable effects, you can help provide more information on the safety of this medicine.

DR-XY28917
Date of Revision: 06/2018
Date of First Authorization: 07/2007
P300000021557
IN 13-012 UAP

Manufactured by AMHERST LABORATORIES, INC.
UNILAB Pharma Campus,Barangay Mamplasan
Biñan, Laguna, Philippines
for UNILAB, Inc.
No. 66 United Street, Mandaluyong City,Metro Manila, Philippines

Trusted Quality Healthcare