placenta. 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 severe hepatic impairment.

Rifampicin is rapidly metabolized in the liver mainly to active 25-0-deacetylrifampicin; rifampicin and deacetylrifampicin are excreted in the bile. Deacetylation diminishes intestinal reabsorption and increases fecal 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 900mg dose 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 renal impairment the half-life of rifampicin is not prolonged at doses of 600mg or less.

Isoniazid
Isoniazid is readily absorbed from the gastrointestinal tract. Peak concentrations of about 3 to 7 micrograms/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 distributes into all body tissues and fluids, including the CSF. It appears in fetal blood if given during pregnancy and is distributed into breast milk.
The plasma half-life for isoniazid ranges from about 1 to 6 hours, with shorter half-lives in fast acetylators. The primary metabolic route is the acetylation of isoniazid to acetylisoniazid by N-acetyltransferase found in the liver and small intestine.
Acetylisoniazid is then hydrolyzed to isonicotinic acid and monoacetylhydrazine; isonicotinic acid is conjugated with glycine to isonicotinyl glycine and monoacetylhydrazine is further acetylated to diacetylhydrazine. Some unmetabolised isoniazid have no tuberculostatic activity, and apart from possibly monoacetylhydrazine, they are also less toxic. The rate of acetylation of isoniazid and monoacetylhydrazine is genetically determined and there is a bimodal distribution of persons who acetylate them either slowly or rapidly.
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.

**PRECAUTIONS:**
Pyrazinamide
Pyrazinamide is contraindicated in patients with liver damage, although it can be used with care when the damage is not severe. Liver function should be assessed before and regularly during treatment.
Pyrazinamide should not be given to patients with acute gout or hyperuricaemia and should be used with caution in patients with a history of gout. Caution should also be observed in patients with renal impairment. Increased difficulty has been reported in controlling diabetes mellitus when diabetics are given pyrazinamide.

Rifampicin
Liver functions should be, checked before treatment with rifampicin and special care should be taken in alcoholic patients or those with pre-existing liver disease who require regular monitoring during theraphy. A self-limiting hyperbilirubinaemia may occur in the first 2-3 weeks of treatment. Alkaline phosphatase values may be raised moderately due to rifampicin's enzyme inducing capacity. When other liver function tests are within normal limits, hyperbilirubinaemia in the first few weeks or moderately elevated transaminase levels are not indications to withdraw rifampicin. However, dose adjustment is necessary when there is other evidence of hepatic impairment and treatment should be suspended when there is evidence of more serious liver toxicity.
Blood counts should be monitored during prolonged treatment and in patients with hepatic disorders, Should thrombocytopenia or purpura occur then rifampicin should be withdrawn permanently.
Use of rifampicin following interruption of treatment has been associated with increased risk of serious adverse effects.
Patients should be advised that rifampicin may colour feces, saliva, sweat, tears, urine and other body fluids orange-red.
Soft contact lenses may become permanently stained.

Isoniazid
Isoniazid should be used with caution in patients with convulsive disorders, a history of psychosis, or hepatic or renal impairment. Patients who are at risk of neuropathy or pyridoxine deficiency, including those who are diabetic, alcoholic, malnourished, uraemic, pregnant, or infected with HIV, should be given pyridoxine, usually in a dose of 10 mg daily, although up to 50mg daily may be used. If symptoms of hepatitis such as malaise, fatigue, anorexia, and nausea develop Isoniazid should be stopped pending evaluation.
Liver function should be checked before treatment with isoniazid and special care should be taken in alcoholic patients or those with pre-existing liver disease. Regular monitoring of liver function is recommended in patients with pre-existing liver disease, and isoniazid treatment should be suspended if serum aspartate aminotransferase concentrations are elevated to more than 3 times the normal upper limit or the bilirubin concentrations rises. When visual symptoms occur during isoniazid treatment periodic eye examinations have been suggested.

**WARNING:**
Pyrazinamide
Patients started on pyrazinamide should have baseline serum uric acid and liver function determinations. Those patients with preexisting liver disease or those at increased risk for drug related hepatitis (e.g., alcohol abusers) should be followed closely. Pyrazinamide should be discontinued and not be resumed if signs of hepatocellular damage or accompanied by an acute gouty arthritis appear.

Rifampicin
Rifampicin has been shown to produce liver dysfunction. Fatalities associated with jaundice have occurred in patients with liver disease and in patients taking rifampicin with other hepatotoxic agents. Patients with impaired liver function should be given rifampicin only in cases of necessity and then with caution and under strict medical supervision. In these patients careful monitoring of liver function, especially SGPT/ALT and SGOT/AST should be carried out prior to theraphy and then every 2 to 4 weeks during theraphy. If signs of hepatocellular damage occur, rifampicin should be withdrawn. In some cases, hyperbilirubinemia resulting from competition between rifampicin and bilirubin for excretory pathways of the liver at the cell level can occur in the early days of treatment. An isolated report showing a moderate rise in bilirubin and/or transaminase level is not in itself an indication for interrupting treatment; rather, the decision should be made after repeating the tests, noting trends in the levels, and considering them in conjunction with the patient's clinical condition. Rifampicin has enzyme-inducing properties, including induction of delta amino levulinic acid synthetase. Isolated reports have associated porphyria exacerbation with rifampicin administration.
The possibility of rapid emergence of resistant meningococci restricts the use of rifampicin to short-term treatment of the asymptomatic carrier state. Rifampicin is not to be used for the treatment of meningococcal disease.

Isoniazid
Severe and sometimes fatal hepatitis associated with isoniazid therapy has been reported and may occur or may develop even after many months of treatment. The risk of developing hepatitis is age related.
Therefore, patients given isoniazid should be carefully monitored and interviewed at monthly intervals. For persons 35 and older, in addition to monthly reviews, hepatic enzymes (specifically, AST and ALT (formerly SGOT and SGPT, respectively) should be measured prior to starting isoniazid therapy and periodically throughout treatment. Isoniazid-associated hepatitis usually occurs during the first three months of treatment. Usually, enzyme levels return to normal despite continuance of drug, but in some cases progressive liver dysfunction occurs.
If abnormalities of liver function exceed three to five times the upper limit of normal, discontinuation of isoniazid should be strongly considered. Liver function tests are not a substitute for a clinical evaluation at monthly intervals or for the prompt assessment of signs or symptoms of adverse reactions occurring between regularly scheduled evaluations. Patients should be instructed to immediately report signs or symptoms consistent with liver damage or other adverse effects. These include any of the following: unexplained anorexia, nausea, vomiting, dark urine, icterus, rash persistent paresthesias of the hands and feet, persistent fatigue, weakness or fever of greater than 3 days duration and/or abdominal tenderness, especially right upper quadrant discomfort. If these symptoms appear or if signs suggestive of hepatic damage are detected, isoniazid should be discontinued promptly, since continued use of the drug in these cases has been reported to cause a more severe form of liver damage. Patients with tuberculosis who have hepatitis attributed to isoniazid should be given appropriate treatment with alternative drugs. If isoniazid must be reinstituted, it should be reinstituted only after symptoms and laboratory abnormalities have cleared. The drug should be restarted in very small and gradually increasing doses and should be withdrawn immediately if there is any indication of recurrent liver involvement. Preventive treatment should be deferred in persons wilh acute hepatic diseases.

**DRUG INTERACTIONS:**
Pyrazinamide
Probenicid known to block the excretion of pyrazinamide.Urinary excretion of urate depends on the relative size and timing of doses of the two drugs.
Drug/Laboratory Test Interactions: Pyrazinamide has been reported to interfere with ACETEST®'ae and KETOSTIX®'ae urine tests to produce a pink-brown color.

Rifampicin
Rifampicin accelerates the metabolism of some drugs by inducing microsomal liver enzymes and possibly by interfering with hepatic uptake but the clinical significance of some of these interactions remains to be determined. Although most drugs involved may recuire an increase in dosage to maintain effectiveness, women taking oral contraceptives should use additional precautions or change to a non-hormonal form of contraception.
The absorption of rifampicin may be reduced by antacids, drugs that reduce gastric motility (anticholinergics and opoids),ketoconazole, or preparations containing bentonite (for example aminosalicylic acid preparations). However, such interactions can be overcome by giving rifampicin in a few hours before any of these drugs.
Antiretroviral drugs: Rifampicins can induce the metabolism of zidovudine, the NNRTIs delavirdine, efavirenz and nevirapine and HIV-protease inhibitors, resulting in potentially subtherapeutic plasma concentrations. In addition, HIV protease inhibitors inhibit the metabolism of rifampicins resulting in elevated plasma-rifampicin concentrations and an increased incidence of adverse effects.
Clofazimine: Use of clofazimine in leprosy patients receiving rifampicins with or without dapsone may decrease the rate of absorption of rifampicin and increase the time to peak plasma concentrations. In patients receiving clofazimine, rifampicin and dapsone, the area under the curve for rifampicin was reduced.
Ketoconazole - Giving rifampicin, ketoconazole and isoniazid together has produced low serum concentrations of each drug resulting in failure of antifungal treatment. Rifampicin serum concentrations are reduced when rifampicin is given with ketoconazole, separation of the doses by 30 minutes to 12 hours may result in similar rifampicin concentrations to those attained when rifampicin is given alone, although serum concentrations of ketoconazole remain depressed regardless of the timing of doses.

Isoniazid
The risk of hepatotoxicity may be increased in patients receiving isoniazid with rifampicin or other potentially hepatotoxic drugs. Isoniazid can inhibit the hepatic metabolism of a number of drugs, in some cases leading to increased toxicity. These include the antiepileptics carbamazepine, ethosuximide and phenytoin, the benzodiazepines, diazepam, and triazolam, chlorzoxazone and theophylline. The metabolism of enflurane may be increase in patients receiving isoniazid, resulting in potentially nephrotoxic levels of flouride. Isoniazid has been associated with increased concentrations or toxicity of clofazimine and cycloserine and warfarin.
Alcohol -The metabolism of isoniazid may be increased in chronic alcoholics; this may lead to reduced isoniazid effectiveness.
These patients may also be at increased risk of developing isoniazid reduced peripheral neuropathies and hepatic damage.
Antacids: oral absorption of isoniazid is reduced by aluminum-containing antacids; isoniazid should be given at least 1 hours before the antacid.
Antifungals: serum concentrations of isoniazid were below the limits of detection in a patient also receiving rifampicin and ketoconazole
Antivirals: The clearance of isoniazid was approximately doubled when zalcitabine was given to 12 HIV positive patients. In addition, care is needed since stavudine and zalcitabine may also cause peripheral neuropathy: use of isoniazid with stavudine has been reported to increase its incidence.
Food : Palpitations, headache, conjunctival irritation, severe flushing, tachycardia, tachypnoea and sweating have been reported in patients taking isoniazid after ingestion of cheese, red wine and some fish. Accumulation of tyramine or histamine has been proposed as the cause of these food-related reactions and they could be mistaken for anaphylaxis.
Isoniazid should not be administered with food. Studies have shown that the bioavailability of isoniazid is reduced significantly when administered with food.
Valproate: A recent case study has shown a possible increase in the plasma level of valproate when co administered with isoniazid. Plasma valproate concentration should be monitored when isoniazid and valproate are co administered, and appropriate dosage adjustments of valproate should be made.

**ADVERSE EFFECTS:**
Pyrazinamide
Hepatoxicity is the most serious adverse effects of pyrazinamide therapy and its frequency appears to be dose related. However, in currently recommended doses, when given with isoniazid and rifampicin, the incidence of hepatitis has been reported to be less than 3%. Patients may experience a transient increase in liver enzyme values; more seriously hepatomegaly, splenomegaly, and jaundice may develop and on rare occasion death has occurred.
Hyperuricaemia commonly occurs and may lead to attacks to gout.
Other adverse effects are anorexia, nausea, vomiting, arthralgia, malaise, fever, sideroblastic anemia and dysuria.
Photosensitivity and skin rashes have been reported on rare occasions.

Rifampicin
Rifampicin is usually well tolerated. Adverse effects are more common during intermittent therapy or after restarting interrupted treatment.