SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE FINISHED PHARMACEUTICAL PRODUCT

Akurit-4

1.1 Strength

Rifampin 150mg, Isoniazid 75mg, Pyrazinamide 400mg and Ethambutol Hydrochloride 275mg

1.2 Pharmaceutical form

Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains:
Rifampin USP 150mg
Isoniazid USP 75mg
Pyrazinamide USP 400 mg
Ethambutol Hydrochloride USP 275 mg

3. PHARMACEUTICAL FORM

Brown coloured, capsule shaped film -coated tablets with breakline on one side & plain on the other side.
The breakline is only to facilitate breaking for ease of swallowing and not to divide into equal doses or the tablet should not be divided.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Rifampin 150mg, Isoniazid 75mg, Pyrazinamide 400 mg and Ethambutol Hydrochloride 275 mg Tablets USP is indicated in the treatment of both pulmonary and extra pulmonary tuberculosis, in the intensive initial phase of treatment.

ANTIBACTERIAL ACTIVITY

Rifampin: Escherichia coli, Pseudomonas, Indole negative and indole positive Proteus, Klebsiella, Staphylococcus aureus, Coagulase-negative staphylococci, Neisseria meningitidis, Haemophilus influenzae, Legionella species, M tuberculosis, M kansassi, M scrofulaceum, M intracellulare & M avium.
Isoniazid: It exerts an active bactericidal action on M tuberculosis which it inhibits in concentrations of 0.05-2 mg/l. Other mycobacteria are generally resistant, although some strains of M kansassi are susceptible.
Ethambutol: M tuberculosis, M fortuitum, M kansassi, M intracellulare, M avium, M ulcerans (some strains) & M marinum (some strains**).**

Pyrazinamide: Its activity against M. tuberculosis is highly pH dependent. It is almost inactive at neutral pH; at pH 5.5 the MIC is 16-32 mg/l.
Other Mycobacteria are resistant. Its action, which depends on intracellular conversion to pyrazinoic acid in M. tuberculosis but evidently not in other mycobacteria, is bactericidal.

4.2 Posology and method of administration
Adults – 3 tablets per day for an average body weight of 50 kg

4.3 Contraindications
Rifampin: Rifampin is contraindicated in patients with a history of hypersensitivity to any of the rifamycin.
Isoniazid: Previous isoniazid-associated hepatic injury; severe adverse reactions to isoniazid, such as fever, chills, and arthritis; acute liver disease of any etiology, a history of previous hypersensitivity reaction to isoniazid, including drug induced hepatitis.
Ethambutol: Ethambutol is contraindicated in patients who are known to be hypersensitive to this drug. It is also contraindicated in patients with known optic neuritis unless clinical judgement determines that it may be used.
Pyrazinamide: Pyrazinamide is contraindicated in patients who are known to be hypersensitive to pyrazinamide. Patients should have baseline serum uric acid and liver function determinations. Patients with preexisting liver disease or those patients at increased risk for drug related hepatitis (e.g. alcohol abusers) should be followed closely.
Because it contains pyrazinamide, 4-drug FDC should be discontinued and not be resumed if signs of hepatocellular damage or hyperuricemia accompanied by an acute gouty arthritis appear. If hyperuricemia accompanied by an acute gouty arthritis occurs without liver dysfunction, the patient should be transferred to a regimen not containing pyrazinamide.

4.4 Special warnings and special precautions for use
Rifampin: Rifampin is not recommended for intermittent therapy; the patient should be cautioned against intentional or accidental interruption of the daily dosage regimen since rare renal hypersensitivity reactions have been reported when therapy was resumed in such cases. Rifampin has been observed to increase the requirements for anticoagulant drugs of the coumarin type. The cause of the phenomenon is unknown. In patients receiving anticoagulants and Rifampin concurrently, it is recommended that the prothrombin time be performed daily or as frequently as necessary to establish and maintain the required dose of anticoagulant.
Urine, feces, saliva, sputum, sweat and tears may be colored red orange by Rifampin and its metabolites. Soft contact lenses may be permanently stained. Individuals to be treated should be made aware of these possibilities.
It has been reported that the reliability of oral contraceptives may be affected in some patients being treated for tuberculosis with Rifampin in combination with at least one other antituberculosis drug. In such cases, alternative contraceptive measures may need to be

considered.
It has also been reported that Rifampin given in combination with other antituberculosis drugs may decrease the pharmacologic activity of methasone, oral hypoglycemics, digitoxin, quinidine, disopyramide, dapsone and corticosteroids. In these cases, dosage adjustment of the interacting drugs is recommended.
Therapeutic levels of Rifampin have been shown to inhibit standard microbiological assays for serum folate and vitamin B12. Alternative methods must be considered when determining folate and vitamin B12 concentrations in the presence of Rifampin.
Since Rifampin has been reported to cross the placental barrier and appear in cord blood and in maternal milk, neonates and newborns of Rifampin-treated mothers should be carefully observed for any evidence of untoward effects.
Isoniazid: All drugs should be stopped and an evaluation of the patient should be made at the first sign of a hypersensitivity reaction.
Use of isoniazid should be carefully monitored in the following:
1. Patients who are receiving phenytoin (diphenylhydantoin) concurrently. Isoniazid may decrease the excretion of phenytoin or may enhance its effects. To avoid phenytoin intoxication, appropriate adjustment of the anticonvulsant dose should be made.
2. Daily users of alcohol. Daily ingestion of alcohol may be associated with a higher incidence of isoniazid hepatitis.
3. Patient with current chronic liver disease or severe renal dysfunction.
Periodic ophthalmoscopic examination during isoniazid therapy is recommended when visual symptoms occur.
Ethambutol: The effects of combinations of ethambutol with other antituberculous drugs on the fetus is not known. While administration of this drug to pregnant human patients has produced no detectable effect upon the fetus, the possible teratogenic potential in women capable of bearing children would be weighed carefully against the benefits of therapy. There are published reports of five women who received the drug during pregnancy without apparent adverse effect upon the fetus.
Ethambutol is not recommended for use in children under 13 years of age since safe conditions for use have not been established.
Patients with decreased renal function need the dosage reduced as determined by serum levels of ethambutol, since the main path of excretion of this drug is by the kidneys.
Because this drug may have adverse effects on vision, physical examination should include ophthalmoscopy, finger perimetry, and testing of colour discrimination. In patients with visual defects such as cataracts, recurrent inflammatory conditions of the eye, optic neuritis, and diabetic retinopathy, the evaluation of changes in visual acuity is more difficult, and care should be taken to be sure the variations in vision are not due to the underlying disease conditions. In such patients expected and possible visual deterioration since evaluation of visual changes is difficult. As with any potent drug, periodic assessment of organ system functions, including renal, hepatic, and hematopoietic, should be made during long-term therapy.

Pyrazinamide: Pyrazinamide inhibits renal excretion of urates, frequently resulting in hyperuricemia which is usually asymptomatic. Pyrazinamide also causes hyperuricemia which is accompanied by acute gouty arthritis.

4.5 Interaction with other FPPs and other forms of interaction

Rifampin

Being an inducer of cytochrome P-450 enzymes, Rifampin may accelerate elimination of certain drugs using this metabolic pathway. These include phenytoin, antiarrhythmics (disopyramide, mexiletine, quinidine), anticoagulants, antifungals (fluconazole, itraconazole, ketoconazole), barbiturates, beta blockers, calcium channel blockers (diltiazem, nifedipine, verapamil), chloramphenicol, ciprofloxacin, corticosteroids, cyclosporine, cardiac glycosides, oral contraceptives, clofibrate, dapsone, diazepam, haloperidol, oral hypoglycemic agents, narcotic analgesics, progestins and theophylline. It may be necessary to adjust the dosage of these drugs if they are given concurrently with Rifampin 150mg, Isoniazid 75mg , Pyrazinamide 400 mg and Ethambutol Hydrochloride 275 mg Tablets USP.

Isoniazid

Isoniazid inhibits the metabolism of anticonvulsants, benzodiazepines, haloperidol, ketoconazole, theophylline and warfarin. It may be necessary to adjust the dosage of these drugs if they are given concurrently with Rifampin 150mg, Isoniazid 75mg , Pyrazinamide 400 mg and Ethambutol Hydrochloride 275 mg Tablets USP.

Pyrazinamide

Animal studies have suggested that Cyclophosphamide toxicity is moderately enhanced by coadministration of pyrazinamide but it is not known whether this occurs in humans.

Pyrazinamide slightly reduces serum levels of isoniazid more so in slow isoniazid acetylators but this is not thought to be of any clinical significance. The drug is used in combination with other agents in the treatment of tuberculosis.

Ethambutol Hydrochloride

No potentially hazardous interactions have been reported. Aluminium hydroxide impairs the absorption of ethambutol and an alternative antacid should be used if required

4.6 Pregnancy and lactation

Rifampin

Pregnancy--Teratogenic Effects

Category C. Rifampin has been shown to be teratogenic in rodents given oral doses of rifampin 15 to 25 times the human dose. Neonates of rifampin-treated mothers should be carefully observed for any evidence of adverse effects. Isolated cases of fetal malformations have been reported; however, there are no adequate and well-controlled studies in pregnant women.

Rifampin should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Rifampin in oral doses of 150 to 250 mg/kg produced teratogenic effects in mice and rats. Malformations were primarily cleft palate in the mouse and spina bifida in the rat. The incidence of these anomalies was dose dependent. When rifampin was given to

pregnant rabbits in doses up to 20 times the usual daily human dose, imperfect osteogenesis and embryotoxicity were reported.

Pregnancy--Non-Teratogenic Effects

When administered during the last few weeks of pregnancy, rifampin can cause post-natal hemorrhages in the mother and infant for which treatment with vitamin K may be indicated.

Isoniazid

It has been reported that in both rats and rabbits, isoniazid may exert an embryocidal effect when administered orally during pregnancy, although no isoniazid-related congenital anomalies have been found in reproduction studies in mammalian species. Isoniazid should be prescribed during pregnancy only when therapeutically necessary. The benefit of preventive therapy should be weighed against a possible risk to the fetus.

Ethambutol Hydrochloride

Animal studies have shown some teratogenic effect, however an extensive review of the literature on ethambutol use during pregnancy led to the conclusion that it was second only to Isoniazid in its safety and that the rate of abnormalities reported was low with most being of a minor orthopedic nature not necessarily related to drug administration.

Pyrazinamide

No data are available on the safety and teratogenicity of pyrazinamide in pregnancy.

4.7 Effects on ability to drive and use medicines

Nil

4.8 Undesirable effects

Rifampin

Nervous System Reactions: Headache, drowsiness, fatigue, ataxia, dizziness, inability to concentrate, mental confusion, visual disturbances, muscular weakness, pain in extremities and generalized numbness

Gastrointestinal Disturbances: In some patients heartburn, epigastric distress, anorexia, nausea, vomiting, gas, cramps, and diarrhea.

Hepatic Reactions: Transient abnormalities in liver function tests (e.g., elevations in serum bilirubin, BSP, alkaline phosphatase, serum transaminases) have been observed. Rarely, hepatitis or a shock like syndrome with hepatic involvement and abnormal liver function tests.

Renal Reactions: Elevations in BUN and serum uric acid have been reported. Rarely, hemolysis, hemoglobinuria, hematuria, interstitial nephritis, renal insufficiency and acute renal failure have been noted. These are generally considered to be hypersensitivity reactions. They usually occur during intermittent therapy or when treatment is resumed following intentional or accidental interruption of a daily dosage regimen, and are reversible when Rifampin is discontinued and appropriate therapy instituted.

Hematologic Reactions: Thrombocytopenia, transient leukopenia, hemolytic anemia, eosinophilia and decreased hemoglobin have been observed. Thrombocytopenia has occurred

when Rifampin and ethambutol were administed concomitantly according to an intermittent dose schedule twice weekly and in high doses.

Allergic And Immunological Reactions: Occasionally pruritus, urticaria, rash, pemphigoid reaction, eosinophilia, sore mouth, sore tongue, and exudative conjunctivitis. Rarely hemolysis, hemoglobinuria, hematuria, renal insufficiency or acute renal failure have been reported which are generally considered to be hypersensitivity reactions. These have usually occurred during intermittent therapy or when treatment was resumed following intentional or accidental interruption of a daily dosage regimen and were reversible when Rifampin was discontinued and appropriate therapy instituted.

Metabolic Reactions: Elevations in BUN and serum uric acid have occurred.

Miscellaneous Reactions: Fever and menstrual disturbances have been noted.

Isoniazid

Nervous System Reactions: Peripheral neuropathy is the most common toxic effect. It is dose-related, occurs most often in the malnourished and in those predisposed to neuritis (e.g., alcoholics and diabetics), and is usually preceded by paresthesias of the feet and hands. The incidence is higher in "slow inactivators". Other neurotoxic effects, which are uncommon with conventional doses, are convulsions, toxic encephalopathy, optic neuritis and atrophy, memory impairment, and toxic psychosis.

Gastrointestinal Reactions: Nausea, vomiting, and epigastric distress.

Hepatic Reactions: Elevated serum transaminases (SGOT; SGPT), bilirubinemia, bilirubinuria, jaundice, and occasionally severe and sometimes fatal hepatitis. The common prodromal symptoms are anorexia, nausea, vomiting, fatigue, malaise, and weaknesses. Mild and transient elevations of serum transaminase levels occurs in 10 to 2 % of persons taking isoniazid. The abnormality usually occurs in the first 4 to 6 months of treatment but can occur at any time during therapy. In most instances, enzyme levels return to normal with no necessity to discontinue medication. In occasional instances, progressive liver damage occurs, with accompanying symptoms. In these cases, the drug should be discontinued immediately. The frequency of progressive liver damage increases with age. It is rare in persons under 20, but occurs in up to 2.3 % of those over 50 years of age.

Hematologic Reactions: Agranulocytosis, hemolytic sideroblastic or aplastic anemia, thrombocytopenia and eosinophilia.

Hypersensitivity Reactions: Fever, skin eruptions (morbilliform, maculopapular, purpuric, or exfoliative), lymphadenopathy and vasculitis.

Metabolic And Endocrine Reactions: Pyridoxine deficiency, pellagra, hyperglycemia, metabolic acidosis, and gynecomastia.

Miscellaneous Reactions: Rheumatic syndrome and systemic lupus erythematosus-like syndrome.

Ethambutol

Ethambutol may produce decreases in visual acuity which appear to be due to optic neuritis and to be related to dose and duration of treatment. The effects are generally reversible when administration of the drug is discontinued promptly. In rare cases recovery may be delayed for

up to 1 year or more and the effect may possibly be irreversible in these cases.
The change in visual acuity may be unilateral or bilateral and hence each eye must be tested separately and both eyes tested together. Testing of visual acuity should be performed before beginning ethambutol therapy and periodically during drug administration, except that it should be done monthly when a patient is on a dosage of more than 15 mg/kg per day. If careful evaluation confirms the magnitude of visual change and fails to reveal another cause, Ethambutol should be discontinued, and the patient reevaluated at frequent intervals.
Progressive decreases in visual acuity during therapy must be considered to be due to ethambutol hydrochloride.
Ethambutol may show subjective visual symptoms before, or simultaneously with, the demonstration of decreases in visual acuity, and all patients receiving ethambutol should be questioned periodically about blurred vision and other subjective eye symptoms.
Other adverse reactions reported include: anaphylactoid reactions, dermatitis pruritus and joint pain; anorexia, nausea, vomiting, gastrointestinal upset, abdominal pain; fever, malaise, headache, and dizziness; mental confusion, disorientation and possible hallucinations.
Numbness and tingling of the extremities due to peripheral neuritis have been reported infrequently.
Elevated serum uric acid levels occurs, and precipitation of acute gout has been reported.
Transient impairment of liver function as indicated by abnormal liver function tests is not an unusual finding. Since ethambutol is recommended for therapy in conjunction with one or more other anti-tuberculous drugs, these changes may be related to the concurrent therapy.

Pyrazinamide

Flushing is quite common and hypersensitivity reactions and photosensitization rarely occur.
Mild degrees of anorexia and nausea are common, but vomiting is less frequent. Clinically, the two most important reactions are hepatitis and arthralgia. The frequency of hepatotoxicity declines with reduction of dosage even in combination with isoniazid or Rifampin.
Inhibition of the renal tubular secretion of uric acid by pyrazinoic acid, the main metabolite of the drug, increases the serum uric acid concentration and may precipitate an acute attack in patients with gout. Hyperuricaemia is reduced by co-administration of Rifampin, evidently by facilitation of uric acid excretion rather than any effect on metabolism. Sideroblastic anaemia is a rare, reversible reaction. Convulsions have been described.

4.9 Overdose

No case of overdose has been reported.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmaco-kinetic properties:

Rifampin: The oral administration of Rifampin produces peak concentrations in plasma in 2 to 4 hours. The half-life of Rifampin varies from 1.5 to 5 hours and is increased in the

presence of hepatic dysfunction; it may be decreased in patients receiving isoniazid concurrently who are slow inactivators of this drug. Up to 30% of a dose of Rifampin is excreted in the urine; less than half of this may be unaltered antibiotic. Adjustment of dosage is not necessary in patients with impaired renal function.

Isoniazid: Peak plasma concentrations of 3 to 5 mcg/ml develop 1 to 2 hours after oral ingestion of usual doses. From 75 to 95% of a dose of isoniazid is excreted in the urine within 24 hours, as metabolites. The main excretory products in man are the result of enzymatic acetylation (acetylisoniazid) and enzymatic hydrolysis (isonicotinic acid). The rate of acetylation significantly alters the concentrations of the drug that are achieved in plasma and its half-life in the circulation. The half-life of the drug may be prolonged in the presence of hepatic insufficiency.

Ethambutol: After oral administration, 75 to 80% of ethambutol is absorbed from the gastrointestinal tract. A single dose of 15 mg/kg produces a plasma concentration of about 5 mcg/ml at 2 to 4 hours. The drug has a half-life of 3 to 4 hours. Within 24 hours, two thirds of an ingested dose of ethambutol is excreted unchanged in the urine; upto 15% is excreted in the form of two metabolites, an aldehyde and a dicarboxylic acid derivative. Renal clearance of ethambutol is approximately 7 ml. min -1. kg 1, and the drug is excreted by tubular secretion in addition to glomerular filtration.

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. It is widely distributed in body tissues and fluids including the liver, lungs, and cerebrospinal fluid. It is approximately 10% bound to plasma proteins. The plasma half-life of pyrazinamide is 9 to 10 hours in patients with normal renal and hepatic function. The half-life of the drug may be prolonged in patients with impaired renal or hepatic function. Within 24 hours, approximately 70% of an oral dose of pyrazinamide is excreted in urine, mainly by glomerular filtration. About 4% to 14% of the dose is excreted as unchanged drug: the remainder is excreted as metabolites.

5.2 Pharmaco-dynamic properties:

Rifampin

The mode of action of Rifampin is by inhibition of DNA-dependent RNA polymerase. This occurs in bacteria in low concentrations, much higher ones being required to inhibit mammalian RNA synthesis. In tuberculosis, Rifampin is bactericidal for both intracellular and extracellular microorganisms. Microbial resistance to Rifampin can develop, although certain Rifampin-resistant bacteria have decreased virulence. It is unusual to encounter initial resistance. Rifampin has been shown to inhibit certain DNA viruses such as herpes, adenovirus and pox virus, but at concentrations 500 - 1000 times higher than those required to inhibit the growth of bacteria.

Bacterial Resistance: Against acute organisms resistance develops more readily and therefore, it is usual to give Rifampin in combination with other agents, as in tuberculosis and leprosy. Bacterial resistance may develop rapidly to Rifampin and occurs as a one - step process. One of every 107 - 108 tubercle bacilli is resistant to Rifampin; so the drug

should not be used on its own. Rifampin is generally administered in a dose of 450 – 600 mg on an empty stomach.

Antibacterial Activity

Rifampin is bactericidal against a wide range of organisms, including mycobacteria.

Despite this broad spectrum of activity, the antibiotic has been principally used in the management of tuberculous infections at all sites and in leprosy. Rifampin inhibits the growth of most Gram-positive and many Gram-negative organisms such as E coli, Proteus spp. and Pseudomonas. The drug is highly active against Neisseria meningitidis and N. gonorrhoea. Rifampin is very active against Legionella species in cell cultures.

Rifampin inhibits growth of Mycobacterium tuberculosis and has some activity against atypical mycobacteria such as M kansasii, M scrofulaceum and M intracellular with MIC values of under 4 mg/l. Rifampin increases the in vitro activity of streptomycin and isoniazid.

Ethambutol

Ethambutol is bacteriostatic. It is effective against Mycobacterium tuberculosis and M. bovis with a MIC of 0.5 to 8 μg per ml but possesses little sterilizing activity. It is effective against tubercle bacilli resistant to other anti-tubercular agents. It is proposed that Ethambutol inhibits cell wall synthesis by preventing the incorporation of mycolic acids.

Another study suggests that it's activity against Mycobacterium spp. but not other bacteria may be due to inhibition of spermidine synthesis specifically in mycobacteria.

Ethambutol is active against virtually all strains of Myco-bacterium tuberculosis and M. bovis and is also active against other mycobacteria such as M. Kansasii. Ethambutol has no effect on other microorganisms. Ethambutol usually suppresses the growth of isoniazid and streptomycin-resistant mycobacteria. Resistance to ethambutol develops very slowly and with difficulty in vitro, but in clinical practice some 50% of patients develop acquired resistance to ethambutol when the drug is given as monotherapy for 6 months.

Isoniazid

INH is bactericidal in vitro and in vivo against actively dividing tubercle bacilli; it is less active against non-dividing tubercle bacilli. Its primary action is to inhibit the synthesis of long chain mycolic acids which are unique constituents of mycobacterial cell walls. Isoniazid in low concentrations may prevent elongation of the very long chain fatty acid precursor of the mycolic acids. Since mycolic acids are unique to mycobacteria this explains the high degree of selectivity of isoniazid for these bacteria. Isoniazid may also have effects of nucleic acid biosynthesis and glycolysis.

INH concentrations of 600 mg/l or greater are required to inhibit Gram-positive and Gramnegative bacteria, but the minimum inhibitory concentration for Mycobacterium tuberculosis is 0.05 - 0.025 mg/l.

INH resistance is a relatively uncommon occurrence in developed countries but is an increasing problem in developing countries. In the United States about 4.0% of Mycobacterium tuberculosis isolates demonstrate primary resistance to INH. Resistance mutants occur at random and spontaneously in growing tubercle bacilli at a mutation rate of 1 - 3 x 10-6 per bacterium per

generation. Although the mechanism is not well understood, such mutants appear to take up drug less readily than sensitive cells rather than to inactivate the drug at an increased rate. Controlled prospective studies are needed to evaluate regimens for treatment of persons infected with or exposed to INH resistant bacilli as the choice between available alternatives is uncertain.

Apart from its antimycobacterial action, isoniazid has no pharmacological effect in man. Isoniazid is well absorbed from an oral dose and peak concentrations occur within 1 – 2 hours. If isoniazid is given daily, inhibitory concentrations of drug are easily achieved.

However, if the drug is given less frequently, the rate of acetylation of the drug (drug inactivation) can be of clinical importance. In rapid acetylators the therapeutic efficacy of isoniazid decreases significantly to a point where relapse is more likely than in slow acetylators when the drug is administered less often than twice weekly. The therapeutic effectiveness of isoniazid is determined by the intensity and duration of exposure to the drug.

For adult patients, daily oral doses of 5 mg/kg (upto 300 mg) are recommended. A higher dose of 10 mg/kg has been used in severely ill patients but there is no clear evidence that this higher dose is more effective than the standard dose. In children and adolescents, a higher daily dose in the range of 10 - 20 mg/kg may be used.

Pyridoxine should be administered with isoniazid to minimize side effects particularly in malnourished patients and those predisposed to neuropathy (the elderly, pregnant women, diabetics, alcoholics and patients with uraemia).

Pyrazinamide

Pyrazinamide, a derivative of nicotinamide, was synthesized in 1952 and shown to possess a high degree of antituberculosis activity in man. Previously regarded as a 'reserve drug', pyrazinamide now has an important role, particularly in the short-course treatment of tuberculosis.

Activity against Mycobacteria Pyrazinamide has a relatively low activity against Mycobacterium tuberculosis. The usual MIC is 20 μg per ml if this is tested at an acid pH of 5.5, but pyrazinamide is almost completely inactive against M.tuberculosis at a neutral pH. In vivo studies show that pyrazinamide is an effective bactericidal antituberculosis drug, and it has a specific sterilizing action against M. tuberculosis in the intracellular environment of macrophages. The acid environment presumably in some way makes M. tuberculosis to pyrazinamide, but this does not occur with M. 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. The 'atypical mycobacteria' are usually pyrazinamide-resistant, but the drug has been used to treat M. avium-intracellular infections.

5.3 pre-clinical safety data:

Rifampicin

Acute and subacute toxicity tests in rodents show good tolerance at well above therapeutic doses. The LD50 in mouse following oral administration is approximately 1250 mg/kg in 24 hours. In rat the LD50 values are 1700 mg/kg for oral administration, 550 mg/kg for intraperitoneal administration and 330 mg/kg for intravenous administration.

Rats given 50 mg/kg and 100 mg/kg daily for 26 weeks showed no notable toxicity, but at doses over 100 mg/kg there were dose related histological changes in the liver. Rabbits also given doses over 100 mg/kg for 4 weeks or more showed progressive hepatotoxicity, including jaundice and fatty changes at 400 mg/kg. Dose related minor histological changes were observed in the liver of monkeys given 40 - 80 mg/kg for 2 to 4 weeks.

Ethambutol

The acute toxicity of ethambutol in mice and rats by oral, subcutaneous, intraperitoneal and intravenous administration was found to be low, the LD50s being of the order of 8000 mg/kg after intravenous dosage with 200 - 300 mg.

In sub-acute and chronic toxicity studies in dogs, cats and monkeys, dosages giving serum concentrations in excess of 50 μg/ml were associated with reversible decolourations of the tapetum lucidum of the fundus in all three species but visual impairment only in monkeys and with ECG changes and eosinophilic hyaline changes and vacuolation in the myocardium.

Isoniazid

Acute and chronic toxicity studies have not been performed in animals.

Pyrazinamide

Hepatotoxicity

This is the most important toxic effect of this drug. Hepatotoxicity first became evident in the USA when pyrazinamide was used as a `first line' drug for tuberculosis in the 1950s. In these early studies a high dose of 40-50 mg per kg body weight was used. Results of A United States Public Health Service Trial (1959) indicated that hepatotoxicity was related to the use of these higher doses. As a result of these and similar studies, the use of pyrazinamide as a 'first-line' drug for tuberculosis was abandoned. Later it became apparent that pyrazinamide's reputation as a toxic drug had been exaggerated because of the circumstances in which it had been used. Apart from being used in high dosage for prolonged periods, it was often used with other toxic drugs such as ethionamide and/or cycloserine in re-treatment regimens, and it was frequently given to middle-aged or elderly patients who are more vulnerable to toxic effects. When pyrazinamide was used in later studies in other countries, hepatic toxicity was not a major problem. If used in moderate daily doses of 20-30 mg per kg body weight, combined with streptomycin plus PAS, toxicity was not marked.

Moreover, even when pyrazinamide was used in high dosage in intermittent regimens (Maximum of 90 mg per kg weekly) combined with streptomycin or streptomycin plus isoniazid, hepatotoxicity was uncommon.

Pyrazinamide has been used extensively in short-course chemotherapy in many countries and there have been no reports of a high incidence of serious toxicity. These have included many studies in which pyrazinamide has been given together with isoniazid and rifampicin.

These regimens have been well tolerated and the addition of pyrazinamide to the other two drugs have not increased the incidence of hepatitis. It has been concluded that pyrazinamide, if used in the proper doses, has a small risk of hepatotoxicity. It is probably not necessary to perform routine liver function tests during antituberculosis therapy unless the patient has liver disease or may be

more prone to liver damage. Transient and symptomless increases in serum hepatic enzyme levels are usual during the early weeks of treatment, whatever the drug regimen, and alone is not an indication to interrupt therapy. If symptoms of hepatitis or grossly elevated transaminase levels are detected, then all drugs should be stopped and, if the liver damage is drug-induced, it usually resolves quickly. Treatment with the same drugs can often be resumed uneventfully but monitoring of liver function is essential.

Arthralgia

The other main side-effect of pyrazinamide is arthralgia associated with raised serum uric acid levels. In the earliest report on the use of pyrazinamide in pulmonary tuberculosis the occurrence of pain and restricted joint movement without evidence of arthritis in a quarter of patients treated. The serum uric acid was elevated in patients receiving pyrazinamide and some of these developed clinical gouts. The hyperuricemic effect of Pyrazinamide has been confirmed by numerous studies. Arthralgia has occurred with varying frequency among patients receiving pyrazinamide in antituberculous regimens.

Some studies have shown that arthralgia is more common when the drug is given daily than when given intermittently. In most recent short-course regimens using pyrazinamide, only a small percentage of patients develop arthralgia, though the percentage may be higher among patients treated in India. Acute gouty arthritis has only rarely been observed in association with pyrazinamide therapy and the arthralgia which occurs differs from gout in a number of respects. The joints most frequently affected by pyrazinamide arthralgia are the shoulders, knees and fingers; symptoms and signs are mild, and arthralgia is usually self-limiting; aspirin has a small beneficial effect but not allopurinol.

In clinical trials in India using short-course regimens for pulmonary tuberculosis containing pyrazinamide andrifampicin, the incidence of arthralgia was appreciably less in patients who received rifampicin than those who did not; this was also demonstrated in a small study carried out to investigate this association. This was in contrast to previous experience in Hong Kong and Singapore, where the incidence of arthralgia and hyperuricemia with regimens containing pyrazinamide was uninfluenced by rifampicin administration.

Pyrazinamide suppresses the urinary excretion of uric acid by attenuating its tubular secretion,
and this is mediated by its metabolite, pyrazinoic acid. After a 3g dose of pyrazinamide the urinary excretion of uric acid is maximally suppressed for 24 h and partially reduced for a further 24 h. After a dose of pyrazinamide, the renal excretion of uric acid at 5 h was less than 40% of the predrug administration value, and it returned nearly to pretreatment levels at 24 h. They also observed that rifampicin enhanced the renal excretion of uric acid, both in the presence and in the absence of pyrazinamide, and also that of pyrazinoic acid. It was postulated that this effect of rifampicin leads to a decrease of the deposition of uric acid in joints and thereby a lower incidence of arthralgia.

Rifampicin did not affect serum uric acid levels, presumably because these were already saturated by the effect of pyrazinamide and would continue to be maintained by mobilization of uric acid from the tissues despite the uricosuric effect of rifampicin.

This effect of rifampicin may be due to inhibition of tubular reabsorption of uric acid and pyrazinoic acid.
A number of complex interactions occur when pyrazinamide and probenecid are given to patients with gout. Pretreatment with pyrazinamide results in prolongation of the half-life of probenicid. As the rate of probenecid metabolism is decreased, its uricosuric action tends to be prolonged and the effect of pyrazinamide is lessened. After probenecid-induced uricosuria, pyrazinamide has a greater effect in suppressing urate excretion. This may be because it lessens the capacity of probenecid to inhibit tubular urate reabsorption while it continues to exert an inhibition on tubular urate secretion. When pyrazinamide and probenecid is coadministered, urinary excretion of urate depends on the relative doses and the times at which the drugs are administered.
Gastrointestinal side-effects
Anorexia and nausea and, less commonly, vomiting may occur in the absence of hepatotoxicity, but liver function tests should be performed in these circumstances.
Hypersensitivity reactions
Cutaneous hypersensitivity reactions and sensitivity are rare, but pyrazinamide commonly causes flushing.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline Cellulose
Crospovidone
Pregelatinized Starch
Ascorbic acid
Gelatin
Colloidal silicon dioxide
Magnesium Stearate
Opadry Brown 80W56578 (Composition: Polyvinyl Alcohol-Part. Hydrolyzed, Talc, Titanium dioxide, Iron Oxide Red, Lecithin (Soya), Xanthan Gum)

6.2 Incompatibilities

Not reported

6.3 Shelf life

36 Months

6.4 Special precautions for storage

Alu/Alu blister: Do not store above 30°C;

6.5 Nature and contents of container

Blister Alu/Alu: 15x6’s, 24x14’s

6.6 Special precautions for disposal and other handling

No special requirements. Any unused product or waste material should be disposed of in accordance with local requirement.

7. MARKETING AUTHORISATION HOLDER

Lupin Limited
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Off Western Express Highway,
Santacruz (East), Mumbai - 400 055
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Phone: +91-2266402323.

8. MARKETING AUTHORISATION NUMBER

RWANDA FDA-HMP-MA-0073

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

First Authorization: 1st June,2021

10. DATE OF REVISION OF THE TEXT

12th May 2022