drug does cross into the fetus and malformations and bleeding tendencies have been reported. It was considered that rifampicin did not increase the overall risk of congenital malformations. Rifampicin treatment can increase the metabolism of vitamin K resulting in clotting disorders associated with vitamin K deficiency. Thus, it is recommended blood coagulation monitoring and prophylactic administration of vitamin K to mothers and neonates when the mother has received rifampicin during pregnancy.

Isoniazid: Isoniazid is recognized as being suitable for use in regimens for the treatment of tuberculosis in pregnant patients. Pyridoxine supplementation is recommended. Preventive therapy with isoniazid is generally delayed until after delivery unless other risk factors are present.

Pyrazinamide: Pyrazinamide is not contraindicated in pregnant patients.

Ethambutol: Ethambutol crosses the placenta and is present in fetal tissue in amounts of at least 74.5% of the maternal serum concentration. Use of ethambutol during pregnancy has not been associated with fetal abnormalities.

The use of these drugs during breastfeeding should be considered only if the expected benefit to the mother outweighs the potential risk to the infant.

Rifampicin is present in small amounts in breast milk. Mothers taking rifampicin may breast feed.
Isoniazid is distributed into breast milk Adverse effects on infants during breast feeding have not been reported, although such infants should be monitored for toxic reactions.
Pyrazinamide is distributed into breast milk.
Ethambutol diffuses into breast milk to produce concentrations similar to those in plasma.

INTERACTIONS:
Rifampicin accelerates the metabolism of some drugs by inducing the microsomal liver enzymes and possibly interfering with hepatic uptake. Although most drugs involved may require an increase in dosage to maintain effectiveness women taking oral contraceptives should change to another form of contraception.

The absorption of rifampicin may be reduced by administration with antacids, drugs that reduce gastric motility (anticholinergics and opiods), ketoconazole or preparations containing bentonite. However, such reactions can be overcome by giving rifampicin in a few hours before any of these drugs.

Isoniazid: The risk of hepatotoxicity may be increased in patients receiving isoniazid in combination 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 diazepaman triazolam , chlorzoxazone and theophylline. The metabolism of enflurane may be increased in patients receiving isoniazid resulting in potentially nephrotoxic levels of fluoride.
Isoniazid has been associated with increased concentrations or toxicity of clofazimine. cycloserine and warfarins.
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-induced peripheral neuropathies and hepatic damage.
Oral absorption of isoniazid is reduced by aluminum-containing antacids; Isoniazid should be given one hour before the antacid.

Pyrazinamide: Probenecid is known to block the excretion of pyrazinamide

OVERDOSE AND TREATMENT:
Symptoms: Overdose of Fixcom 4 produces signs and symptoms within 30 min to 3 hrs after ingestion. Nausea, vomiting, lethargy, dizziness, slurring of speech, blurring of vision and visual hallucinations are among the early manifestations. Actual unconsciousness may occur with severe hepatic involvement. Brownish-red or orange discoloration of the skin, urine, sweat, saliva, tears and feces may be proportional to the amount ingested. Liver enlargement possibly with tenderness can develop within a few hours after severe overdose and jaundice may develop rapidly. Hepatic involvement may be more marked in patients with prior impairment of hepatic function. With marked overdose, respiratory distress and CNS depression, progressing rapidly from stupor to profound coma, are to be expected, along with severe, intractable seizures. Severe metabolic acidosis, acetonuria and hyperglycemia are typical laboratory finding. Loss of visual acuity may indicate an overdose of ethambutol. Abnormal liver function tests have been associated with overdoses of Pyrazinamide.
Treatment: Discontinue Fixcom 4. Secure the airway and establish adequate respiratory exchange. Pyridoxine should be administered in a dose of 1g for each gram of isoniazid apparently ingested. Gastric lavage within the first 2-3 hrs is advised, but should not be attempted until convulsions are under control. Gastric lavage with activated charcoal slurry instilled into the stomach following evacuation of gastric contents could help and absorb any remaining drug in the gastrointestinal tract. Antiemetic medication may be required to control severe nausea and/or vomiting. Forced osmotic diuresis (with measured intake and output) will help to promote excretion of the drug. Extracorporal hemodialysis may be required.

AVAILABILITY: Blisters Pack of 8's (Box of 80's)
Blisters Pack of 28's (Box of 168's)

For suspected adverse drug reaction, report to the FDA: www.fda.gov.ph

Registration Number: DRP - 1444
Date of First Authorization: July 2005
Revision Date: September 20, 2016

STORE AT ROOM TEMPERATURES NOT EXCEEDING 30°C

Manufactured for
Natrapharm, Inc
The Patriot Building
Km 18, West Service Road,
SLEX, Sucat, Parañaque City
By Lloyd Laboratories, Inc.
No. 10 Lloyd Ave.,
First Bulacan Industrial City,
City of Malolos, Bulacan

NTFX4RPE000IN1601

Natrapharm

Rifampicin / Isoniazid / Pyrazinamide / Ethambutol

Fixcom® 4

150mg / 75mg / 400mg / 275mg Film coated tablet
Antituberculosis

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

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

DOSAGE:
Anti-tuberculosis short course chemotherapy recommended by World Health Organization (WHO) involves an initial phase using a combination of drugs to produce rapid killing of the tubercle bacilli. For the initial phase: Rifampicin + Isoniazid + Pyrazinamide + Ethambutol (FIXCOM 4) is given for 2 months.

Below 55 kg - 3 tablets per day
55 kg - 70 kg - 4 tablets per day
Above 70 kg - 5 tablets per day
The tablets should be taken one hour before or two hours after meals

Or as prescribed by the physician

ADVERSE EFFECTS:
Rifampicin - Rifampicin is usually well tolerated. Adverse effects are more common during intermittent therapy or after restarting interrupted treatment.
Some patients may experience a cutaneos syndrome which presents 2 to 3 hours after a daily or intermittent dose as facial flushing, itching, rash, or rarely eye irritation. A 12-hour "flu" syndrome of fever, chills, bone pains, shortness of breath and malaise has been associated with intermittent administration. It usually occurs after 3 to 6 months of intermittent administration and has a higher incidence with doses of 20 mg or more per kg body weight given once weekly than with currently recommended regimens. Anaphylaxis or shock has occured rarely.
Gastrointestinal adverse effects include nausea, vomiting, anorexia, diarrhea and epigastric distress. Gastrointesinal bleeding and erosive gastritis, ulcerative colitis and eosinophilic colitis have been reported. Administration on an empty stomach is recommended for maximal absorption, but this has to be balanced against administration after a meal to minimize gastrointestinal intolerance. Pseudomembranous colitis has been reported.
Rifampicin produces transient abnormalities in liver function. Hepatitis occurs rarely. Fatalities due to hepatoxicity have been reported occasionally.
Rifampicin can cause thrombocytopenia and purpura, usually when administered as an intermittent regiment, and if this occurs further administration of rifampicin is contra-indicated. Other haematological adverse effects include eosinophilia, leucopenia and haemolytic anaemia.

Alterations in kidney function and renal failure have occurred, particularly during intermittent therapy. Menstrual disturbances have been reported.

Nervous system adverse effects include headache, drowsiness, ataxia, dizziness and numbness.

Oedema, myopathy, and muscular weakness have been reported.

Rifampicin causes a harmless orange-red discoloration of the urine and other body fluids.

Isoniazid – Isoniazid is generally well tolerated at currently recommended doses. However, patients who are slow acetylators of isoniazid appear to have a higher incidence of some adverse effects. Also patients whose nutrition is poor are at risk of peripheral neuritis which one of the commonest adverse effects of isoniazid. Other neurological adverse effects include psychotic reactions and convulsions. Pyridoxine may be given to prevent or treat these adverse effects.Transient increase in liver enzymes occur in 10 to 20% of patients during the first few months and usually return to normal despite continued treatment. Elevated liver enzymes associated with clinical signs of hepatitis such as nausea and vomiting, or fatigue may indicate hepatic damage: in these circumstances, isoniazid should be stopped pending evaluation and should only be reintroduced cautiously once hepatic functions has recovered. The incidence of liver damage is highest in patients over 35 years of age. The influence of acetylator status is uncertain. Fatalities have occurred following liver necrosis.
Haematological effects reported following use of isoniazid include various anaemias, agranulocytosis, thrombocytopenia, and eosinophilia.
Hypersensitivity reactions occur infrequently and include skin eruptions (including erythema and multiforme), fever and casculitis.
Other adverse effects include nausea, vomiting, pellagra, purpura, hyperglycaemia, lupus-like syndrome, urinary retention and gynaecomastia.
Symptoms of overdosage include slurred speech, metabolic acidosis, hyperglycaemia, convulsions and coma; fatalities may occur.

Pyrazinamide – Hepatoxicity is the most serious side-effect of pyrazinamide therapy and its frequency appears to be dose related. However, in currently recommended dose, 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 occasions death has occurred. Hyperuricaemia commonly occurs and may lead to attacks of gout.
Other side-effects are anorexia, nausea, vomiting, arthralgia, malaise, fever, sideroblastic anemia and dysuria. Photosensivity and skin rashes have been reported on rare occasions.

Ethambutol - The most important adverse effect of ethambutol is retrobulbar neuritis with a reduction in visual acuity, constriction of visual field. central or peripheral scotoma, and green-red colour blindness. One or both eyes may be affected. The degree of visual impairment appears

to depend on the dose and duration of therapy; toxicity is observed most frequently at daily doses of 25mg per kg body-weight and after 2 months of therapy. Recovery of vision usually takes place over a period of a few weeks or months, but in rare cases it may take up to one year or more or the effect may be permanent. Retinal haemorrhage has occurred rarely.

Renal clearance of urate may be reduced and acute gout has been precipitated rarely. Hypersensitivity reactions including skin rashes, pruritis, leucopenia, fever, and joint pains have occurred but appear to be rare with ethambutol. Other adverse effects which have been reported include confusion, disorientation, hallucinations, headache, dizziness, malaise, jaundice or transient liver dysfunction, peripheral neuritis, thrombocytopenia, pulmonary infiltrates, eosinophilia, and gastrointestinal disturbances such as nausea, vomiting, anorexia, and abdominal pain.
Teratogenicity has been observed in animals.
Blood concentrations of ethambutol following overdosage may be reduced by haemodialysis or peritoneal dialysis.

PHARMACODYNAMICS/ANTIMICROBIAL ACTIONS:
Rifampicin - Rifampicin is bactericidal against a wide range of micro-organisms and interferes with their synthesis of nucleic acids by inhibiting DNA-dependent RNA polymerase. It has the ability to kill intracellular organisms. It is active against mycobacteria, including *Mycobacterium tuberculosis* and *M. leprae*, and having high sterilizing activity against these organisms, it possesses the ability to eliminate semi-dormant or persisting organisms. Rifampicin is active against Gram-positive bacteria, especially staphylococci, but less active against Gram-negative organisms. The most sensitive Gram-negative bacteria include *Neisseria meningitides, N. gonorrhoeae, Haemophilus influenzae* and *Logionella spp.* Rifampicin also has activity against *Chlamydia trachomatis* and some anaerobic bacteria. At high concentrations it is active against some viruses. Rifampicin has no effect on fungi but has been reported to enhance the antifungal activity of amphotericin B. Minimum inhibitory concentrations tend to vary with the medium used; MICs for the most sensitive organisms (Chlamydia, staphylococci) tend to range from about 0.01 to 0.02 *u*g per mL, while the MIC for most susceptible mycobacteria ranges from 0.1 to 0.2 *u*g per mL. The concomitant use of other antimicrobials may enhance or antagonize the bactericidal activity of rifampicin.
Strains of *Mycobacterium tuberculosis*, *M. leprae* and other usually susceptible bacteria gave demonstrated resistance, both initially and during treatment. Thus in tuberculosis and leprosy regiments, rifampicin is used in combination with other drugs to delay or prevent the development of rifampicin resistance.

Isoniazid: Isoniazid is highly active against *Mycobacterium tuberculosis* which it inhibits in vitro at concentrations of 0.02 to 0.2 *u*g per mL. Isoniazid may have activity against some strains of other mycobacteria including *M. kansasii.*
Although it is rapidly bactericidal against actively dividing *M. tuberculosis*, it is considered to be only bacteriostatic against semi-dormant organisms and has less sterilizing activity that rifampicin or pyrazinamide.
Resistance to isoniazid develops rapidly if it is used alone in the treatment of clinical infection, and may be due in some strains to loss of the gene for catalase production. Resistance is delayed or prevented by combination with other antimycobacterials and it appears to be highly effective in preventing emergence of resistance to other antituberculous drugs. Resistance does not appear to be a problem when isoniazid is used alone in prophylaxis, probably because the bacillary load is low.

Pyrazinamide: Pyrazinamide has a bactericidal effect on *Mycobacterium tuberculosis* but appears to have no activity against other mycobacteria or micro-organisms in vitro. The MIC for *M. tuberculosis* is less than 20 *u*g per mL at pH 5.6: it is almost completely inactive at a neutral pH. Pyrazinamide is effective against persisting tubercle bacilli within the acidic intracellular environment of the macrophages. The initial inflammatory response to chemotherapy increases the number of organisms in the acidic environment. As inflammation subsides and pH increase, the sterilizing activity of pyrazinamide decreases. This pH-dependent activity explains the clinical effectiveness of pyrazinamide as part of the initial 8-week phase in short-course treatment regimens.

Ethambutol: Ethambutol is bacteriostatic against *Mycobacterium tuberculosis* with an MIC of 0.5 to 0.8 *u*g per mL; it is bactericidal at higher concentrations. It possesses little sterilizing activity. Resistant strains of *M. tuberculosis* are readily produced if ethambutol is used alone.

PRECAUTIONS:
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 therapy. Rifampicin's contra-indicated in patients with jaundice. A self-limiting hyperbilirubinaemia may occur in the first 2 or 3 weeks of treatment. Alkaline phosphatase values may be raised moderately due to rifampicin's enzyme-inducing capacity. When other liver functions tests are within normal limits, hyperbilirubinaemia in the first few weeks of moderately elevated alkaline phosphates 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. In patients who develop haemolytc anaemia or renal failure, withdrawal of rifampicin is recommended. Administration 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, sputum, sweat, tears, urine and other body-fluids. Soft contact lenses worn by patients receiving rifampicin may become permanently stained.

Isoniazid - Isoniazid should be administered with caution to patients with convulsive disorders, a history of psychosis, or hepatic or renal dysfunction. Patients who are at risk of neuropathy or pyridoxine deficiency, including those who are diabetic, alcoholic, malnourished, uraemic, pregnant, or infected with HIV, should receive pyridoxine usually in a dose of 10mg daily, although some have suggested using up to 50mg daily. If symptoms of hepatitis such as malaise, fatigue, anorexia, and nausea develop isoniazid should be discontinued 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 3 to 5 times the normal upper limit or the bilirubin concentration rises.
Periodic eye examination during isoniazid treatment have also been suggested.

Pyrazinamide - Pyrazinamide is contraindicated in patients with liver damage, although some consider that it can be used with care when the liver 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 impaired renal function. Increased difficulty has been reported in controlling diabetes mellitus when diabetics are given pyrazinamide.

Ethambutol - Ethambutol is generally contra-indicated in patients with optic neuritis. It should be used with great care in patients with visual defects, the elderly, and in children in whom evaluation of changes in visual acuity may be difficult; it should be generally not be used in children under 6 years of age and some consider that it should not be used in children under 13 years of age nor in patients with visual defects. Ocular examination is recommended before treatment with ethambutol and some consider regular examinations are necessary during treatment especially in children. Patients should be advised to report visual disturbances immediately and to discontinue ethambutol pending visual evaluation.
Ethambutol should be given in reduced dosage to patients with impaired kidney function and dosage adjustments may need to be made according to serum concentrations.
Ethambutol may precipitate attacks of gout.
Although ethambutol crosses the placenta and may be teratogenic in animals, problems in humans have not been documented. It is generally considered that the benefits of ethambutol in the treatment of tuberculosis outweigh any potential risks in pregnancy.

PHARMACOKINETICS:
Rifampicin: Rifampicin is readily absorbed from the gastrointestinal tract and peak plasma concentrations of about 7 to 10 ug per mL have been reported 2 to 4 hours after a dose of 600mg, although there may be considerable interindividual variation. Food may reduce and delay absorption. Rifampicin is approximately 80% bound to plasma proteins. It is widely distributed in body tissues and fluids and diffusion into the CSF is increased when the meninges are inflamed. Rifampicin crosses the placenta and is distributed into breast milk. 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 liver disease.
Rifampicin is rapidly metabolized in the liver mainly to active 25-O-deacetyrifampicin; rifampicin and deacetylrifampicin are excreted in the bile. Deacetylation diminishes intestinal reabsorption and increases faecal 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 dose of 900 mg 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 impaired renal function the half-life of rifampicin is not prolonged at doses of 600mg or less.

Pyrazinamide is readily absorbed from the gastrointestinal tract. Peak serum concentrations occur about 2 hours after a dose by mouth and have been reported to be about 35 ug per mL after 1.5g and 66 ug per mL after 3 g. Pyrazinamide is widely distributed in the body fluids and tissues and diffuses into the CSF. The half-life has been reported to be about 9 to 10 hours. It is metabolized primarily in the liver by hydrolysis to the major active metabolite pyrazinoic acid which is subsequently hydoxylated to the major excretory product 5-hydroxypyrazinoic acid. It is excreted through the kidney mainly by glomerular filtration. About 70% of a dose appears in the urine within 24 hours mainly as metabolites and 4 to 14% as unchanged drug. Pyrazinamide is removed by dialysis.

Isoniazid is readily absorbed from the gastrointestinal tract. Peak concentrations of about 3 to 8 ug per 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 diffuses into all body tissues and fluids , including the CSF. The plasma half-life for isoniazid ranges from about 1 to 6 hours, those who are fast acetylators having shorter half-lives. The primary metabolic route is the acetylation of isoniazid to acetylisoniazid by N-acetyltransferase found in the liver and small intestine.

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.
Ethambutol about 80% of an oral dose of ethambutol 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 25mg per kg bodyweight, peak plasma concentrations of up to 5 ug per mL appear within 4 hours, and are less than1 ug per mL by 24 hours.

Ethambutol is distributed to most tissues, including the lungs, kidneys and erythrocytes. If diffuses into the CSF when the meninges are inflamed. It has been reported to cross the placenta and is distributed into breast milk. The elimination half-life following oral administration is about 3 to 4 hours. Ethambutol is partially metabolized in the liver to the aldehyde and dicarboxylic acid derivatives which are inactive and then excreted in the urine. 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. Although the absorption of ethambutol is not generally regarded as being impaired by food, a study in 14 healthy subjects suggested that administration with a high fat meal or an antacid could delay absorption and reduce the maximum plasma concentration.

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

USE IN PREGNANCY AND LACTATION:
There are no adequate and well-controlled studies from the use of rifampicin, isoniazid, pyrazinamide and ethambutol on pregnancy and the fetus. Thus, these drugs should be used during pregnancy only if the benefit justifies the potential risk to the fetus.

Rifampicin: The International Union Against Tuberculosis and the WHO Expert Committee on Leprosy recommend treatment of pregnant patients with the same rifampicin-containing multidrug regimens as would be used in nonpregnant patients.

While administration of rifampicin to pregnant patients is generally considered to be safe, the