Pyrazinamide+ Ethambutol HCl+ Rifampicin+ Isoniazid

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Myrin-P Forte®

400 mg/ 275 mg/ 150 mg/ 75 mg Tablet

1.0. PHARMACOLOGIC CATEGORY

Antituberculosis

2.0. DESCRIPTION

Ethambutol has a chemical name (*S*,*S*)-*N,N*′-Ethylenebis (2-aminobutan-1-ol) dihydrochloride.

It is a white or almost white, hygroscopic, crystalline powder. Freely soluble in water; soluble in alcohol. A 2% solution in water has a pH of 3.7 to 4.0.

Rifampicin has a chemical name 3-(4-Methylpiperazine-1-yliminomethyl) rifamycin SV; (12*Z*,14*E*,24*E*)-(2*S*,16*S*,17*S*,18*R*,19*R*,20*R*,21*S*,22*R*,23*S*)-1,2-Dihydro-5,6,9,17,19-pentahydroxy-23-methoxy-2,4,12,16,18,20,22-heptamethyl-8-(4-methylpiperazin-1-yliminomethyl)-1,11-dioxo-2,7-(epoxypentadeca[1,11,13] trienimino) naphtho[2,1-*b*] furan-21-yl acetate.

It is a reddish-brown or brownish-red, crystalline powder. Slightly soluble in water, in alcohol, and in acetone; soluble in methyl alcohol. A 1% suspension has a pH of 4.5 to 6.5.

Isoniazid has a chemical name Isonicotinohydrazide.

It is a white or almost white, crystalline powder or colorless crystals. Freely soluble in water; sparingly soluble in alcohol. A 5% solution in water has a pH of 6.0 to 8.0.

Pyrazinamide has a chemical name Pyrazine-2-carboxamide.

It is a white or almost white, crystalline powder. It shows polymorphism. Sparingly soluble in water; slightly soluble in alcohol and in dichloromethane.

3.0. FORMULATION/ COMPOSITION

Each Myrin – P Forte Tablet contains:
Pyrazinamide…….400 mg
Ethambutol HCl…….275 mg
Rifampicin…… 150 mg
Isoniazid……..75 mg

4.0. CLINICAL PARTICULARS

4.1. Therapeutic Indications

Pyrazinamide + Ethambutol HCl + Rifampicin + Isoniazid (Myrin-P Forte) is indicated for the initial or intensive phase treatment of new and re-treatment cases of pulmonary and extrapulmonary tuberculosis (TB) caused by susceptible strains of mycobacteria.

New patients: Never had treatment for TB, or have taken anti-TB drugs for less than 1 month. These patients may have positive or negative bacteriology and may have disease at any anatomical site.

Previously treated patients: Patients who have received 1 month or more of anti-TB drugs in the past, may have positive or negative bacteriology and may have disease at any anatomical site.

4.2. Dosage and Method of Administration

Pyrazinamide + Ethambutol HCl + Rifampicin + Isoniazid (Myrin-P Forte) should be taken 1 hour before or 2 hours after a meal. Should gastrointestinal irritation occur, the combination may be taken with food or antacids, but not aluminum-containing antacids.

The recommended dosage and treatment regimen for tuberculosis is dependent on the patient's medical history, response to treatment, and the sensitivity of the isolate. Dosage should be consistent with guidelines issued by the World Health Organization (WHO).

Adult Dosage

WHO guidelines indicate that **Pyrazinamide + Ethambutol HCl + Rifampicin + Isoniazid (Myrin-P Forte)** should be given daily during the initial or intensive phase of treatment with the dose adjusted according to body weight, as follows:

Drug	**Recommended Daily Dose**	
	Dosage and Range (mg/kg body weight)	**Maximum (mg)**
Isoniazid	5 (4-6)	300
Rifampicin	10 (8-12)	600
Pyrazinamide	25 (20-30)	-
Ethambutol	15 (15-20)	-

Dosage schedule for Fixed Dose Combinations of WHO recommended strengths for adults

Patient's Body Weight (kg)	Initial/Intensive Phase
30-37	2 tablets
38-54	3 tablets
55-70	4 tablets
≥ 71	5 tablets

Treatment duration is usually 2 months. Patients who are still sputum smear-positive after completion of the initial phase, should be evaluated for further treatment according to WHO or local guidelines for the treatment of tuberculosis.

Pediatric dosage

The efficacy of the combination has not been established in children, and this product should not be used in children under 13 years of age since safe conditions for use have not been established.

Geriatric dosage

As with any drug, caution should be exercised when using **Pyrazinamide + Ethambutol HCl + Rifampicin + Isoniazid (Myrin-P Forte)** to treat elderly patients.

Renal insufficiency

Ethambutol accumulates in patients with renal insufficiency. Pyrazinamide is also excreted through the kidney as unchanged drug. If renal impairment is severe or if patients are slow acetylators, a reduction in dosage may be required. Patients with decreased renal function need the dosage reduced as determined by serum levels of ethambutol hydrochloride, since the main path of excretion of this drug is by the kidneys.

Hepatic insufficiency

Dose adjustment of **Pyrazinamide + Ethambutol HCl + Rifampicin + Isoniazid (Myrin-P Forte)** may be necessary in patients with hepatic insufficiency or patients who are slow acetylators. Patients with acute or chronic liver disease and patients who are slow acetylators have higher serum isoniazid concentrations and exhibit a longer serum half-life for isoniazid. The plasma half-life of pyrazinamide may be prolonged in patients with hepatic insufficiency. The clearance of rifampicin is significantly decreased in patients with liver disease.

4.3. Contraindications

Pyrazinamide + Ethambutol HCl + Rifampicin + Isoniazid (Myrin-P Forte) should not be used in patients with a known hypersensitivity to ethambutol, isoniazid, pyrazinamide or rifampicin or to any of the excipients in this product. **Pyrazinamide + Ethambutol HCl + Rifampicin + Isoniazid (Myrin-P Forte)** is also contraindicated in the presence of alcoholism, optic neuritis, in the presence of jaundice, or in patients with known retrobulbar neuritis unless the doctor determines that it may be used. **Pyrazinamide + Ethambutol HCl + Rifampicin + Isoniazid (Myrin-P Forte)** is also contraindicated in patients who are unable to appreciate and report visual side effects or changes in vision (e.g. young children and patients with mental illness or mental deficiency).

Pyrazinamide is contraindicated in persons:

- with severe hepatic damage.
- on concomitant therapy with rifampicin who are concurrently taking other medications associated with liver injury, drink excessive amounts of alcohol (even if alcohol use is discontinued during treatment), have underlying liver disease, or have a history of isoniazid associated liver injury.

4.4. Special Warnings and Precautions for Use

There have been reports of severe cutaneous adverse reactions (SCARs), such as Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), and acute generalized exanthematous pustulosis (AGEP) with anti-tuberculosis drugs (See **Section 4.8 Undesirable effects).** If patients develop a skin rash they should be monitored closely and suspected drug(s) discontinued if lesions progress. Identifying the specific drug is difficult, as multiple anti-tuberculosis drugs are prescribed in association concurrently. Specifically, for DRESS, a multi-system potential life-threatening SCAR, time to onset of the first symptoms may be prolonged. DRESS is a clinical diagnosis, and its clinical presentation remains the basis for decision making. An early withdrawal of the suspect drug is essential because of the syndrome's mortality and visceral involvement (e.g., liver, bone marrow, or kidney).

Ethambutol hydrochloride may produce decreases in visual acuity which may appear to be due to optic / retrobulbar neuritis. This effect may be related to dose and duration of treatment. This effect is generally reversible when administration of the drug is discontinued promptly. However, irreversible blindness has been reported. (See **Section 4.8. Undesirable effects**).

Liver toxicities including fatalities have been reported. Baseline and periodic assessment of hepatic function should be performed. Those patients with preexisting liver disease or those at increased risk for drug-related hepatitis (e.g. alcohol abusers) should be followed closely (See **Section 4.8. Undesirable effects**).

The drug should be discontinued and not be resumed if signs of hepatocellular damage appear.

Rifampicin / pyrazinamide combination therapy should generally not be offered for treatment of latent tuberculosis infection.

Ethambutol has a unique effect on the eye. It is, therefore, recommended that all patients taking **Pyrazinamide + Ethambutol HCl + Rifampicin + Isoniazid (Myrin-P Forte)** should undergo a full ophthalmic examination before starting treatment and periodically during drug administration. This examination should include visual acuity, color vision, perimetry, and ophthalmoscopy. In patients with visual defects such as cataract, recurrent inflammatory conditions of the eye, optic neuritis, and diabetic retinopathy, the evaluation of changes in visual acuity is more difficult. In such patient's consideration should be given to the relationship between benefits expected from **Pyrazinamide + Ethambutol HCl + Rifampicin + Isoniazid (Myrin-P Forte)** administration and possible visual deterioration. See **Section 4.8. Undesirable effects**.

Pyrazinamide + Ethambutol HCl + Rifampicin + Isoniazid (Myrin -P Forte) is not recommended for use in children under 13 years of age since safe conditions of use have not been established. The pyrazinamide in **Pyrazinamide + Ethambutol HCl + Rifampicin + Isoniazid (Myrin-P Forte)** inhibits renal excretion of urates, frequently resulting in hyperuricemia that is usually asymptomatic. Blood uric acid determination should be made at baseline and periodically during treatment. If hyperuricemia is accompanied by acute gouty arthritis, **Pyrazinamide + Ethambutol HCl + Rifampicin + Isoniazid + (Myrin-P Forte)** should be discontinued. Caution should be exercised when **Pyrazinamide + Ethambutol HCl + Rifampicin + Isoniazid (Myrin-P Forte)** is administered to patients with a history of gout.

Pyrazinamide + Ethambutol HCl + Rifampicin + Isoniazid (Myrin-P Forte) is a combination drug, which includes isoniazid, rifampicin, and ethambutol. Each of these individual drugs has been associated with severe and sometimes fatal liver dysfunction. **Pyrazinamide + Ethambutol HCl + Rifampicin + Isoniazid (Myrin-P Forte)** also contains pyrazinamide, which is potentially hepatotoxic. Hepatitis associated with the isoniazid component is more likely in people over 50 years of age and in those who consume alcohol daily. Patients should be instructed to report immediately any of the prodromal symptoms of liver disease or hepatitis such as fatigue, malaise, anorexia, nausea, vomiting or jaundice. If symptoms or signs suggestive of hepatic damage are detected, **Pyrazinamide + Ethambutol HCl + Rifampicin + Isoniazid (Myrin-P Forte)** should be discontinued promptly. Urine, feces, saliva, sputum and tears may be colored red-orange by the rifampicin component of **Pyrazinamide + Ethambutol HCl + Rifampicin + Isoniazid (Myrin-P Forte).** Soft contact lenses may be permanently stained.

As with any potent drug, periodic assessment of organ system functions, including renal, hepatic and hematopoietic, should be made during **Pyrazinamide + Ethambutol HCl + Rifampicin + Isoniazid (Myrin-P Forte)** therapy.

Pyridoxine deficiency is sometimes observed in adults taking high doses of isoniazid. Treatment with high doses of vitamin B6 may be necessary.

Pyrazinamide has been reported to interfere with ACETEST® and KETOSTIX® urine tests to produce a pink-brown color.

Patients at risk for peripheral neuropathy as a result of malnutrition, chronic alcohol dependence, or diabetes should additionally receive pyridoxine, 10 mg daily. Where the standard of health in the community is low, this should be offered routinely.

Pyrazinamide + Ethambutol HCl + Rifampicin + Isoniazid (Myrin-P Forte) should be administered with care to epileptic patients, since it may induce convulsions, or to patients in psychotic states characterized by mania or hypomania.

Pyrazinamide + Ethambutol HCl + Rifampicin + Isoniazid (Myrin-P Forte) should be used with caution in patients with diabetes mellitus, as management may be more difficult.

Pyrazinamide + Ethambutol HCl + Rifampicin + Isoniazid (Myrin-P Forte) may diminish visual acuity and color vision, which may affect the ability to drive and use machines.

Laboratory Tests

Baseline liver function studies, especially ALT (SGPT), AST (SGOT), and bilirubin should be determined prior to therapy. AST, ALT, and bilirubin as well as other appropriate laboratory testing should be performed at periodic intervals and if any clinical signs or symptoms of hepatotoxicity occur during therapy.

4.5. Interaction with Other Medicinal Products and Other Forms of Interaction

Interactions relating to Ethambutol

Concurrent administration of ethambutol with other neurotoxic medicines may increase the potential for neurotoxicity, such as optic and peripheral neuritis.

Antacids containing aluminum hydroxide have impaired the absorption of ethambutol.

Ethambutol may react with phentolamine (Rogitine) to elicit a false-positive test for pheochromocytoma.

Interactions relating to Rifampicin

Rifampicin has been observed to decrease the anticoagulant effect of coumarin-type drugs. It is recommended that prothrombin time be measured daily or as frequently as necessary to establish and maintain the required dose of coumarin.

It has been reported that the reliability of oral contraceptives may be affected in patients being treated for tuberculosis with rifampicin in combination with at least 1 other antituberculosis drug. In such cases, alternative contraceptive measures may need to be considered.

Rifampicin may increase the metabolism of the following medicines by induction of hepatic microsomal enzymes, resulting in lower serum concentrations:

Aminophylline, theophylline, sulfonylurea oral anti-diabetic agents, phenobarbital, systemic beta-adrenergic blocking agents, chloramphenicol, clofibrate, corticosteroids, cyclosporin, dapsone, diazepam, digitalis glycosides, disopyramide, mexiletine, quinidine, tocainide, estramustine, fluconazole, methadone, phenytoin, trimethoprim, oral verapamil.

Concurrent use of clofazimine has resulted in reduced absorption of rifampicin, delaying its time-to-peak concentration and increasing its half-life.

Therapeutic levels of rifampicin have been shown to inhibit standard microbiological assays of serum folate and vitamin B12. Alternative methods must be considered when determining folate and vitamin B12 concentrations in the presence of rifampicin.

Probenecid may compete with rifampicin for hepatic uptake resulting in increased and more prolonged rifampicin uptake and/or toxicity; however, the effect is inconsistent and concurrent probenecid use to increase rifampicin serum concentrations is not recommended.

Interactions relating to Isoniazid

Chronic use of isoniazid may decrease the plasma clearance and prolong the duration of action of alfentanil, coumarin, indandione derivative anticoagulants, benzodiazepines, carbamazepine, and theophylline.

The use of phenytoin should be carefully monitored in patients who are receiving isoniazid concurrently. Isoniazid may decrease excretion of phenytoin or may enhance its effects.

Concurrent use of chronic paracetamol, alcohol, rifampicin and other hepatotoxic medications may increase the potential for isoniazid-induced hepatotoxicity. Aluminum-containing antacids may delay and decrease absorption and serum concentrations of isoniazid.

Concurrent ingestion of certain types of cheese such as Swiss or Cheshire, or fish such as tuna or sardines may result in itching of the skin, rapid or pounding heart, chills, and headache, which is thought to be due to the inhibition of plasma monoamine oxidase and diamine oxidase by isoniazid, interfering with the metabolism of tyramine and histamine found in fish and cheese.

Glucocorticoid corticosteroids may increase hepatic metabolism and/or excretion of isoniazid.

Concurrent use with cycloserine, disulfiram, and other neurotoxic medicines may increase the potential for CNS toxicity.

Isoniazid may increase the formation of a potentially neurotoxic inorganic fluoride metabolite when used concurrently with enflurane.

Concurrent use of isoniazid with ketoconazole or parenteral miconazole is not recommended.

False-positive reactions with copper sulfate urine glucose tests may occur.

Interactions relating to Pyrazinamide
Pyrazinamide may increase serum uric acid concentrations and decrease the efficacy of gout therapy. Dosage adjustments of these medications may be necessary to control hyperuricemia and gout.

4.6. Fertility, Pregnancy and Lactation

The components of **Pyrazinamide + Ethambutol HCl + Rifampicin + Isoniazid (Myrin -P Forte)** have harmful pharmacological effects on pregnancy and the fetus. There are no adequate data from the use of rifampicin, ethambutol, pyrazinamide and isoniazid in pregnant women. Studies in animals have shown reproductive toxicity. The potential risk for humans is unknown.

Rifampicin has been shown to be teratogenic in animals on very high doses. When administered during the last few weeks of pregnancy, rifampicin can cause post-natal hemorrhages in the mother and infant for which treatment with vitamin K may be indicated. Because rifampicin has been reported to cross the placental barrier and appear in cord blood, neonates of rifampicin-treated mothers should be carefully observed for any evidence of adverse effects.

There are no adequate and well-controlled studies in pregnant women. There are reports of ophthalmic abnormalities occurring in infants born to women on antituberculous therapy that included ethambutol hydrochloride. Ethambutol hydrochloride should be used during pregnancy only if the benefit justifies the potential risk to the fetus.

Ethambutol hydrochloride has been shown be teratogenic in pregnant mice and rabbits when given in high doses. When pregnant mice or rabbits were treated with high doses of ethambutol hydrochloride, fetal mortality was slightly but not significantly ($P>0.05$) increased. Female rats treated with ethambutol hydrochloride displayed slight but insignificant ($P>0.05$) decreases in fertility and litter size.

In fetuses born of mice treated with high doses of ethambutol hydrochloride during pregnancy, a low incidence of cleft palate, exencephaly and abnormality of the vertebral column were observed. Minor abnormalities of the cervical vertebra were seen in the newborn of rats treated with high doses of ethambutol hydrochloride during pregnancy. Rabbits receiving high doses of ethambutol hydrochloride during pregnancy gave birth to two fetuses with monophthalmia, one with a shortened right forearm accompanied by bilateral wrist-joint contracture and one with harelip and cleft palate.

Isoniazid has been reported to be embryocidal in pregnant rats and rabbits.

Rifampicin, isoniazid, pyrazinamide and ethambutol are excreted in breast milk. Therefore, infants should not be breastfed by patients receiving **Pyrazinamide + Ethambutol HCl + Rifampicin + Isoniazid (Myrin-P Forte).**

4.7. Effects on Ability to Drive and Use Machines

Pyrazinamide + Ethambutol HCl + Rifampicin + Isoniazid (Myrin-P Forte) may diminish visual acuity and color vision, which may affect the ability to drive and use machines.

4.8. Undesirable Effects

Pyrazinamide + Ethambutol HCl + Rifampicin + Isoniazid (Myrin-P Forte) is a combination of ethambutol, rifampicin, isoniazid, and pyrazinamide. Each component has specific reported adverse reactions shown below.

Adverse Reactions Relating to Ethambutol:

The following reactions have occurred with ethambutol. Since ethambutol is a component of **Pyrazinamide + Ethambutol HCl + Rifampicin + Isoniazid (Myrin-P Forte)**, these reactions may also occur with the use of **Pyrazinamide + Ethambutol HCl + Rifampicin + Isoniazid (Myrin-P Forte)** Tablets**.**

Blood and Lymphatic System Disorders

Leukopenia, thrombocytopenia, neutropenia.

Immune System Disorders

Anaphylactic/anaphylactoid reaction (including shock and fatalities).
Hypersensitivities syndrome consisting of cutaneous reaction (such as rash or exfoliative dermatitis), eosinophilia, and one or more of the following: hepatitis, pneumonitis, nephritis, myocarditis, and pericarditis. Fever and lymphadenopathy may be present.

Metabolism and Nutrition Disorders

Anorexia, elevations of serum uric acid concentration.

Nervous System Disorders

Dizziness, hypoesthesia, paresthesia.

Eye Disorders

Ethambutol may produce decreases in visual acuity including irreversible blindness, which appear to be due to optic neuritis. This effect may be related to dose and duration of treatment, and patients receiving ethambutol for prolonged periods at doses >20 mg/kg have an increased risk for development of optic neuritis. This effect is generally reversible when administration of the drug is discontinued promptly, and recovery of visual acuity generally occurs over a period of weeks to months after the drug has been discontinued. Some patients have received ethambutol again after such recovery without recurrence of visual acuity loss.

However, in rare cases recovery may be delayed for up to one year or more, and irreversible blindness has also been reported. In addition, children and adults of low body weight (<40 kg) have an increased risk for development of optic neuritis. Because ethambutol has a unique effect on the eye, it is recommended that patients undergo a full ophthalmologic examination before starting treatment and periodically during drug administration.

This examination should include visual acuity, color vision, perimetry and ophthalmoscopy. Because this drug may have adverse effects on vision, physical examination should include ophthalmoscopy, finger perimetry and testing of color 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 that variations in vision are not due to the underlying disease conditions. In such patients, consideration should be given to relationship between benefits expected and possible visual deterioration since evaluation of visual changes is difficult. 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 medicine administration, except that it should be done once monthly when the patient is on a dosage of 15 mg/kg/day or more. Snellen eye charts are recommended for testing of visual acuity. Clinical studies have shown that there are definite fluctuations of 1 or 2 lines of the Snellen chart in the visual acuity of many tuberculous patients not receiving ethambutol.

The table below may be useful in interpreting possible changes in visual acuity attributable to ethambutol.

Initial Snellen Value	Value Indicating Significant Decrease	Significant Number of Lines	Decrease-Number of Points
20/13	20/25	3	12
20/15	20/25	2	10
20/20	20/30	2	10
20/25	20/40	2	15
20/30	20/50	2	20
20/40	20/70	2	30
20/50	20/70	1	20

In general, changes in visual acuity less than those indicated under “Significant Number of Lines” and “Decrease-Number of Points”, may be due to chance findings, limitations of the testing method or physiologic variability. Conversely, changes in visual acuity equaling or exceeding those under “Significant Number of Lines” and “Decrease-Number of Points” indicate need for retesting and careful evaluation of the patient’s visual status. If careful evaluation confirms that magnitude of visual change and fails to reveal another cause, ethambutol should be discontinued and the patient re-evaluated at frequent intervals. Progressive decreases in visual acuity during therapy must be considered to be due to ethambutol. If corrective glasses are used prior to treatment, these must be worn during visual acuity testing. During 1 to 2 years of therapy, a refractive error may develop which must be corrected in order to obtain accurate test results. Testing of visual acuity through a pinhole eliminates the refractive error. Patients developing visual abnormality during

ethambutol treatment may show subjective visual symptoms before, or simultaneous 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.

In addition, visual field defect, color blindness, scotoma, optic neuropathy and retrobulbar neuritis have been reported.

Patients should be advised to report promptly to their physician any change in visual acuity.

Gastrointestinal Disorders

Epigastric distress, constipation, nausea, vomiting, abdominal pain, anorexia, metallic taste, dry mouth.

Hepatobiliary Disorders

Impairment of liver function, as indicated by abnormalities in liver function tests and liver toxicities including fatalities, has been reported. Jaundice and transient liver dysfunction have also been reported. Because ethambutol is recommended for therapy in conjunction with 1 or more other antituberculosis drugs, these changes may be related to concurrent therapy.

Skin and Subcutaneous Tissue Disorders

Pruritus, rash, Stevens-Johnson Syndrome, toxic epidermal necrolysis.

Musculoskeletal, Connective Tissue, and Bone Disorders

Joint pains, acute gout.

Respiratory Disorders, Thoracic and Mediastinal Disorders

Pulmonary infiltrates with or without eosinophilia.

Renal and Urinary Disorders

Gout, hyperuricemia.

General Disorders and Administration Site Conditions

Malaise, fever.

Adverse Reactions Relating to Rifampicin:

The following reactions have occurred with rifampicin. Because rifampicin is a component of **Pyrazinamide +Ethambutol HCl + Rifampicin + Isoniazid (Myrin-P Forte)**, these reactions may also occur with the use of **Pyrazinamide + Ethambutol HCl + Rifampicin + Isoniazid (Myrin-P Forte).**

Blood and Lymphatic System Disorders

Thrombocytopenia, leukopenia, hemolytic anemia, anemia, eosinophilia.

Thrombocytopenia has occurred when ethambutol and rifampicin were administered concomitantly according to an intermittent dose schedule twice weekly and in high doses.

Immune System Disorders

Hypersensitivity reactions.

Metabolism and Nutrition Disorders

Elevations in serum uric acid.

Nervous System Disorders

Headache, drowsiness, fatigue, ataxia, dizziness, inability to concentrate, mental confusion, muscular weakness, generalized numbness, pain in the extremities.

Eye Disorders

Visual disturbances, exudative conjunctivitis.

Gastrointestinal Disorders

Heartburn, nausea, vomiting, diarrhea, epigastric distress, anorexia, gas, cramps, sore mouth, sore tongue, fungal overgrowth.

Hepatobiliary Disorders

Hepatitis or hepatitis prodromal syndrome, shock-like syndrome with hepatic involvement, abnormal liver function tests (elevation in serum bilirubin, serum transaminases, and alkaline phosphatase).

Hepatitis from rifampicin may occur in patients with normal hepatic function. Chronic liver disease, alcoholism, and old age appear to increase the incidence of severe hepatic problems when rifampicin is given alone or concurrently with isoniazid.

Skin and Subcutaneous Tissue Disorders

Pruritus, urticaria, rash, pemphigoid reaction, purpura.

Renal and Urinary System Disorders

Elevations in BUN, interstitial nephritis, alteration in kidney function.

Hemolysis, hemoglobinuria, hematuria, renal insufficiency or acute renal failure have been reported and are generally considered to be hypersensitivity reactions. These have occurred during intermittent therapy or when treatment was resumed following intentional or accidental interruption of a daily dosage regimen and were reversible when rifampicin was discontinued and appropriate therapy instituted.

Reproductive System and Breast Disorders

Menstrual disturbances.

General Disorders and Administration Site Conditions

Fever, "flu-like" syndrome.

Adverse Reactions Relating to Isoniazid:

The following reactions have occurred with isoniazid. Because isoniazid is a component of **Pyrazinamide + Ethambutol HCl + Rifampicin + Isoniazid (Myrin-P Forte)**, these reactions may also occur with the use of **Pyrazinamide + Ethambutol HCl + Rifampicin + Isoniazid (Myrin-P Forte).**

Blood and Lymphatic System Disorders

Agranulocytosis, eosinophilia, anemia, thrombocytopenia, methemoglobinemia, vasculitis, lymphadenopathy.

Immune System Disorders

Allergic reactions, lupus-like syndrome, rheumatoid syndrome.

Hypersensitivity may result in fever, various skin eruptions, hepatitis, rash (including morbilliform, maculopapular, purpuric, and urticarial), vasculitis, and lymphedema.

Nervous System Disorders

Peripheral neuropathy is the most common toxic effect of isoniazid. 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 paresthesia of the feet and hands. The incidence is higher in slow acetylators.

Isoniazid may cause peripheral neuritis by acting as a pyridoxine antagonist. Pyridoxine has been used successfully for prophylaxis and treatment of isoniazid-induced peripheral neuritis. Headache, insomnia, restlessness, mental confusion, toxic psychoses, increased reflexes, muscle twitching, paresthesias.

Convulsions have occurred in apparently normal individuals when given isoniazid in high doses.

Eye Disorders

Optic neuritis and optic atrophy have been reported. Ophthalmologic examinations should be carried out wherever visual complaints occur.

Ear and Labyrinth Disorders

Tinnitus.

Metabolism and Nutrition Disorders

Pellagra, hyperglycemia, metabolic acidosis, gynecomastia.

Gastrointestinal Disorders

Epigastric distress, nausea, vomiting, constipation.

Hepatobiliary Disorders

Severe and sometimes fatal hepatitis may occur and may develop even after many months of treatment. The risk of developing hepatitis is age related and is increased with daily consumption of alcohol.

Cases of pancreatitis have mainly been seen in patients treated with combination therapy for active tuberculosis.

Skin and Subcutaneous Tissue Disorders

Rash, exfoliative dermatitis.

Musculoskeletal, Connective Tissue, and Bone Disorders

Arthritic symptoms.

Renal and Urinary Disorders

Urinary disturbance in male (prostatic obstruction syndrome), urinary retention.

General Disorders and Administration Site Conditions

Fever, dryness of the mouth.

Adverse Reactions Relating to Pyrazinamide:

The principal adverse effect is a hepatic reaction (See **Section 4.4. Special warnings and precautions for use**). Hepatotoxicity appears to be dose related, and may appear at any time during therapy. Jaundice, hepatitis, and hepatic failure have been reported. Fatalities have been reported with hepatitis and hepatic failure. Increased hepatotoxicity may occur with the

co-administration with other antituberculous medications (See **Section 4.4. Special warnings and precautions for use**).

The following reactions have occurred with pyrazinamide. Because pyrazinamide is a component of **Pyrazinamide + Ethambutol HCl + Rifampicin + Isoniazid (Myrin- P Forte)**, these reactions may also occur with the use of **Pyrazinamide + Ethambutol HCl + Rifampicin + Isoniazid (Myrin-P Forte).**

Blood and Lymphatic System Disorders

Thrombocytopenia, sideroblastic anemia with erythroid hyperplasia, vacuolation of erythrocytes, abnormalities in blood clotting mechanisms, porphyria.

Immune System Disorders

Hypersensitivity reactions including rash, urticaria, pruritus.

Metabolism and Nutrition Disorders

Anorexia, hyperuricemia. Increased difficulty has been reported in controlling diabetes mellitus when diabetics are given pyrazinamide.

Gastrointestinal Disorders

Nausea, vomiting.

Skin and Subcutaneous Tissue Disorders

Acne, photosensitivity, skin rashes.

Renal and Urinary System Disorders

Dysuria, interstitial nephritis.

Musculoskeletal, Connective Tissue, and Bone Disorders

Arthralgia, gout, myalgia.

General Disorders

Fever, malaise.

4.9. Overdose and Treatment

Overdose of **Pyrazinamide + Ethambutol HCl + Rifampicin + Isoniazid (Myrin-P Forte)** produces signs and symptoms within 30 minutes to 3 hours 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 findings. Loss of visual acuity may indicate an overdose of ethambutol. Abnormal liver function tests have been associated with overdoses of pyrazinamide.

Treatment

Discontinue **Pyrazinamide + Ethambutol HCl + Rifampicin + Isoniazid (Myrin-P Forte).** Secure the airway and establish adequate respiratory exchange. Pyridoxine should be administered in a dose of 1 gram for each gram of isoniazid apparently ingested. Gastric lavage within the first 2 to 3 hours 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/vomiting. Forced osmotic diuresis (with measured intake and output) will help to promote excretion of the drug. Extracorporeal hemodialysis may be required.

5.0. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic Properties

Pyrazinamide + Ethambutol HCl + Rifampicin + Isoniazid (Myrin-P Forte) has tuberculostatic properties.

The mechanism of action of ethambutol is not fully known. It diffuses into mycobacteria and appears to suppress multiplication by interfering with RNA synthesis. It is effective only against mycobacteria that are actively dividing.

Rifampicin inhibits bacterial RNA synthesis by bonding strongly to the beta subunit of DNA-dependent RNA polymerase, preventing the attachment of the enzyme to DNA and thus blocking initiation of RNA transcription.

Isoniazid is a bactericidal antitubercular agent, which is active against actively dividing mycobacteria, and its mode of action may relate to inhibition of mycolic acid synthesis and the disruption of the cell wall in susceptible organisms.

The mechanism of action of pyrazinamide is unknown. Pyrazinamide may be bacteriostatic or bactericidal depending on its concentration and the susceptibility of the organism.

5.2. Pharmacokinetic Properties

Data from a relative bioavailability study in healthy volunteers receiving **Pyrazinamide + Ethambutol HCl + Rifampicin + Isoniazid (Myrin-P Forte)** in the fasted state show that

each of the 4 active ingredients rifampicin, isoniazid, pyrazinamide and ethambutol, is bioequivalent to the respective reference drug product when these four products are given together.

Ethambutol
Ethambutol is readily absorbed from the gastrointestinal tract. A single dose of 25 mg/kg produces a peak plasma concentration of 2 to 5 mcg/mL between 2 to 4 hours. It is distributed into most tissues including the lung and localized within pulmonary alveolar and axillary lymph node macrophages.

Within 24 hours after administration, nearly 75% of an ingested dose of ethambutol is excreted as the unchanged drug, and up to 15% is excreted as the 2 metabolites in urine via glomerular filtration and tubular secretion. The mean elimination half-life is approximately 3 hours. Ethambutol accumulates in patients with impaired renal function.

Ethambutol crosses the placenta and is excreted in breast milk.

Rifampicin

Rifampicin is well absorbed following oral administration. A peak plasma concentration of 7 to 9 mcg /mL is reached within 2 to 4 hours after a dose of 600 mg. Food decreases the absorption of rifampicin. Rifampicin undergoes enterohepatic recirculation after absorption. It diffuses well into most body tissues including the cerebrospinal fluid and is metabolized primarily into the deacetylated metabolite. This deacetylated metabolite possesses the antibacterial activity of the unchanged drug. Approximately 65% of a dose of rifampicin is excreted in the feces and nearly 30% in the urine less than half of which may be unchanged drug. The elimination half-life of rifampicin following initial doses varies from 2 to 5 hours and decreases to 2 to 3 hours after repeated administration due to increased hepatic metabolism. Although renal clearance of rifampicin is reduced in patients with impaired renal function, dosage adjustment in these patients is not necessary. The clearance of rifampicin is significantly decreased in patients with liver disease. Refer to **Sections 4.3. Contraindications, 4.4. Special warnings and precautions for use and 4.8. Undesirable effects** for more information regarding the use of rifampicin in patients with hepatic insufficiency.

Rifampicin crosses the placenta and is excreted in breast milk.

Isoniazid

Isoniazid is rapidly absorbed and peak plasma concentrations are attained 1 to 2 hours after oral ingestion. Food decreases the bioavailability of isoniazid. Tissue distribution of isoniazid is extensive. Significant levels of isoniazid are achieved in several body fluids (pleural, ascitic and cerebrospinal fluids) and tissues. Isoniazid is metabolized primarily by acetylation and dehydrazination. The rate of acetylation is genetically determined. The plasma concentrations and half-life of the drug are, therefore, dependent on the acetylation rate of individuals. The mean elimination half-life in adults varies widely from 1.2 hours to 5.0 hours. Nearly 75% to 95% of a dose of isoniazid is excreted mainly as metabolites in urine within 24 hours. Consideration should be given to the accumulation of the drug in patients

with renal impairment. Patients with acute or chronic liver disease have higher serum isoniazid concentrations and exhibit a longer serum half-life for isoniazid. Dosage adjustment may be necessary in these patients to avoid adverse effects of the drug.

Isoniazid crosses the placenta and is excreted in breast milk.

Pyrazinamide

Pyrazinamide is well absorbed from the gastrointestinal tract. The bioavailability of pyrazinamide is unaltered by food. Pyrazinamide is widely distributed in most body fluids and tissues including the liver, lungs and cerebrospinal fluid. Pyrazinamide is hydrolyzed to its active metabolite, pyrazinoic acid, which is subsequently hydroxylated to 5-hydroxy pyrazinoic acid. The elimination half-life of pyrazinamide is approximately 9 to 10 hours in patients with normal renal and hepatic function. The plasma half-life may be prolonged in patients with impaired renal or hepatic function. Pyrazinamide is excreted primarily by glomerular filtration. Nearly 70% of an oral dose is excreted mainly as metabolites in urine.

6.0. PHARMACEUTICAL PARTICULARS

6.1. Storage Condition

Store at temperatures not exceeding 30°C.
Protect from light, heat and moisture.

6.2. Availability

Blister Pack x 8's (Box of 80 tablets)

7.0. FDA REGISTRATION NUMBER

400 mg/275 mg/150 mg/75 mg Tablet: DRP – 3810

8.0. DATE OF FIRST AUTHORIZATION /RENEWAL OF THE AUTHORIZATION

400 mg/275 mg/150 mg/75 mg Tablet: 05 Jan 1998

Keep out of reach of children.

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

Seek medical attention immediately at the first sign of any adverse drug reaction.

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

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