Each tablet contains:

**Ethambutol HCl** ................. 275 mg
**Rifampicin** .................. 150 mg
**Isoniazid** .................. 75 mg
**Pyrazinamide** ............. 400 mg

**Myrin-P Forte® Tablet**

**ANTITUBERCULOSIS**

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

**PHARMACOLOGICAL ACTION**
**Ethambutol HCl / Rifampicin / Isoniazid / Pyrazinamide (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.

**PHARMACOKINETICS**
Data from a relative bioavailability study in healthy volunteers receiving **Ethambutol HCl / Rifampicin / Isoniazid / Pyrazinamide (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 **Contraindications** and **Warnings** and to **Special Precautions and Adverse Reactions** 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.

**INDICATIONS**

**Ethambutol HCl / Rifampicin / Isoniazid / Pyrazinamide (Myrin-P Forte)** is indicated for the initial phase treatment and re-treatment of all forms of tuberculosis in category I and II patients caused by susceptible strains of mycobacteria.

**Category I:** New cases of smear-positive pulmonary tuberculosis and other newly diagnosed seriously ill patients with severe forms of tuberculosis.

**Category II:** Relapse or treatment failure patients.

**CONTRAINDICATIONS**

**Ethambutol HCl / Rifampicin / Isoniazid / Pyrazinamide (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. **Ethambutol HCl / Rifampicin / Isoniazid / Pyrazinamide (Myrin-P Forte)** is also contraindicated in the presence of alcoholism, optic neuritis, impaired hepatic function and severe renal insufficiency, hyperuricemia and/or gouty arthritis, in the presence of jaundice, or in patients with known retrobulbar neuritis unless the doctor determines that it may be used. **Ethambutol HCl / Rifampicin / Isoniazid / Pyrazinamide (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.

**SPECIAL WARNINGS**

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 **Special Precautions and Adverse Reactions**).

Liver toxicities including fatalities have been reported (See **Special Precautions and Adverse Reactions**). Baseline and periodic assessment of hepatic function should be performed.

Patients started on pyrazinamide should have baseline liver function determinations. Those patients with preexisting liver disease or those at increased risk for drug-related hepatitis (e.g. alcohol abusers) should be followed closely.

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

Rifampicin / pyrazinamide combination therapy should be used with caution, especially in patients at risk for hepatotoxicity, and should not be used in patients with a history of liver disease.

Rifampicin / pyrazinamide combination therapy should generally not be offered for treatment of latent tuberculosis infection.
WARNINGS
Ethambutol has a unique effect on the eye. It is, therefore, recommended that all patients taking Ethambutol HCl / Rifampicin / Isoniazid / Pyrazinamide (Myrin-P Forte) should undergo a full ophthalmic examination before starting treatment and periodically during drug administration. This examination should include visual acuity, colour 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 patients consideration should be given to the relationship between benefits expected from Ethambutol HCl / Rifampicin / Isoniazid / Pyrazinamide (Myrin-P Forte) administration and possible visual deterioration. See Special Precautions and Adverse Reactions.

Ethambutol HCl / Rifampicin / Isoniazid / Pyrazinamide (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 Ethambutol HCl / Rifampicin / Isoniazid / Pyrazinamide (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, Ethambutol HCl / Rifampicin / Isoniazid / Pyrazinamide (Myrin-P Forte) should be discontinued. Caution should be exercised when Ethambutol HCl / Rifampicin / Isoniazid / Pyrazinamide (Myrin-P Forte) is administered to patients with a history of gout.

Ethambutol HCl / Rifampicin / Isoniazid / Pyrazinamide (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. Ethambutol HCl / Rifampicin / Isoniazid / Pyrazinamide (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, Ethambutol HCl / Rifampicin / Isoniazid / Pyrazinamide (Myrin-P Forte) should be discontinued promptly.

Urine, feces, saliva, sputum and tears may be colored red-orange by the rifampicin component of Ethambutol HCl / Rifampicin / Isoniazid / Pyrazinamide (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 Ethambutol HCl / Rifampicin / Isoniazid / Pyrazinamide (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 colour.

PREGNANCY AND LACTATION
The components of Ethambutol HCl / Rifampicin / Isoniazid / Pyrazinamide (Myrin-P Forte Tablets) 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 vertebrae 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.

Ethambutol is excreted into breast milk. The use of Ethambutol should be considered only if the expected benefit to the mother outweighs the potential risk to the infant.

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

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

**DOSAGE AND DIRECTIONS FOR USE**

Ethambutol HCl / Rifampicin / Isoniazid / Pyrazinamide (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**

For Category I patients, Ethambutol HCl / Rifampicin / Isoniazid / Pyrazinamide (Myrin-P Forte) is given daily during the initial phase (8 weeks) of treatment. If sputum is smear-positive after the initial 8 weeks, the initial phase treatment with Ethambutol HCl / Rifampicin / Isoniazid / Pyrazinamide (Myrin-P Forte) should be continued for a further 4 weeks.
For Category II patients, Ethambutol HCl / Rifampicin / Isoniazid / Pyrazinamide (Myrin-P Forte) is given daily during the initial phase (12 weeks) of treatment. Streptomycin should be given in addition to Ethambutol HCl / Rifampicin / Isoniazid / Pyrazinamide (Myrin-P Forte) during the first 8 weeks of the initial phase. If sputum is smear-positive after the initial 12 weeks of treatment, Ethambutol HCl / Rifampicin / Isoniazid / Pyrazinamide (Myrin-P Forte) should be given for an additional 4 weeks. Patients in category II are at an increased risk of developing multidrug resistant disease and should receive fully supervised treatment for at least the first 12 weeks.

WHO guidelines indicate that Ethambutol HCl / Rifampicin / Isoniazid / Pyrazinamide (Myrin-P Forte) should be given daily during the initial phase treatment of Category I and Category II patients with the dose adjusted according to body weight, as follows:

- 40 to 54 kg: 3 tablets
- 55 to 70 kg: 4 tablets
- > 71 kg: 5 tablets

Ethambutol HCl / Rifampicin / Isoniazid / Pyrazinamide (Myrin-P Forte) should not be used to treat patients of low body weight (<40 kg).

Category I and II 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 Ethambutol HCl / Rifampicin / Isoniazid / Pyrazinamide (Myrin-P Forte) to treat elderly patients.

**Renal insufficiency**
Ethambutol accumulates in patients with renal insufficiency. Pyrazinamide is also excreted thru the kidney as unchanged drug. If renal impairment is severe or if patients are slow acetylators, a reduction in dosage may be required.

**Hepatic Insufficiency**
Dose adjustment of Ethambutol HCl / Rifampicin / Isoniazid / Pyrazinamide (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.

**SPECIAL PRECAUTIONS AND ADVERSE REACTIONS**
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.
Ethambutol HCl / Rifampicin / Isoniazid / Pyrazinamide (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.

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

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

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.

As with any potent drug, baseline and periodic assessment of organ system functions, including renal, hepatic and hematopoietic, should be performed.

**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.

Ethambutol HCl / Rifampicin / Isoniazid / Pyrazinamide (Myrin-P Forte) is not recommended for use in pediatric patients under thirteen years of age since safe conditions for use have not been established. Ethambutol HCl / Rifampicin / Isoniazid / Pyrazinamide (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 Ethambutol HCl / Rifampicin / Isoniazid / Pyrazinamide (Myrin-P Forte), these reactions may also occur with the use of Ethambutol HCl / Rifampicin / Isoniazid / Pyrazinamide (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, hypoaesthesia, paraesthesia.

**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 >20mg/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, colour 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.

<table>
<thead>
<tr>
<th>Initial Snellen Value</th>
<th>Value Indicating Significant Decrease</th>
<th>Significant Number of Lines</th>
<th>Decrease-Number of Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>20/13</td>
<td>20/25</td>
<td>3</td>
<td>12</td>
</tr>
<tr>
<td>20/15</td>
<td>20/25</td>
<td>2</td>
<td>10</td>
</tr>
<tr>
<td>20/20</td>
<td>20/30</td>
<td>2</td>
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<td>20/25</td>
<td>20/40</td>
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<td>15</td>
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<tr>
<td>20/30</td>
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<td>2</td>
<td>20</td>
</tr>
<tr>
<td>20/40</td>
<td>20/70</td>
<td>2</td>
<td>30</td>
</tr>
<tr>
<td>20/50</td>
<td>20/70</td>
<td>1</td>
<td>20</td>
</tr>
</tbody>
</table>

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 equalling 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.

**Interactions**
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.

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

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 coumadin.

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:


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 $B_{12}$. Alternative methods must be considered when determining folate and vitamin $B_{12}$ 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.

**Adverse Reactions Relating to Isoniazid:**

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

**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.

**Interactions**
Chronic use of isoniazid may decrease the plasma clearance and prolong the duration of action of
alfentanil, coumarin, inandione 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 sulphate urine glucose tests may occur.

**Adverse Reactions Relating to Pyrazinamide:**
The principal adverse effect is a hepatic reaction (See *Warnings*). 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 *Special Precautions and Adverse Reactions*).

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

**Hepatobiliary Disorders**
The principal effect is an hepatic reaction. Hepatotoxicity appears to be dose-related and may appear at any time during therapy. Hepatitis and hepatic failure (including fatalities) have been reported. Patients may have increased liver enzymes, including AST and ALT, and increased serum bilirubin. Hepatomegaly, splenomegaly, and jaundice may develop.

**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.

Interactions
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.

Increased hepatotoxicity may occur with the co-administration with other antituberculous medications (See Contraindications, Special Warnings, Special Precautions and Adverse Reactions.)

Hepatotoxicity has also been reported with rifampicin/pyrazinamide combination therapy. (See Special Warnings, Special Precautions and Adverse Reactions.)

SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF TREATMENT
Overdose of Ethambutol HCl / Rifampicin / Isoniazid / Pyrazinamide (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 of Overdose
Discontinue Ethambutol HCl / Rifampicin / Isoniazid / Pyrazinamide (Myrin-P Forte). Secure the airway and establish adequate respiratory exchange. Pyridoxine should be administered in a dose of 1 gram for each gram ofisoniazid 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. Extracorporal hemodialysis may be required.

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

AVAILABILITY
Blister strips containing 8 tablets each in packs of 10 x 8's.

STORAGE CONDITION
Store at a temperature not exceeding 25°C. Protect from light, heat and moisture.
KEEP OUT OF REACH OF CHILDREN.

Manufactured by:
**WYETH PAKISTAN LIMITED**
S-33, Hawkes Bay Road, S.I.T.E.,
Karachi, Pakistan

Imported by:
**WYETH PHILIPPINES, INC.**
2236 Chino Roces Avenue
Makati City, Philippines