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MYRIN[®] Tablets

(Ethambutol HCl-Rifampicin-Isoniazid)

1. NAME OF THE MEDICINAL PRODUCT

MYRIN[®], MYRIN[®] FORTE

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Combination of Ethambutol HCl, Rifampicin, Isoniazid as:

MYRIN[®], MYRIN[®] FORTE

Each MYRIN[®] tablet contains:

Active ingredient	Composition
Ethambutol HCl	300 mg
Rifampicin	150 mg
Isoniazid	75 mg

Myrin[®] Forte tablet contains:

Active ingredient	Composition
Ethambutol HCl	275 mg
Rifampicin	150 mg
Isoniazid	75 mg

3. PHARMACEUTICAL FORM

Tablets

4. CLINICAL PARTICULARS

4.1. THERAPEUTIC INDICATIONS

MYRIN[®] is indicated in continuation phase therapy of new and re- treatment cases. In populations with known or suspected high levels of Isoniazid resistance, new TB patients may receive MYRIN[®] therapy in the continuation phases an acceptable alternative to Rifampicin and Isoniazid.

4.2. POSOLOGY AND METHOD OF ADMINISTRATION

MYRIN[®] 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.

Proposed Dosage

The daily dosage range for three essential drugs recommended by authorities in the short course chemotherapy are:

Ethambutol 15 mg – 25 mg/kg
Rifampicin 10 mg/kg up to 600 mg
Isoniazid 5 mg - 10 mg/kg up to 300 mg

Each MYRIN[®] tablet contains:

Ethambutol HCl 300 mg, Rifampicin 150 mg and Isoniazid 75 mg

Patients should be given the following single daily dose one to two hours **before a meal**.

One tablet/15 kg body weight.

Alternatively, the following dosage regimen may be used.

(Always calculate dosage according to weight of the patient. Use of separate drugs is advised in case of weight dosage discrepancy with fixed dose combinations.)

<u>PATIENT BODY WEIGHT (KG)</u>	<u>Continuation Phase</u>
	<u>04 Months in NEW CASES</u>
	<u>05 Months in RE-TREATMENT CASES</u>
	<u>MYRIN[®]</u>
<u>30-39</u>	<u>02 Tablets</u>
<u>40-54</u>	<u>03 Tablets</u>
<u>55 & above</u>	<u>04 Tablets</u>

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 MYRIN[®] to treat elderly patients.

Renal Insufficiency

Ethambutol accumulates in patients with renal insufficiency. If renal impairment is severe or if patients are slow acetylators, a reduction in dosage may be required.

Hepatic Insufficiency

Dose adjustment of MYRIN[®] 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 clearance of rifampicin is significantly decreased in patients with liver disease.

4.3. CONTRAINDICATIONS

MYRIN[®] should not be used in patients with a known hypersensitivity to ethambutol, rifampicin or isoniazid, or to any of the excipients in this product.

MYRIN[®] 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.

MYRIN[®] 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).

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.

Ethambutol has a unique effect on the eye. It is, therefore, recommended that all patients taking MYRIN[®] 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 MYRIN[®] administration and possible visual deterioration (see section 4.8. Undesirable Effects).

Urine, feces, saliva, sputum and tears may be colored red-orange by the rifampicin component of MYRIN[®]. 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 MYRIN[®] therapy.

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

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.

MYRIN[®] should be administered with care to epileptic patients, since it may induce convulsions, or to patients in psychotic states characterized by mania or hypomania.

MYRIN[®] should be used with caution in patients with diabetes mellitus, as management may be more difficult.

MYRIN[®] may diminish visual acuity and color 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.

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 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:

Aminophylline, theophylline, sulphonylurea 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.

4.6. FERTILITY, PREGNANCY AND LACTATION

The components of MYRIN[®] have harmful pharmacological effects on pregnancy and the fetus. There are no adequate data from the use of rifampicin, ethambutol 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 to 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 hare lip and cleft palate.

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

Rifampicin and isoniazid are excreted in breast milk. Therefore, infants should not be breast fed by patients receiving MYRIN[®]

4.7. EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

MYRIN[®] may diminish visual acuity and color vision, which may affect the ability to drive and use machines.

4.8. UNDESIRABLE EFFECTS

MYRIN[®] is a combination of ethambutol, rifampicin and isoniazid. 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 MYRIN[®], these reactions may also occur with the use of MYRIN[®].

Blood and Lymphatic System Disorders

Leukopenia, thrombocytopenia, neutropenia.

Immune System Disorders

Anaphylactic/anaphylactoid reaction (including shock and fatalities).

Hypersensitivity 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, retrobulbar neuritis and congenital ophthalmic abnormalities 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 (aspartate aminotransferase increased, alanine aminotransferase increased) 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 MYRIN[®], these reactions may also occur with the use of MYRIN[®].

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 MYRIN[®], these reactions may also occur with the use of MYRIN[®].

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.

4.9. OVERDOSE

Overdose of MYRIN[®] 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

Treatment

Discontinue MYRIN[®]. 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.

Active diuresis (with measured intake and output) will help to promote excretion of the drug. Bile drainage may be indicated in the presence of serious impairment of hepatic function lasting more than 24-48 hours. Under these circumstances, extracorporeal hemodialysis may be required.

5. PHARMACOLOGICAL PROPERTIES

5.1. PHARMACODYNAMIC PROPERTIES

MYRIN[®] 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.

5.2. PHARMACOKINETIC PROPERTIES

Data from a relative bioavailability study in healthy volunteers receiving MYRIN[®] in the fasted state show that each of the 3 active ingredients rifampicin, isoniazid 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 Precaution 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.

5.3. PRECLINICAL SAFETY DATA

Information not available

6. PHARMACEUTICAL PARTICULARS

6.1. LIST OF EXCIPIENTS

- Sucrose
- Sorbitol Solution
- Gelatin Bloom
- Sodium Starch Glycolate
- Sodium Lauryl Sulphate
- Cellulose Microcrystalline
- Magnesium Stearate

Stearic Acid
Opadry
Light Mineral oil
Talc powder: *
Purified water: *

* Used in the manufacturing process but does not appear in the final product

6.2. INCOMPATIBILITIES

Information not available

6.3. SHELF LIFE

24 Months

6.4. SPECIAL PRECAUTIONS FOR STORAGE

Store in a cool dry place below 30°C.
Protect from heat and moisture.
Drugs should be kept out of the reach of children

6.5. NATURE AND CONTENTS OF CONTAINER

MYRIN®:

Pack: 80's

MYRIN FORTE®:

Pack: 80's & 100's

Myrin/LPD/PK-05

According to Philippines LPD Dated: 01 November 2020 and approved information in Pakistan

Marketed by:

Pfizer Pakistan Limited

Please visit our website www.pfizer.com.pk for latest version of Product leaflet.

7. REFERENCES

- 1- WHO Treatment of Tuberculosis Guidelines – Fourth Edition
- 2- Pakistan Chest Society – National Guidelines for Management of Tuberculosis – PCS Publication No.3
- 3- Isoniazid_RMC_Minutes_2019_02_15