Myrin®-P Forte
(Ethambutol HCl + Rifampicin + Isoniazid + Pyrazinamide) Tablets

1. NAME OF THE MEDICINAL PRODUCT

Myrin®-P Forte

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Combination of Ethambutol HCl, Rifampicin, Isoniazid, and Pyrazinamide is available as:

Each Myrin®-P Forte tablet (As per WHO recommended Anti-TB formulation) contains:

Active ingredient	Composition
Ethambutol hydrochloride	275 mg
Rifampicin	150 mg
Isoniazid	75 mg
Pyrazinamide	400 mg

3. PHARMACEUTICAL FORM

Tablet

4. CLINICAL PARTICULARS

4.1. THERAPEUTIC INDICATIONS

For initial treatment of tuberculosis according to World Health Organisation (WHO) guidelines.

Consideration should also be given to other official guidance on the appropriate use of anti-tuberculosis agents.

4.2. POSOLOGY AND METHOD OF ADMINISTRATION

Posology

Myrin®-P Forte should be administered under the supervision of a physician trained in the management of tuberculosis.

The recommended dose and dosage schedules for Myrin®-P Forte are based on WHO guidelines:

- Fixed-dose-combination tablets for the treatment of tuberculosis; WHO/CDS/CPC/TB/99.267, 1999.

- The rationale for recommending fixed-dose combination tablets for treatment of tuberculosis; Bulletin of the World Health Organisation, 2001, 79: 61-68.

- Informal Consultation on 4-drug Fixed-Dose Combination, Geneva 2001.

- Treatment of Tuberculosis Guideline, 4th Ed. WHO/HTM/TB/2009.420.

These dose and dose schedules may differ from recommendations on the use of anti-tuberculosis agents given in other official guidance.

Myrin®-P Forte is a fixed combination product intended for use in the initial intensive phase of anti-tuberculous treatment. Myrin®-P Forte should be administered on a daily basis throughout the 2 month initial phase of treatment. When indicated, other anti-tuberculous medicinal products such as streptomycin may be added in the initial phase of treatment.

Myrin®-P Forte is a fixed combination product that should only be used when the fixed ratio of rifampicin 150 mg, isoniazid 75 mg, pyrazinamide 400 mg and ethambutol hydrochloride 275 mg will permit treatment of an individual patient in line with official recommendations and practice.

Table 1: WHO-recommended essential anti-TB drugs

Essential drug	**Abbreviation**	**Recommended dosage (dose range), mg/kg Daily**
Isoniazid	H	5 (4-6)
Rifampicin	R	10 (8-12)
Pyrazinamide	Z	25 (20-30)
Streptomycine	S	15 (12-18)
Ethambutol	E	15 (15-20)

Method of administration

Myrin®-P Forte tablets are administered orally. The tablets should be given as a single dose (number of tablets depending on the patient's bodyweight, see Table 2), in a fasting state at least 1 hour before a meal.

Table 2: WHO-recommended number of tablets with fixed-dose combinations of anti-TB drugs in adults

			Duration	**Patient's bodyweight (in kg)**			
				30-39	**40-54**	**55-70**	**>70**
		Initial phase – daily					
either	Myrin®-P Forte	HRZE (75 mg+150 mg+400 mg+275 mg)	2 months	2	3	4	5
or (1)	HRZ	HRZ (75 mg+150 mg+400 mg)[1]	2 months	2	3	4	5
or (2)	Myrin®-P Forte + **S**	HRZE (75 mg+150 mg+400 mg+275 mg)	2 months	2	3	4	5
		+ S (vial 1 g)[2]		0.5	0.75	1	1
	and (subsequent)						
	Myrin®-P Forte	HRZE (75 mg+150 mg+400 mg+275 mg)[2]	1 month	2	3	4	5

		Continuation phase-daily					
either	RIN 150/75mg Tablets	HR (75 mg+150 mg)	4 months	2	3	4	5
or	Separate drugs	HE (150 mg+400 mg)	6 months	1.5	2	3	3
or [2]	RIN 150/75mg Tablets + E	HR (75 mg+150 mg)	5 months	2	3	4	5
		+ E (400 mg)[2]		1.5	2	3	3

[1]*In patients with non-cavitary, smear-negative pulmonary tuberculosis known to be HIV negative, patients known to be infected with fully drug susceptible bacilli and young children with primary TB.*

[2]*In patients with previously treated sputum smear-positive pulmonary tuberculosis: relapse, treatment after interruption, treatment failure, according to the category II of WHO recommendations.*

In case of chronic and multidrug-resistant tuberculosis cases (still sputum-positive after supervised re-treatment), specially designed standardised or individualised regimens are suggested for this category of patients (category IV of WHO recommendations).

Use in patients with body weight less than 30 kg:

Myrin®-P Forte is not a suitable dosage form for use in the treatment of patients with a body weight of less than 30 kg (see section **4.4. Special Warnings and Precautions for Use**).

Paediatric population:

Myrin®-P Forte is not a suitable dosage form for use in the treatment of children with a body weight of less than 30 kg. Myrin®-P Forte is not recommended in children under 8 years of age because of risk of aspiration and possible difficulties in evaluation of changes of visual acuity (see section **4.4. Special Warnings and Precautions for Use**).

Older people:

No special dosage regimen is necessary, but concurrent hepatic and/or renal insufficiency should be taken into account. Supplementation of pyridoxine (vitamin B6) may be useful.

Hepatic insufficiency:

Myrin®-P Forte should be used with caution and under strict medical supervision in impaired liver function (see section **4.4. Special Warnings and Precautions for Use**). Myrin®-P Forte is contraindicated in patients with a history of drug induced hepatitis and in patients with acute liver diseases (see section **4.3. Contraindications**).

Renal insufficiency:

Myrin®-P Forte should be used with caution in patients with moderate renal impairment (creatinine clearance 30 – 60 ml/min, see section **4.4. Special Warnings and Precautions for Use**). Myrin®-P Forte is contra-indicated in patients with severe renal impairment (creatinine clearance <30 ml/min, see section **4.3. Contraindications**).

Interruption of treatment

If initial intensive phase treatment with Myrin®-P Forte is interrupted for any reason including non-compliance, a fixed drug combination product such as Myrin®-P Forte is contraindicated for the resumption of treatment.

Rifampicin, isoniazid, pyrazinamide and ethambutol hydrochloride must be administered separately for the resumption of treatment, because rifampicin needs to be reintroduced at a lower dose. Reference should be made to official guidance on the appropriate resumption of treatment with anti-tuberculosis agents.

4.3. CONTRAINDICATIONS

• Hypersensitivity to rifamycins, isoniazid, pyrazinamide, ethambutol hydrochloride and/or to any of the excipients listed in section **6.1. List of Excipients**.

• A history of drug induced hepatitis and acute liver diseases regardless of its origin.

• Porphyria.

• Acute gouty arthritis.

• Severe renal impairment (creatinine clearance < 30 ml/min) (see section **4.4. Special Warnings and Precautions for Use**).

• Concomitant use with voriconazole and protease inhibitors, except ritonavir when given at full dose or 600 mg twice daily (see section **4.5. Interaction with Other Medicinal Products and Other Forms of Interaction**).

4.4. SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Warnings

In cases of known acetylation phenotypes, patients with extremely fast or extremely slow acetylating capability should receive the four components separately in order to facilitate dose adjustment of isoniazid.

Myrin®-P Forte should be withdrawn immediately if severe acute hypersensitivity reactions occur, such as thrombocytopenia, purpura, haemolytic anaemia, dyspnoea and asthma-like attacks, shock or renal failure as these are side effects that rifampicin may provoke in exceptional cases. Patients developing such reactions must never again be treated with rifampicin.

Myrin®-P Forte should be withdrawn if other signs of hypersensitivity appear, such as fever or skin reactions. For safety reasons, treatment should not be continued or resumed with rifampicin.

Myrin®-P Forte should be used with care in patients with visual defects. Ocular examinations including acuity, colour discrimination and visual field are recommended before starting treatment and periodically during treatment, especially if high doses are used. Patients should be questioned at every visit about their vision and advised to discontinue Myrin®-P Forte if a visual disturbance arises pending clinical evaluation.

Myrin®-P Forte is not recommended for children under 8 years of age because of risk of aspiration and because of the ethambutol hydrochloride component. Visual disturbances that may occur as a result of using ethambutol and that require immediate discontinuation of treatment may be difficult to diagnose in young children.

Myrin®-P Forte is not a suitable dosage form for use in the treatment of patients with a body weight of less than 30 kg.

Precautions

The precautions for the use of Myrin®-P Forte are the same as those that apply for the administration of rifampicin, isoniazid, pyrazinamide and ethambutol as individual medicinal products.

Patients should be advised against interrupting treatment.

Impaired liver function, undernourishment, alcoholism

Rifampicin, isoniazid, pyrazinamide and ethambutol are metabolised in the liver. Elevated transaminase levels, above the upper limit of normal (ULN), commonly occur. Liver dysfunction that may occur in the first few weeks of treatment usually returns to the normal range spontaneously, without interruption of treatment, and usually by the third month of treatment.

With rifampicin, although slight elevations of liver enzymes are common, clinical jaundice or evidence of hepatitis are rare. In patients taking both isoniazid and rifampicin, a cholestatic pattern with elevated alkaline phosphatase suggests that rifampicin is the causative agent, whereas a rise in transaminases may be caused by isoniazid, or rifampicin, or pyrazinamide, or the combination of the three agents.

Patients with impaired liver function should be treated with caution and under strict medical supervision.

In these patients, careful monitoring of liver function, especially serum glutamic pyruvic transaminase (SGPT/ALAT) and serum glutamic oxaloacetic transaminase (SGOT/ASAT) should be carried out prior to therapy and repeated weekly or fortnightly during therapy. If signs of hepatocellular damage occur, Myrin®-P Forte should be withdrawn.

A moderate rise in bilirubin and/or transaminase levels is not in itself an indication for interrupting treatment; rather, the decision should be made after repeating these liver function tests, noting trends in the levels, and considering them in conjunction with the patient's clinical condition.

Interrupting isoniazid treatment is recommended when there is clinical jaundice or transaminases exceeding 3 times the ULN. The fixed drug combination, Myrin®-P Forte, should be replaced by individual component formulations of rifampicin, isoniazid, pyrazinamide and ethambutol hydrochloride in order to facilitate treatment in these clinical circumstances.

Withdrawing rifampicin, pyrazinamide and ethambutol is recommended if liver function does not return to normal or transaminases exceed 5 times the ULN. The fixed drug combination, Myrin®-P Forte, should be replaced by individual component formulations in order to facilitate treatment in these clinical circumstances.

Use of isoniazid should be carefully monitored in patients with chronic liver disease. Severe and sometimes fatal hepatitis caused by isoniazid may occur and may develop even after many months of treatment. Hepatotoxicity associated with isoniazid therapy (thought to be caused by the metabolite diacetyl hydrazine) is rare in patients up to 20 years of age, but more common with increasing age and affecting up to 3% of patients aged over 50 years. The incidence of severe hepatotoxicity can be minimised by careful monitoring of liver function. Patients should be monitored with regard to the appearance of prodromal symptoms of hepatitis, such as fatigue, weakness, malaise, anorexia, nausea or vomiting. If these symptoms appear or if signs of hepatic damage are detected, treatment should be

discontinued promptly. Continued use of Myrin®-P Forte in these patients may cause a more severe form of liver damage.

In patients with chronic liver disease, as well as in chronic alcoholics and undernourished patients, the therapeutic benefits of treatment with Myrin®-P Forte must be weighed against the possible risks. If anti-tuberculous treatment is considered necessary, the dosage of rifampicin, isoniazid, pyrazinamide and ethambutol may need to be modified and Myrin®-P Forte should not be used in such patients because it is only possible to adjust the dosage by administering rifampicin, isoniazid, pyrazinamide and ethambutol separately.

For undernourished or elderly patients supplementation of pyridoxine (vitamin B6) may be useful, because isoniazid in high doses can lead to pyridoxine (vitamin B6) deficiency.

Impaired renal function

In severe renal insufficiency, the elimination of isoniazid, pyrazinamide and ethambutol can be delayed leading to a higher systemic exposure, which can result in an increase in adverse events. Myrin®-P Forte should be used with caution in patients with moderate renal impairment (creatinine clearance 30-60 ml/min).

Gout

Pyrazinamide and ethambutol should be used with caution in patients with a history of gout. Regular monitoring of serum uric acid should be undertaken. Myrin®-P Forte treatment should be stopped in gouty arthritis.

Haematology

Full blood count should be monitored during prolonged treatment and in patients with hepatic disorders. Rifampicin should be withdrawn permanently if thrombocytopenia or purpura occur. The possibility of pyrazinamide having an undesirable effect on blood clotting time or vascular integrity should be borne in mind in patients with haemoptysis.

Diabetes mellitus

Increased difficulty has been reported in controlling diabetes mellitus when such patients are given isoniazid.

Epilepsy

Patients suffering from convulsive disorders must be kept under special observation during treatment with Myrin®-P Forte because of the neurotoxic effects of isoniazid and ethambutol hydrochloride.

Neuropathy

Caution should be exercised in subjects with peripheral or optic neuritis. Regular neurological examination is necessary with special care in patients with a history of alcohol abuse. Use of pyridoxine (vitamin B6) may prevent or diminish neuropathy due to isoniazid treatment especially in elderly and in malnourished patients. Pyridoxine should be given in line with official guidelines.

Contraception

Additional non-hormonal means of contraception must be employed to prevent the possibility of pregnancy during treatment with rifampicin (see section **4.5. Interaction with Other Medicinal Products and Other Forms of Interaction**).

Alcohol

Patients should abstain from alcohol while receiving treatment with Myrin®-P Forte.

Laboratory tests

Full blood counts, liver function tests (SGPT/ALAT, SGOT/ASAT), renal function tests and monitoring serum uric acid should be performed before treatment and at regular intervals during treatment. Ocular examination is recommended during treatment with ethambutol hydrochloride.

Concomitant medications

Rifampicin is a potent inducer of the cytochrome P450 system, and may increase the metabolism of concomitantly administered drugs resulting in subtherapeutic plasma levels and a lack of effect. Drugs that are eliminated by hepatic metabolism should only be used concomitantly with Myrin®-P Forte if the plasma level or clinical response/undesirable effects can be monitored and the dose can be adequately adjusted (see section **4.5. Interaction with Other Medicinal Products and Other Forms of Interaction**).

Use of the following medicinal products concomitantly with Myrin®-P Forte is not recommended: nevirapine, simvastatin, oral contraceptives and ritonavir (when given in low doses as a booster a marked reduction of plasma concentration might occur) (see section **4.5. Interaction with Other Medicinal Products and Other Forms of Interaction**).

Rifampicin has enzyme induction properties that can enhance the metabolism of endogenous substrates including adrenal hormones, thyroid hormones and vitamin D. Isolated reports have associated porphyria exacerbation with rifampicin administration.

This medicine contains less than 1 mmol sodium (23 mg) per film-coated tablet, that is to say essentially 'sodium-free'.

4.5. INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

Influence of other medicinal products on Myrin®-P Forte

Antacids reduce the bioavailability of rifampicin, isoniazid and ethambutol. To avoid this interaction, Myrin®-P Forte should be taken at least 1 hour before antacids. Corticosteroids can reduce the plasma levels of isoniazid, by increasing its metabolic and/or renal clearance.

Influence of Myrin®-P Forte on other medicinal products

Rifampicin is the most potent inducer of the cytochrome P450 system (CYP450), notably of the two subfamilies CYP3A and CYP2C, which represent more than 80% of the isoenzymes of CYP450. Thus, rifampicin may increase the metabolism of numerous concomitantly administered medicinal products which are metabolised, partially or totally, by these two subfamilies of CYP450. Moreover, rifampicin also induces UDP-glucuronyltransferase, another enzyme involved in the metabolism of several medicinal products. This can result in subtherapeutic plasma levels of the simultaneous administered

medicinal products, with a decreased or even a loss of effect. Isoniazid inhibits the metabolism of some medicinal products leading to increased plasma concentrations.

Moreover, some medicinal products are affected in the opposite direction by rifampicin and isoniazid, e.g., phenytoin, warfarin and theophylline. The net effect cannot be predicted and may change over time.

Plasma concentrations of morphine may be reduced by rifampicin. The analgesic effect of morphine should be monitored and doses of morphine adjusted during and after treatment with rifampicin.

Medicinal products that are eliminated by metabolism should only be used concomitantly with Myrin®-P Forte if the plasma concentrations or clinical response/undesirable effects can be monitored and the dose can be adequately adjusted. Monitoring should be performed regularly during Myrin®-P Forte therapy and for 2-3 weeks after discontinuation of the therapy.

The enzyme inducing effects of rifampicin reach a peak within 10 days and gradually decrease over a period of 2 or more weeks after discontinuation of rifampicin treatment, factors that must be taken into account if the dose of other medicinal products is increased during treatment with Myrin®-P Forte.

When considering the impact of Myrin®-P Forte on the concentrations of other simultaneously administered medicinal products, recommendations are the following:

Interactions with rifampicin:

Use of the following medicinal products concomitantly with Myrin®-P Forte is contra-indicated: voriconazole and protease inhibitors, except ritonavir when given at full dose or 600 mg twice daily (see section **4.3. Contraindications**).

Use of the following medicinal products concomitantly with Myrin®-P Forte is not recommended: nevirapine, simvastatin, oral contraceptives and ritonavir (when given in low doses as a booster a marked reduction of plasma concentration might occur) (see section **4.4. Special Warnings and Precautions for Use**).

Use of the following medicinal products concomitantly with Myrin®-P Forte requires a precaution for use by monitoring specific parameters or through a clinical surveillance:

- Analgesics (e.g., methadone, narcotic analgesics, morphine, etoricoxib, rofecoxib)

- Antiarrhythmics (disopyramide, mexiletine, quinidine, propafenone, tocainide, lorcainide)

- Antibacterials (e.g., chloramphenicol, clarithromycin, dapsone, doxycycline, fluoroquinolones, telithromycin, linezolid, p-aminosalicylic acid)

- Anticoagulants (e.g., coumarins)

- Antidiabetics

- Antiepileptics (e.g., phenytoine, tiagabine, carbamazepine)

- Antifungals (e.g., fluconazole, itraconazole, ketoconazole, voriconazole, terbinafine)

- Antipsychotics (e.g., haloperidol, clozapine, aripiprazole)

- Antivirals (e.g., saquinavir, indinavir, efavirenz, amprenavir, nilfinavir, atazanavir, lopinavir, nevirapine, zidovudine)

- Anxiolytics and hypnotics (e.g., diazepam, benzodiazepines, buspirone, zopiclone, zolpidem, zaleplon)

- Atovaquone

- Barbiturates (e.g., hexobarbital)

- Beta-blockers (e.g., bisoprolol, propranolol, metoprolol, carvedilol (because of its use in cardiac insufficiency and its low therapeutic margin in this indication))

- Calcium channel blockers (e.g., diltiazem, nifedipine, verapamil, nimodipine, isradipine, nicardipine, nisoldipine, amlodipine)

- Corticosteroids

- Cardiac glycosides (digitoxin, digoxin)

- Cimetidine

- Clofibrate

- Cytotoxics (e.g., imatinib, gefitinib, irinotecan)

- Diuretics (e.g., eplerenone)

- Oestrogen, progestogens

- Fexofenadine

- Hormone antagonists (antioestrogens e.g., tamoxifen, toremifene; gestrinone)

- Immunosuppressive agents (e.g., ciclosporin, sirolimus, tacrolimus, leflunomide, azathioprine)

- Losartan, imidapril, enalapril

- Praziquantel

- Quinine

- Selective 5-HT3 receptor antagonists (e.g., ondansetron, tropisetron)

- Statins metabolised by CYP 3A4 (e.g., simvastatin)

- Fluvastatin

- Systemic hormonal contraceptives

- Theophylline

- Thyroid hormone (e.g., levothyroxine)

- Tricyclic antidepressants (e.g., amitriptyline, nortriptyline)

Interactions with isoniazid:

Use of the following medicinal products concomitantly with Myrin®-P Forte requires a precaution for use by monitoring specific parameters or through a clinical surveillance: halogenated volatile anaesthetics, glucocorticoids, ketoconazole, phenytoin, pyrazinamide, stavudine, carbamazepine, benzodiazepines, ethosuximide, theophylline.

Interactions with pyrazinamide:

Use of the following medicinal products concomitantly with Myrin®-P Forte requires a precaution for use by monitoring specific parameters or through a clinical surveillance: probenecid, sulfinpyrazon.

Rifampicin may reduce the effectiveness of oral contraceptives and patients treated with Myrin®-P Forte should use a non-hormonal method of contraception.

Oral typhoid vaccine might be inactivated by concomitant antibiotic administration.

Isoniazid is an inhibitor of monoamine oxidase (MAO) and diamine oxidase (DAO), which can reduce tyramine and histamine metabolism, causing symptoms such as headache, sweating, palpitations, flushing, and hypotension. Patients should therefore be advised against ingesting foods rich in tyramine and/or histamine, such as cured meat, some cheeses (e.g., matured cheeses), wine, beer and some fish (e.g., tuna, mackerel, salmon).

Rifampicin can delay the biliary excretion of contrast media during gallbladder radiographic examination.

Microbiological methods used to determinate folic acid and cyanocobalamine (vitamin B12) plasma concentrations cannot be used during rifampicin treatment as rifampicin is in competition with bilirubin and BSP. To avoid false positive reactions, BSP test should be carried out the morning before rifampicin administration.

4.6. FERTILITY, PREGNANCY AND LACTATION

Pregnancy

Treatment should be considered on a case-by-case basis after benefit of medicinal product combination has been assessed. Consequently, Myrin®-P Forte could be given during pregnancy if the potential benefit for the mother is judged to outweigh the potential risk to the foetus.

Rifampicin

At very high doses in animals rifampicin has been shown to have teratogenic effects (see section **5.3. Preclinical Safety Data**). There are no well controlled studies with rifampicin in pregnant women. Although rifampicin has been reported to cross the placental barrier and appear in cord blood, the effect of rifampicin, alone or in combination with other antituberculosis drugs, on the human foetus is not known. Therefore, rifampicin should be used in pregnant women or in women of child bearing potential only if the potential benefit justifies the potential risk to the foetus. Administration of rifampicin during the last few weeks of pregnancy can cause postnatal haemorrhage in the mother and new born infant.

Isoniazid

On limited data, congenital malformations have not been observed to be any more frequent than what may be expected in a normal population. Isoniazid crosses the placenta. Isoniazid might exert neurotoxic effects on the child. Animal studies have shown reproductive toxicity (see section **5.3. Preclinical Safety Data**).

Pyrazinamide

No animal reproductive studies have been conducted with pyrazinamide. Nor is it known whether pyrazinamide can cause foetal damage when administered to a pregnant woman.

Ethambutol

Ethambutol crosses the placenta, and may result in foetal plasma concentrations that are approximately 30% of maternal plasma concentrations. Limited clinical data on exposed pregnancies suggest no increase in the rate of foetal malformations in humans. Animal studies have shown a teratogenic potential (see section **5.3. Preclinical Safety Data**).

- In case of third trimester exposure, maternal administration of oral phytomenadione (vitamin K) during the last month of pregnancy and neonatal administration at delivery are recommended, because rifampicin can lead to maternal or neonatal haemorrhage.

- Supplementation of pyridoxine (vitamin B6) is recommended during pregnancy, because isoniazid might exert neurotoxic effects on the child.

Breast-feeding

Rifampicin, isoniazid, pyrazinamide and ethambutol pass into the breast milk, but no undesirable effects on breast-fed infants have been observed. Breast-feeding is, however, not recommended in view of the theoretical possibility of neurotoxic effects due to isoniazid and ethambutol.

4.7. EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Myrin®-P Forte has minor to moderate influence on the ability to drive and use machines.

Undesirable effects of ethambutol, such as confusion, disorientation, hallucinations, dizziness, malaise and visual disturbances (blurred vision, red-green colour blindness, loss of vision) may impair the patient's ability to drive or operate machinery.

4.8. UNDESIRABLE EFFECTS

Frequency estimates:	*Common:*	≥1/100
	Uncommon:	≥1/1,000 and < 1/100
	Rare:	≥1/10,000 and < 1/1,000
	Very rare:	<1/10,000
	Not known:	cannot be estimated from the available data

Undesirable effects of rifampicin which may occur during continuous daily or intermittent therapy

Blood and lymphatic system disorders	*Rare:*	Transient leucopenia, eosinophilia, agranulocytosis. Thrombocytopenia and thrombocytopenic purpura are encountered more frequently with intermittent therapy than with continuous daily treatment, during which they occur only in very rare cases. When rifampicin administration has been continued after the occurrence of purpura, cerebral haemorrhage and fatalities have been reported. (see section **4.4. Special Warnings and Precautions for Use**). Haemolysis, haemolytic anaemia. Disseminated intravascular coagulation has also been reported.
Endocrine disorders	*Rare:*	Menstrual disturbances (in extreme cases amenorrhoea); induction of crisis in Addison patients (see section **4.5.**

		Interaction with Other Medicinal Products and Other Forms of Interaction)
Psychiatric disorders	*Rare:*	Mental confusion, psychosis.
Nervous system disorders	*Common:*	Tiredness, drowsiness, headache, light-headedness, dizziness
	Rare:	Ataxia, muscular weakness, myopathy
Eye disorders	*Common:*	Reddening of the eyes, permanent discolouration of soft contact lenses
	Rare:	Visual disturbances, Severe signs and symptoms, such as e.g., exudative conjunctivitis
Gastrointestinal disorders	*Common:*	Anorexia, nausea, abdominal pain, bloatedness
	Rare:	Vomiting or diarrhoea, isolated occurrences of erosive gastritis and pseudomembranous colitis, pancreatitis
Skin and subcutaneous tissue disorders	*Common:*	Flushing, itching with or without skin rash, urticaria
	Rare:	Severe skin reactions such as Stevens-Johnson syndrome and generalised hypersensitivity reactions, e.g., exfoliative dermatitis, Lyell's syndrome and pemphigoid reactions
Hepatobiliary disorders	*Common:*	Asymptomatic increase in liver enzymes (see section **4.4. Special Warnings and Precautions for Use**)
	Rare:	Hepatitis or jaundice, induction of porphyria (see section **4.3. Contraindications**)
Renal and urinary disorders	*Rare:*	Elevations of BUN (blood urea nitrogen) and serum uric acid have been reported. Acute renal failure due to haemoglobinuria, haematuria, interstitial nephritis, glomerulonephritis and tubular necrosis has been reported.
General disorders and administration site conditions	*Common:*	Reddish discoloration of body fluids and secretions such as e.g., urine, sputum, lacrimal fluid, faeces, saliva and sweat.
	Rare:	Collapse, shock, oedema

Undesirable effects of rifampicin mainly occurring during intermittent therapy or on resumption of treatment after temporary interruption

In patients taking rifampicin other than on a daily basis or in those resuming treatment with the medicinal product after a temporary interruption, an influenza-like syndrome may occur, this being very probably of immunopathological origin. It is characterised by fever, shivering and possibly headache, dizziness and musculoskeletal pain. In rare cases this “flu-like syndrome” may be followed by thrombocytopenia, purpura, dyspnoea, asthma-like attacks, haemolytic anaemia, shock and acute renal failure. These serious complications may, however, also set in suddenly without preceding “flu-like syndrome”, mainly when treatment is resumed after a temporary interruption or when rifampicin is given only once a week in high doses (≥25 mg/kg) (see section **4.4. Special Warnings and Precautions for Use**). When rifampicin is administered in lower doses (600 mg) 2-3 times a week, the syndrome is encountered less commonly, its incidence then being comparable to that observed during daily medication (see section **4.4. Special Warnings and Precautions for Use**).

Undesirable effects of isoniazid

Blood and lymphatic system disorders	*Rare:*	Eosinophilia, thrombocytopenia, anaemia (haemolytic, sideroblastic)
	Very rare:	Agranulocytosis
Endocrine disorders	*Rare:*	Isoniazid may interfere with liver metabolism of several hormones, resulting in menstrual disturbances, gynaecomastia, Cushing syndrome, pubertas praecox, and difficult controllable diabetes, hyperglycaemia (see section **4.4. Special Warnings and Precautions for Use**) and metabolic acidosis
Psychiatric disorders	*Rare:*	Psychoses, hyperactivity, euphoria, insomnia
Nervous system disorders	*Common:*	Peripheral neuropathy (dose dependent and more common in undernourished patients, alcoholics, slow acetylators and diabetics), usually preceded by paresthesias of feet and hands (see section **4.4. Special Warnings and Precautions for Use**)
	Rare:	Damage to the optic nerve (see section **4.4. Special Warnings and Precautions for Use**), convulsions, dizziness, light-headedness, headache, toxic encephalopathy. High doses may increase seizure frequency in epileptics (see section **4.4. Special Warnings and Precautions for Use**)
Vascular disorders	*Not known:*	Vasculitis
Gastrointestinal disorders	*Common:*	Nausea, vomiting, epigastric distress
	Not known:	Pancreatitis
Hepatobiliary disorders	*Common:*	Disturbances of liver function (usually mild and transient elevation of serum transaminase level). The most common prodromal symptoms are anorexia, nausea, vomiting, fatigue, malaise and weakness (see section **4.4. Special Warnings and Precautions for Use**).
	Uncommon:	Hepatitis
	Rare:	Severe hepatitis
	Very rare:	Fulminant hepatitis
Skin and subcutaneous tissue disorders	*Rare:*	Toxic epidermal necrolysis, eosinophilia systemic symptoms
General disorders and administration site conditions	*Common:*	Allergic and other reactions, like drug exanthema and fever
	Rare:	Allergic and other reactions, like dry mouth, heartburn, disorders of micturition, rheumatic syndrome, lupus erythematosus-like signs and symptoms, pellagra, lymphadenopathy, acne.

Undesirable effects of pyrazinamide

Blood and lymphatic system disorders	*Rare:*	Thrombocytopenia, sideroblastic anaemia, undesirable effects on blood clotting mechanisms, splenomegaly

Gastrointestinal disorders	*Common:*	Nausea, vomiting, anorexia, abdominal pain
Hepatobiliary disorders	*Common:*	Moderate and transient rises in serum transaminase level during the early phase of treatment (see section **4.4. Special Warnings and Precautions for Use**). Porphyria (see section **4.3. Contraindications**)
	Rare:	Severe hepatotoxicity appears to be related to dose; hepatomegaly, jaundice
Renal and urinary disorders	*Common:*	Hyperuricaemia (often asymptomatic), gout requiring treatment (see section **4.3. Contraindications** and section **4.4. Special Warnings and Precautions for Use**).
	Rare:	Interstitial nephritis, dysuria
General disorders and administration site conditions	*Common:*	Allergic and other reactions, like mild arthralgia and myalgia
	Rare:	Allergic and other reactions, like skin rash, photosensitivity, urticaria, pruritus, fever, acne

Undesirable effects of ethambutol

Blood and lymphatic system disorders	*Rare:*	Thrombocytopenia, leucopenia
Psychiatric disorders	*Uncommon:*	Hallucinations
Nervous system disorders	*Uncommon:*	Dizziness, disorientation, confusion, headache, malaise
	Rare:	Peripheral neuritis (numbness, tingling, burning pain, or weakness in hands or feet) (see section **4.4. Special Warnings and Precautions for Use**).
Eye disorders	*Rare:*	Dose-dependent retrobulbar optic neuritis (blurred vision, eye pain, red-green colour blindness, loss of vision) (see section **4.4. Special Warnings and Precautions for Use**).
Gastrointestinal disorders	*Uncommon:*	Abdominal pain, loss of appetite, nausea and vomiting, anorexia
Skin and subcutaneous tissue disorders	*Uncommon:*	Pruritus, urticaria, rash
Renal and urinary disorders	*Uncommon:*	Hyperuricaemia that might result in acute gouty arthritis (chills; pain and swelling of joints, especially big toe, ankle, or knee; tight, hot skin over affected joints) (see section **4.3. Contraindications** and section **4.4. Special Warnings and Precautions for Use**).
General disorders and administration site conditions	*Rare:*	Hypersensitivity (skin rash, fever, joint pain), anaphylactic reactions

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

4.9. OVERDOSE

Rifampicin

Signs and Symptoms:

Nausea, vomiting, abdominal pain, pruritus, headache and increasing lethargy will probably occur within a short time after acute ingestion; unconsciousness may occur when there is severe hepatic disease. Transient increases in liver enzymes and/or bilirubin may occur. Brownish-red or orange colouration of the skin, urine, sweat, saliva, tears and faeces will occur, and its intensity is proportional to the amount ingested. Facial or periorbital oedema has also been reported in paediatric patients. Hypotension, sinus tachycardia, ventricular arrhythmias, seizures and cardiac arrest were reported in some fatal cases.

The minimum acute lethal or toxic dose is not well established. However, nonfatal acute overdoses in adults have been reported with doses ranging from 9 to 12 g rifampicin. Fatal acute overdoses in adults have been reported with doses ranging from 14-60 g. Alcohol or a history of alcohol abuse was involved in some of the fatal and nonfatal reports.

Nonfatal overdoses in paediatric patients ages 1 to 4 years old of 100 mg/kg for one to two doses have been reported.

Management:

Intensive supportive measures should be instituted and individual symptoms treated as they arise. Since nausea and vomiting are likely to be present, gastric lavage is probably preferable to induction of emesis. Following evacuation of the gastric contents, the instillation of activated charcoal slurry into the stomach may help absorb any remaining drug from the gastrointestinal tract. Antiemetic medication may be required to control severe nausea and vomiting. Active diuresis (with measured intake and output) will help promote excretion of the drug. Haemodialysis may be of value in some patients

Isoniazid

Toxicity: The toxicity is potentiated by alcohol. Lethal dose 80-150 mg/kg bodyweight. 5 g to 15-year-old resulted in lethal intoxication. 900 mg to 8-year-old resulted in moderate intoxication. 2-3 g to 3-year-old resulted in severe intoxication. 3 g to 15-year-old and 5 - 7.5 g to adults resulted in extremely severe intoxication.

Symptoms: Typical symptoms are seizures and metabolic acidosis, ketonuria, hyperglycemia. In addition, periorbital myoclonus, dizziness, tinnitus, tremor, hyperreflexia, paresthesias, hallucinations, impaired consciousness. Respiratory depression, apnoea. Tachycardia, arrhythmias, hypotension. Nausea, vomiting. Fever, rhabdomyolysis, DIC, hyperglycaemia, hyperkalaemia. Liver involvement.

Doses of isoniazid exceeding 10 mg/kg may adversely affect the nervous system, e.g., in the form of peripheral neuropathy, and thus impair the patient's ability to drive or operate machinery.

Management: If authorised, evacuation of the stomach (provided the patient is not experiencing seizures), charcoal. Blood samples must be collected for immediate determination of blood gases, electrolytes, BUN, glucose etc. In the event of seizures and metabolic acidosis, pyridoxine is given at 1 g per g isoniazid. In the event of seizures and unknown dose, 5 g pyridoxine is given iv. In the absence of seizures, 2 - 3 g pyridoxine is given prophylactically intravenously. Pyridoxine should be diluted to reduce vascular irritation and is administered for 30 minutes via infusion pump or syringe pump. The

dose is repeated if necessary. Diazepam potentiates the effect of pyridoxine. A high dose of diazepam can also be tried to combat seizures if pyridoxine is unavailable. In severe cases, respiratory therapy. Correction of metabolic acidosis and electrolyte disturbances. Ensure good diuresis. Haemodialysis or haemoperfusion in the event of extremely severe intoxication. Symptomatic treatment.

Pyrazinamide

Abnormal liver function tests, hyperuricaemia.

Ethambutol

Loss of appetite, gastro-intestinal disturbances, fever, headache, dizziness, confusion, hallucinations.

5. PHARMACOLOGICAL PROPERTIES

5.1. PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Combinations of drugs for treatment of tuberculosis (rifampicin, pyrazinamide, ethambutol and isoniazid).

ATC code: J04A M06.

Rifampicin is a rifamycin antibiotic. Isoniazid, pyrazinamide and ethambutol are bactericidal antituberculous agents.

Mechanism of action

Rifampicin exerts, both *in vitro* and *in vivo* bactericidal effects on *Mycobacterium tuberculosis*. It also exhibits variable activity against other atypical species of *Mycobacterium*.

In vivo rifampicin exerts its bacterial effect not only on micro-organisms in the extracellular spaces but also on those located intracellularly.

Rifampicin inhibits the DNA-dependent RNA polymerase of sensitive bacterial strains, but without affecting the host enzymatic systems.

Isoniazid exerts a bactericidal effect mainly on rapidly growing populations of *Mycobacterium tuberculosis*. Its mechanism of action is probably based chiefly on inhibition of mycolic acid synthesis, mycolic acid being an important constituent of the mycobacterial cell wall.

Pyrazinamide: The exact mechanism of action is unknown. *In vitro* and *in vivo* studies have demonstrated that pyrazinamide is only active at a slightly acidic pH (pH 5.5).

Ethambutol: The mechanism of action 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.

Susceptibility

Rifampicin in concentrations of 0.005 to 0.2 µg/ml inhibits the growth of *M. tuberculosis in vitro*. Rifampicin increases the *in vitro* activity of streptomycin and isoniazid against *M. tuberculosis*, but not that of ethambutol.

Isoniazid is bacteriostatic for “dormant” bacteria but is bactericidal for rapidly dividing micro-organisms. The minimal tuberculostatic concentration is 0.025 to 0.05 µg/ml.

The pyrazinamide MIC for *M. tuberculosis* has been reported to be in the range 12.5-20 µg/ml.

Ethambutol's MIC for *M. tuberculosis* determined in various types of liquid and solid media has been reported to range from 0.5 to 2 µg/ml. The antimicrobial effect of ethambutol is delayed for at least 24 hours and the degree of inhibition can be ascribed rather to the exposure time than to increasing concentrations in the medium.

Once the initial intensive phase of treatment has been completed treatment can be continued with the combination rifampicin-isoniazid on a daily basis.

This regimen (initial intensive phase followed by continuation phase treatment) is appropriate in case of new tuberculosis patients, in case of relapse, in case of treatment after interruption or treatment failure.

The following resistance rates have been observed in new pulmonary TB cases (never treated patients) within the EU and EEA countries (data according to the ECDC Surveillance Report, 2012):

Agent	**Resistance**
Isoniazid	7.8% (range: 0 - 31.3%)
Rifampicin	3.0% (range: 0 – 19.1%)
Isoniazid and Rifampicin (Multidrug resistance)	2.6% (range: 0 – 18.6%)
Ethambutol	No data provided
Pyrazinamide	No data provided

Extrapulmonary tuberculosis

The treatment of extrapulmonary tuberculosis with short-course chemotherapy is recommended by WHO, IUATLD and several national committees like the American Thoracic Society although there have not been the same kinds of carefully conducted trials for extrapulmonary tuberculosis as for pulmonary tuberculosis.

5.2. PHARMACOKINETIC PROPERTIES

Rifampicin

Rifampicin is well absorbed when taken on an empty stomach. The rate and extent of absorption is decreased when taken with food. Maximum plasma concentrations are reached about 2 h after administration. Rifampicin is rapidly distributed throughout the body. The concentration in cerebrospinal fluid is, however, generally low, except in meningitis. The volume of distribution is about 55 L. The protein binding is high (80%). Rifampicin is deacetylated to the active metabolite desacetylrifampicin. Rifampicin and desacetylrifampicin are excreted in the bile and rifampicin undergoes enterohepatic recycling. About 10% of the dose is excreted unchanged in urine.

The elimination half-life initially is 3 to 5 hours, decreasing to 2-3 hours on repeated administration. The rate of elimination is increased during the first 6 to 10 days of therapy, due to auto-induction of hepatic microsomal oxidative enzymes. After high doses excretion may be slower because of saturation of the biliary excretion.

Isoniazid

Isoniazid is rapidly absorbed following oral administration. The rate and extent of absorption is decreased when taken with food. Maximum plasma concentrations are reached 1-2 h after a dose. Isoniazid is widely distributed to most body fluids and tissues. The volume of distribution is about 43 L. Protein binding is very low, approximately 0 to 10%. Isoniazid is acetylated by N-acetyltransferase to N-acetylisoniazid. It is then biotransformed to isonicotinic acid and monoacetylhydrazine. Monoacetylhydrazine is associated with hepatotoxicity via formation of a reactive intermediate metabolite. The rate of acetylation is genetically determined; slow acetylators are characterised by a relative lack of hepatic N-acetyltransferase. Approximately 50% of Caucasians and African Americans are slow acetylators. The majority of Eskimos and Asians with Mongolese ethnicity such as Japanese, Chinese and Vietnamese are rapid acetylators.

The half-life is generally between 1 and 4 hours, but can vary between 0.5 to 6 hours, depending of the rate of acetylation. Approximately 75-95% of the dose is excreted by the kidneys within 24 hours, primarily as the inactive metabolites N-acetylisoniazid and isonicotinic acid.

Pyrazinamide

Pyrazinamide is well absorbed from the gastrointestinal tract. The absorption is not affected by concomitant food intake. Maximum plasma concentrations are reached after 1-2 hours in adults and about 3 hours in children. Pyrazinamide is rapidly distributed throughout the body. Pyrazinamide is hydrolysed by a microsomal deaminase to pyrazinoic acid, an active metabolite, and then hydroxylated by xanthine oxidase to 5-hydroxypyrazinoic acid. Pyrazinamide is renally excreted, mainly as metabolites. Only 3% of the dose is excreted unchanged in urine. The half-life is about 10 hours.

Ethambutol

Ethambutol is well absorbed following oral administration. The bioavailability is approximately 80%. The absorption is not affected by concomitant food intake. Maximum plasma concentrations are reached 2-4 hours after dose. Ethambutol is widely distributed to most tissues. It is not distributed to cerebrospinal fluid. However, in patients with tuberculous meningitis the concentration in cerebrospinal fluid may reach therapeutic levels. Concentrations in erythrocytes are 2-3 times higher than in serum. Protein binding is low (20 to 30%). The volume of distribution is about 20 L. Ethambutol is metabolised in the liver, up to 15% to inactive metabolites. The half-life of ethambutol is 3 to 4 hours, but increases up to 8 hours in patients with impaired renal function. Up to 80% excreted renally within 24 hours (at least 50% unchanged and up to 15% as inactive metabolites). About 20% is excreted unchanged in the faeces.

Characteristics in special risk groups

Rifampicin

With impaired renal function, the elimination half-life becomes prolonged at doses exceeding 600 mg daily (10 mg/kg). Rifampicin is not removed from the blood by haemodialysis.

In patients with impaired liver function, the plasma concentrations are raised and the elimination half-life prolonged. For treatment of patients with impaired liver function, see section **4.4. Special Warnings and Precautions for Use**.

Isoniazid

In slow acetylators with severely impaired renal function, accumulation of isoniazid may occur. In such cases, the serum concentration of isoniazid should be closely monitored and, if necessary, the dosage reduced.

In the presence of impaired liver function the elimination half-life of isoniazid is prolonged. For use in patients with impaired liver function, see section **4.4. Special Warnings and Precautions for Use**.

Pyrazinamide

Patients with hepatic cirrhotic insufficiency exhibit a marked reduction of the pyrazinamide clearance and an increase in half-life. The area under the curve of pyrazinoic acid (the main metabolite) is increased three-fold (see also section **4.4. Special Warnings and Precautions for Use**).

There is no information regarding the pharmacokinetics of pyrazinamide in renal impairment. Pyrazinamide is removed from blood by haemodialysis.

Ethambutol

The elimination half-life of ethambutol is increased in patients with impaired renal function, which may require an adjustment of dosage. Ethambutol is not removed from the blood by haemodialysis.

5.3. PRECLINICAL SAFETY DATA

Rifampicin

In female mice a significant increase in hepatomas was observed after 1 year of treatment with rifampicin in quantities equivalent to 2-10 times the maximum clinical doses. In mice of another strain and in rats carcinogenicity studies were negative.

Rifampicin is thought not to be mutagenic in bacteria, *Drosophilia melanogaster* or mice *in vivo*. An increase in chromatid breaks was noted when whole blood cell cultures were treated with rifampicin. Rifampicin has been reported to possess immunosuppressive potential in rabbits, mice, rats, guinea pigs, human lymphocytes *in vitro* and humans.

In pregnant rats, mice and rabbits, an unspecific embryotoxic effect occurred after doses exceeding 150 mg/kg daily. In rats and mice increased occurrence of spina bifida and cleft palate was observed within the same dose range.

Isoniazid

Isoniazid has a weak direct genotoxic effect and is a promutagenic substance through formation of the toxic metabolites hydrazine and acetyl hydrazine via metabolic activation. Chromosomal changes have not been documented in lymphocytes from patients who were treated with isoniazid, while an increased frequency of chromosomal changes were documented in connection with combination treatment.

Conflicting data are reported on the isoniazid potential to induce teratogenic effects in animal models. Isoniazid may exert an embryocidal effect. No effects on fertility have been noted.

Limited evidence shows that isoniazid produces lung tumours in mice after various modes of administration. Available evidence of human exposure has not suggested that isoniazid is carcinogenic in humans at doses applicable to the treatment and prophylaxis of tuberculosis.

Pyrazinamide

Pyrazinamide was not found to be carcinogenic in rats or male mice while no conclusion was possible for female mice. Pyrazinamide was not mutagenic in the Ames bacterial test, but induced chromosomal aberrations in human lymphocytes.

Ethambutol

Conflicting results are available on genotoxicity (negative in human lymphocyte cell cultures, positive in mouse micronucleus). In mice, ethambutol administered together with sodium nitrite gave rise to an increased frequency of lymphomas and lung tumours, while ethambutol alone did not cause any increase in tumour frequency.

Cleft palate, exencephaly and vertebral column abnormalities have been observed with high doses in studies of reproduction toxicity in mice. Studies in rats and rabbits have shown that ethambutol in high doses causes minor abnormalities of the cervical vertebrae and monophthalmia, limb reduction defects, hare lip and cleft palate in the offspring.

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

Please see pack for expiry of product.

6.4. SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C.

6.5. NATURE AND CONTENTS OF CONTAINER

Pack size: 80's

Myrin-P Forte LPD/PK-01
According to Rimstar (Sandoz UK) label dated 30 September 2020 and WHO guidelines

Marketed by:
Pfizer Pakistan Limited

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