1. Name of the Medicinal Product

(Rifampicin 150 mg/ Isoniazid 75 mg/ Pyrazinamide 400 mg/ Ethambutol Hydrochloride 275 mg Tablets USP)

2. Qualitative and Quantitative Composition

Each film coated tablet contains:
Rifampicin USP .....150 mg
Isoniazid USP .....75 mg
Pyrazinamide USP .....400 mg
Ethambutol Hydrochloride USP .....275 mg

3. Pharmaceutical Form

Film Coated Tablet

Pinkish brown coloured, oblong, biconvex, film coated tablets having a breakline on one side.

4. Clinical Particulars

4.1 Therapeutic Indications

Rifampicin 150 mg/Isoniazid 75 mg/Pyrazinamide 400 mg/Ethambutol Hydrochloride 275 mg Tablets USP is indicated for the initial phase of treating tuberculosis caused by Mycobacterium tuberculosis.

4.2 Posology and Method of Administration

Oral use.

Rifampicin 150 mg/Isoniazid 75 mg/Pyrazinamide 400 mg/Ethambutol Hydrochloride 275 mg Tablets USP should be given as a single daily dose.

For children weighing 21–30 kg the daily dose is 2 tablets as a single dose; the tablets should be used only for children who can swallow solid tablets.

Patient's body weight	**Dose**
30–39 kg	2 tablets as a single daily dose
40–54 kg	3 tablets as a single daily dose
55–70 kg	4 tablets as a single daily dose
Over 70 kg	5 tablets as a single daily dose

Rifampicin 150 mg/Isoniazid 75 mg/Pyrazinamide 400 mg/Ethambutol Hydrochloride 275 mg Tablets USP should be taken on an empty stomach (at least one hour before or two hours after a meal). Biovailability may be reduced if taken with food e.g. to improve gastrointestinal tolerance.

If one of the active ingredients of this medicine needs to be discontinued or if the dose needs to be reduced then separate preparations of the ingredients (ethambutol, isoniazid, pyrazinamide, rifampicin) should be used.

Renal impairment
Since dose adjustment may be necessary in patients with renal impairment (creatinine clearance ≤ 50 ml/minute), it is recommended that separate preparations of ethambutol, isoniazid, pyrazinamide, and rifampicin be administered.

Hepatic impairment
Limited data indicate that the pharmacokinetics of isoniazid and rifampicin are altered in patients with hepatic impairment. Therefore, patients with hepatic impairment should be closely observed for signs of toxicity. Rifampicin 150 mg/Isoniazid 75 mg/Pyrazinamide 400 mg/Ethambutol Hydrochloride 275 mg Tablets USP must not be used in patients with acute liver disease.

Children, adolescents and patients weighing less than 20 kg
Rifampicin 150 mg/Isoniazid 75 mg/Pyrazinamide 400 mg/Ethambutol Hydrochloride 275 mg Tablets USP is not suitable for patients with a body weight below 20 kg, since appropriate dose adjustments cannot be made.

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

Interruption of treatment
If initial-phase treatment with Rifampicin 150 mg/Isoniazid 75 mg/Pyrazinamide 400 mg/Ethambutol Hydrochloride 275 mg Tablets USP is interrupted for any reason including non-adherence, the product should not be use for resuming treatment. Ethambutol, isoniazid, pyrazinamide and rifampicin must be administered separately for the resumption of treatment because rifampicin needs to be reintroduced at a lower dose. Official guidance should be consulted on the resumption of treatment with anti-tuberculosis agents.

4.3 Contraindications
- Hypersensitivity to ethambutol isoniazid, pyrazinamide, rifamycins, or to any of the excipients
- History of drug-induced hepatitis and acute liver disease regardless of origin
- Porphyria
- Acute gout
- Concomitant use of Rifampicin 150 mg/Isoniazid 75 mg/Pyrazinamide 400 mg/Ethambutol Hydrochloride 275 mg Tablets USP with voriconazole or with any protease inhibitor (for treating HIV infection) is contraindicated

4.4 Special Warnings and Precautions for Use
Impaired liver function, undernourishment,

alcoholism
Ethambutol, isoniazid, pyrazinamide, and rifampicin are metabolised in the liver. Transaminase levels are commonly elevated above the upper limit of normal. Liver dysfunction that may occur in the first few weeks of treatment usually returns to the normal range, with no interruption in treatment, and usually by the third month of treatment.
Slight elevations of liver enzymes are common with rifampicin but 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 cause, whereas a rise in transaminases may be caused by isoniazid, or rifampicin, or pyrazinamide, or a combination of the three.

Patients with impaired liver function should be treated with caution and under strict medical supervision. In these patients, liver function, especially serum glutamic pyruvic transaminase (SGPT/ALAT) and serum glutamic oxaloacetic transaminase (SGOT/ASAT) should be determined before therapy and monitored carefully during therapy. If signs of hepatocellular damage occur, Rifampicin 150 mg/Isoniazid 75 mg/Pyrazinamide 400 mg/Ethambutol Hydrochloride 275 mg Tablets USP should be withdrawn.

A moderate rise in bilirubin or in 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 upper limit of normal.

Rifampicin 150 mg/Isoniazid 75 mg/Pyrazinamide 400 mg/Ethambutol Hydrochloride 275 mg Tablets USP should be replaced by preparations containing the individual components 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 upper limit of normal. In these circumstances, Rifampicin 150 mg/Isoniazid 75 mg/Pyrazinamide 400 mg/Ethambutol Hydrochloride 275 mg Tablets USP should be replaced by preparations containing the individual components.

Use of isoniazid should be carefully monitored in patients with chronic liver disease. Severe and sometimes fatal hepatitis caused by isoniazid may occur even after many months of treatment. Hepatotoxicity associated with isoniazid therapy (thought to be caused by the metabolite diacetylhydrazine) is rare in patients aged up to 20 years but is more common with increasing age and can affect up to 3% of patients aged over 50 years.

The incidence of severe hepatotoxicity can be minimised by carefully

monitoring liver function. Patients should be instructed to immediately report signs and symptoms of liver damage or other adverse effects, including unexplained anorexia, nausea, vomiting, dark urine, icterus, rash, persistent paraesthesia of the hands and feet, persistent fatigue, weakness lasting longer than 3 days or abdominal tenderness especially of the right upper quadrant. If these symptoms appear or if signs of hepatic damage are detected, treatment should be discontinued promptly. Continued use of Rifampicin 150 mg/Isoniazid 75 mg/Pyrazinamide 400 mg/Ethambutol Hydrochloride 275 mg Tablets USP in these patients may cause a more severe form of liver damage.
In patients with chronic liver disease, in those with a history of alcohol abuse, in injection drug users, and in undernourished patients, the therapeutic benefits of treatment with Rifampicin 150 mg/Isoniazid 75 mg/Pyrazinamide 400 mg/Ethambutol Hydrochloride 275 mg Tablets USP must be weighed against the possible risks. The dosage of ethambutol isoniazid, pyrazinamide and rifampicin may need to be modified and Rifampicin 150 mg/Isoniazid 75 mg/Pyrazinamide 400 mg/Ethambutol Hydrochloride 275 mg Tablets USP should not be used in such patients because dose adjustment is possible only by giving the component ingredients separately.

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

Visual acuity
Rifampicin 150 mg/Isoniazid 75 mg/Pyrazinamide 400 mg/Ethambutol Hydrochloride 275 mg Tablets USP should be used with care in patients with visual defects. Ethambutol can cause ocular toxicity.

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 they should be advised to report promptly any visual disturbance.

Rifampicin 150 mg/Isoniazid 75 mg/Pyrazinamide 400 mg/Ethambutol Hydrochloride 275 mg Tablets USP must be discontinued immediately if visual disturbances emerge.

Visual disturbances may be difficult to diagnose in patients who cannot report changes in visual acuity (e.g. children) and they should be monitored closely for ocular toxicity.

Hypersensitivity
Rifampicin may cause a hypersensitivity syndrome including 'flu-like symptoms (e.g. fever, shivering, headache, dizziness and musculoskeletal pain) and organ manifestations. The risk is higher on intermittent therapy or if treatment is resumed after discontinuation. Rifampicin 150 mg/Isoniazid

75 mg/Pyrazinamide 400 mg/Ethambutol Hydrochloride 275 mg Tablets USP should be withdrawn immediately in case of severe acute hypersensitivity reactions 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.

Rifampicin 150 mg/Isoniazid 75 mg/Pyrazinamide 400 mg/Ethambutol Hydrochloride 275 mg Tablets USP 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.

Cross-sensitivity
Patients hypersensitive to ethionamide, niacin (nicotinic acid), or other chemically related medications may also be hypersensitive to isoniazid or pyrazinamide.

Neuropathy
Rifampicin 150 mg/Isoniazid 75 mg/Pyrazinamide 400 mg/Ethambutol Hydrochloride 275 mg Tablets USP should be used with care in patients with peripheral or optic neuritis. Regular neurological examination is necessary with special care in patients who are malnourished, who have diabetes, or have a history of alcohol abuse. Use of pyridoxine (vitamin B6) may prevent or diminish neuropathy due to isoniazid. Pyridoxine should be given routinely in a dose of 10 mg daily.

Epilepsy and psychotic disorders
Rifampicin 150 mg/Isoniazid 75 mg/Pyrazinamide 400 mg/Ethambutol Hydrochloride 275 mg Tablets USP should be used with caution in patients with seizure disorders or a history of psychosis. Isoniazid and ethambutol have neurotoxic effects.

Haematological toxicity
Since rifampicin treatment has been associated with haemolytic anaemia, leucopenia and thrombocytopenia, full blood count should be monitored throughout therapy with Rifampicin 150 mg/Isoniazid 75 mg/Pyrazinamide 400 mg/Ethambutol Hydrochloride 275 mg Tablets USP. In case of severe haematological disturbances Rifampicin 150 mg/Isoniazid 75 mg/Pyrazinamide 400 mg/Ethambutol Hydrochloride 275 mg Tablets USP must be discontinued. Rifampicin should be withdrawn permanently if thrombocytopenia or purpura occur. The possibility of pyrazinamide affecting clotting time or vascular integrity should be considered in case of haemoptysis.

Hyperuricaemia and gout
Pyrazinamide and ethambutol may increase serum uric acid and cause gout. Patients with a history of gout should be carefully monitored. Serum uric acid should be determined before starting therapy with Rifampicin 150

mg/Isoniazid 75 mg/Pyrazinamide 400 mg/Ethambutol Hydrochloride 275 mg Tablets USP. Treatment with Rifampicin 150 mg/Isoniazid 75 mg/Pyrazinamide 400 mg/Ethambutol Hydrochloride 275 mg Tablets USP should be stopped in gouty arthritis.

Renal impairment
In renal insufficiency, the clearance of pyrazinamide, ethambutol and isoniazid is delayed, increasing systemic exposure and thereby their adverse effects. In case of renal insufficiency, Rifampicin 150 mg/Isoniazid 75 mg/Pyrazinamide 400 mg/Ethambutol Hydrochloride 275 mg Tablets USP should not be used because doses of the individual components may need to be modified.

Diabetes mellitus
Isoniazid may affect control of blood sugar in diabetes mellitus. Patients with diabetes should be monitored carefully.

Concomitant medicines
Rifampicin is a strong inducer of hepatic drug metabolism and may increase the metabolism of medicines given concomitantly, thereby reducing their effect. The therapeutic effect and adverse effects of concomitant medicines eliminated by hepatic metabolism should be monitored and the dose adjusted if necessary.
Rifampicin 150 mg/Isoniazid 75 mg/Pyrazinamide 400 mg/Ethambutol Hydrochloride 275 mg Tablets USP may reduce efficacy of drugs such as antiretrovirals, antiepileptics, immunosuppressants and coumarin derivatives (see section 4.5). Use of the following with Rifampicin 150 mg/Isoniazid 75 mg/Pyrazinamide 400 mg/Ethambutol Hydrochloride 275 mg Tablets USP is not recommended: nevirapine, simvastatin, oral contraceptives and ritonavir (when given in low dose as a booster, the plasma concentration may be markedly reduced).

Contraception
Oral contraceptives, and possibly other forms of hormonal contraception (e.g. patches and transdermal implants), do not provide adequate protection against conception when given with rifampicin. Barrier or other non-hormonal methods of contraception should be used during treatment with Rifampicin 150 mg/Isoniazid 75 mg/Pyrazinamide 400 mg/Ethambutol Hydrochloride 275 mg Tablets USP.

Porphyria
Rifampicin 150 mg/Isoniazid 75 mg/Pyrazinamide 400 mg/Ethambutol Hydrochloride 275 mg Tablets USP should be used with caution in patients with porphyria, since the enzyme induction by rifampicin may cause symptoms.

Discoloration of body fluids

Rifampicin 150 mg/Isoniazid 75 mg/Pyrazinamide 400 mg/Ethambutol Hydrochloride 275 mg Tablets USP may cause a reddish-orange discoloration of body fluids such as urine, sputum and tears. This is due to rifampicin, and does not require medical attention.

Laboratory monitoring
Full blood count, liver function and serum uric acid should be determined before and at regular intervals during treatment with Rifampicin 150 mg/Isoniazid 75 mg/Pyrazinamide 400 mg/Ethambutol Hydrochloride 275 mg Tablets USP.

4.5 Interaction with Other Medicinal Products and Other forms of Interaction
Rifampicin is a very potent inducer of the hepatic and intestinal cytochrome P450 enzyme system, as well as of glucuronidation and the p-glycoprotein transport system. Co-administration of rifampicin with drugs that undergo biotransformation through these metabolic pathways is likely to accelerate elimination of these drugs. The effects approach their maximum after about 10 days of rifampicin treatment, and gradually return to normal within 2 weeks or longer after discontinuation. This must be taken into account when co-treating with other drugs. To maintain optimum therapeutic blood levels, doses of drugs metabolised by these enzymes may require adjustment when starting or stopping concomitant use of Rifampicin 150 mg/Isoniazid 75 mg/Pyrazinamide 400 mg/Ethambutol Hydrochloride 275 mg Tablets USP.

Isoniazid inhibits the cytochrome isoenzymes CYP2C19 and CYP3A4 in vitro. Thus it may increase exposure to drugs eliminated mainly through either of these pathways. However, these effects are likely to be outweighed by the hepatic enzyme induction due to rifampicin in Rifampicin 150 mg/Isoniazid 75 mg/Pyrazinamide 400 mg/Ethambutol Hydrochloride 275 mg Tablets USP. Insofar as has been investigated, the net effect of giving rifampicin and isoniazid on drug clearance will be an increase due to rifampicin rather than a decrease due to isoniazid.

Concurrent use with other hepatotoxic or neurotoxic medications may increase the hepatotoxicity and neurotoxicity of isoniazid, and should be avoided.

With some exceptions (see below) ethambutol and pyrazinamide, are considerably less likely to interact pharmacokinetically with other drugs. Co-treatment using pyrazinamide with other potentially hepatotoxic drugs should be avoided.

Mainly due to rifampicin, Rifampicin 150 mg/Isoniazid 75 mg/Pyrazinamide 400 mg/Ethambutol Hydrochloride 275 mg Tablets USP may interact with a very large number of other drugs, primarily by reducing the exposure to co-administered agents, reducing their efficacy and increasing the risk of therapeutic failure. For a large number of important medicines, no interaction data with rifampicin are available. However, clinically significant reductions

in drug exposure may occur. When co-prescribing any drug together with Rifampicin 150 mg/Isoniazid 75 mg/Pyrazinamide 400 mg/Ethambutol Hydrochloride 275 mg Tablets USP, the possibility of a drug-drug interaction should be considered. The following list of drug interactions with Rifampicin 150 mg/Isoniazid 75 mg/Pyrazinamide 400 mg/Ethambutol Hydrochloride 275 mg Tablets USP is not exhaustive, but is a selection of interactions of putative importance.

Other interactions
Interactions between Rifampicin 150 mg/Isoniazid 75 mg/Pyrazinamide 400 mg/Ethambutol Hydrochloride 275 mg Tablets USP and other medicines are listed below (increased exposure is shown as "↑", decreased exposure as "↓", no change as "↔").

Drugs by Therapeutic Area	**Interaction**	**Recommendations on co-administration**
INFECTION Antiretrovirals: nucleoside analogues		
Zidovudine + Rifampicin	Zidovudine AUC ↓ 47%	The clinical significance of the lowered zidovudine exposure is unknown. Dose modifications of zidovudine in this situation have not been formally evaluated.
Stavudine Didanosine Lamivudine Emtricitabine		No interaction expected
Tenofovir disoproxil fumarate + Rifampicin	Tenofovir AUC ↓ 13%	No dose adjustment required.
Abacavir + Rifampicin	Empirical data are lacking, but rifampicin may decrease abacavir exposure through induction of glucuronidation.	Efficacy of abacavir should be closely monitored in co-treatment.
Antiretrovirals: non-nucleoside analogues		
Efavirenz + Rifampicin	Efavirenz AUC ↓ 26%	When co-treating with Rifampicin 150 mg/Isoniazid 75 mg/Pyrazinamide 400 mg/Ethambutol Hydrochloride 275 mg Tablets USP, consider increase of the efavirenz dose to 800 mg daily.
Nevirapine + Rifampicin	Nevirapine AUC ↓ 58%	Concomitant use of Rifampicin 150 mg/Isoniazid 75 mg/Pyrazinamide 400 mg/Ethambutol Hydrochloride 275 mg Tablets USP and nevirapine is not recommended because neither appropriate doses of nevirapine nor the safety of this combination have been established.

Etravirine + Rifampicin	Rifampicin is likely to significantly reduce exposure to etravirine.	Co-treatment of Rifampicin 150 mg/Isoniazid 75 mg/Pyrazinamide 400 mg/Ethambutol Hydrochloride 275 mg Tablets USP and etravirine should be avoided.

Antiretrovirals: protease inhibitors		
Fosamprenavir + Rifampicin Saquinavir Indinavir Ritonavir Nelfinavir Lopinavir Atanzanavir Tipranavir Darunavir	Protease inhibitor exposure will be reduced to subtherapeutic level, due to interaction with rifampicin. Attempts to increase doses or to increase ritonavir-boosting are ill-tolerated with a high rate of hepatotoxicity.	Rifampicin 150 mg/Isoniazid 75 mg/Pyrazinamide 400 mg/Ethambutol Hydrochloride 275 mg Tablets USP should not be co-administered with HIV protease inhibitors.
Antiretrovirals: others		
Raltegravir + Rifampicin	Raltegravir AUC ↓ 40%	Avoid co-treatment. If deemed necessary, consider an increase of the raltegravir dose to 800 mg twice daily
Maraviroc + Rifampicin	Maraviroc AUC ↓ 63%	Avoid co-treatment. If deemed necessary, the maraviroc dose should be increased to 600 mg twice daily.
Antifungals		
Ketoconazole + Rifampicin	Ketoconazole AUC ↓ 80%	Co-administration should be avoided. If deemed necessary, a dose increase of ketoconazole may be required.
Fluconazole + Rifampicin	Fluconazole AUC ↓ 23%	Monitor therapeutic effect. An increased dose of fluconazole may be required.
Itraconazole + Rifampicin	Itraconazole AUC ↓ > 64–88%	Co-administration should be avoided.
Voriconazole + Rifampicin	Voriconazole AUC ↓ 96%	Co-administration is contraindicated. If necessary, rifabutin should be substituted for rifampicin.

Antibacterials and antituberculotics		
Clarithromycin + Rifampicin	Clarithromycin mean serum concentration ↓ 85%. 14-OH clarithromycin levels unchanged.	Co-administration should be avoided.
Chloramphenicol + Rifampicin	Case reports indicate > 60–80% reduction of chloramphenicol exposure.	Co-administration should be avoided.
Ciprofloxacin + Rifampicin	No significant interaction	No dose adjustment required.

Ofloxacin + Pyrazinamide Levofloxacin	Co-treatment with pyrazinamide and either of these fluoroquinolones has been associated with high levels of adverse events (e.g. hepatic, gastrointestinal, musculoskeletal), leading to discontinuation of therapy	Co-treatment of Rifampicin 150 mg/Isoniazid 75 mg/Pyrazinamide 400 mg/Ethambutol Hydrochloride 275 mg Tablets USP and either of these agents is not recommended. However, if deemed necessary, the patient should be monitored carefully for toxicity.
Doxycycline + Rifampicin	Doxycycline AUC ↓ 50–60%	If co-treatment is considered necessary, the dose of doxycycline should be doubled.
Metronidazole + Rifampicin	Metronidazole intravenous AUC ↓ 33%	The clinical relevance of the interaction is unknown. No dose adjustment is recommended. Monitor efficacy.
Sulfamethoxazole + Rifampicin	Sulfamethoxazole AUC ↓ 23%	Interaction probably not clinically significant. Monitor efficacy.
Trimethoprim + Rifampicin	Trimethoprim AUC ↓ 47%	Monitor efficacy. A dose increase of trimethoprim may be required.
Ethionamide + Rifampicin		Rifampicin and ethionamide should not be co-administered, due to an increased risk of hepatotoxicity.

Antimalarials		
Chloroquine + Rifampicin	Empirical data are not available. Since chloroquine undergoes polymorphic hepatic metabolism, lower levels are likely during rifampicin co-therapy.	Avoid co-administration.
Atovaquone + Rifampicin	Atovaquone AUC ↓ 50% Rifampicin AUC ↑ 30%	Avoid co-administration.
Mefloquine + Rifampicin	Mefloquine AUC ↓ 68%	Avoid co-administration.
Amodiaquine + Rifampicin	Empirical data are not available. Since amodiaquine undergoes hepatic metabolism, it is likely that clearance is increased when co-treating with rifampicin.	Avoid co-administration.
Quinine + Rifampicin	Quinine AUC ↓ ≈ 80%. This has been associated with significantly higher recrudescence rates.	Co-administration should be avoided. If co-administration is deemed necessary, an increased dose of quinine should be considered.

Lumefantrine + Rifampicin	Empirical data are not available. Since lumefantrine is metabolised by CYP3A, lower levels are expected with rifampicin co-treatment.	Avoid co-administration.
Artemisinin and derivatives + Rifampicin	Empirical data are not available. During co-treatment with rifampicin, lower levels of arteminisin and its derivatives may be expected.	Avoid co-administration.

ANALGESICS, ANTIPYRETICS, NON-STEROIDAL ANTI-INFLAMMATORY DRUGS		
Morphine + Rifampicin	Morphine oral AUC ↓ 30%	Co-treatment should be avoided. If necessary, monitor clinical effects and increase dose if necessary.
Codeine + Rifampicin	Plasma levels of morphine, the active moiety of codeine, are likely to be substantially reduced.	Monitor clinical effect and increase codeine dose if necessary.
Methadone + Rifampicin	Methadone AUC ↓ 33–66%	Monitor for possible withdrawal effects, and increase methadone dose as appropriate.
Paracetamol + Rifampicin	Rifampicin may increase paracetamol glucuronidation and decrease its effect. Co-administration may increase the risk of hepatotoxicity, but data are inconclusive.	Co-administration of Rifampicin 150 mg/Isoniazid 75 mg/Pyrazinamide 400 mg/Ethambutol Hydrochloride 275 mg Tablets USP and paracetamol should be avoided.
Paracetamol + Isoniazid		Concurrent use with isoniazid may increase hepatotoxicity
ANTICONVULSANTS		
Carbamazepine + Rifampicin	Rifampicin is expected to decrease the serum concentration of carbamazepine.	Co-administration of Rifampicin 150 mg/Isoniazid 75 mg/Pyrazinamide 400 mg/Ethambutol Hydrochloride 275 mg Tablets USP and carbamazepine should be avoided.
Carbamazepine + Isoniazid		The risk of hepatotoxicity with isoniazid appears to be increased when co-treating with carbamazepine.

Phenobarbital + Rifampicin	Phenobarbital and rifampicin are both strong hepatic enzyme inducers, and each drug may lower the plasma concentrations of the other.	Co-administration of Rifampicin 150 mg/Isoniazid 75 mg/Pyrazinamide 400 mg/Ethambutol Hydrochloride 275 mg Tablets USP and phenobarbital should be undertaken with caution, including monitoring of clinical effects and, if possible, plasma drug concentrations.
Phenobarbital + Isoniazid		Co-treatment with phenobarbital and isoniazid may increase the risk of hepatotoxicity.

Phenytoin + Rifampicin	Phenytoin intravenous AUC ↓ 42%	Co-treatment with Rifampicin 150 mg/Isoniazid 75 mg/Pyrazinamide 400 mg/Ethambutol
Phenytoin + Isoniazid	Co-treatment with phenytoin and isoniazid may result in an increased risk of hepatotoxicity.	Hydrochloride 275 mg Tablets USP and phenytoin should be avoided.
Valproic acid + Rifampicin	Though interaction studies are lacking, valproic acid is eliminated through hepatic metabolism, including glucuronidation. Reduced plasma levels of valproic acid are likely with concomitant use.	Co-treatment should be avoided. If necessary, therapeutic efficacy and, if possible, plasma concentrations of valproic acid, should be carefully monitored.
Lamotrigine + Rifampicin	Lamotrigine AUC ↓ 45%	Co-treatment should be avoided. If deemed necessary, increase lamotrigine dose as appropriate.
IMMUNOSUPPRESSANTS		
Ciclosporin + Rifampicin	Several studies and case reports have shown substantially increased ciclosporin clearance when co-administered with rifampicin.	Co-administration should be avoided. If deemed necessary, plasma drug concentrations of ciclosporin should be monitored and doses adapted accordingly (3–5 fold increases in ciclosporin dose have been required).
Tacrolimus + Rifampicin	Tacrolimus intravenous AUC ↓ 35%; oral ↓ 70%	Co-administration of Rifampicin 150 mg/Isoniazid 75 mg/Pyrazinamide 400 mg/Ethambutol Hydrochloride 275 mg Tablets USP and tacrolimus should be avoided. If deemed necessary, plasma drug concentration of tacrolimus should be monitored, and the dose increased as appropriate.

CARDIOVASCULAR MEDICINES

Warfarin + Rifampicin + Isoniazid	Warfarin AUC ↓ 85% Increased anticoagulant response to warfarin has been reported when co-administered with isoniazid	Co-administration should be avoided.
Atenolol + Rifampicin	Atenolol AUC ↓ 19%	No dose adjustment required.
Verapamil + Rifampicin	S-verapamil oral CL/F ↑ 32-fold. With intreavenous S-verapamil, CL ↑ 1.3-fold	Rifampicin 150 mg/Isoniazid 75 mg/Pyrazinamide 400 mg/Ethambutol Hydrochloride 275 mg Tablets USP should not be co-administered with verapamil given by mouth. If verapamil is given intravenously, the therapeutic effect should be monitored carefully; dose adjustment may be required.
Digoxin + Rifampicin	Digoxin oral AUC ↓ 30%	When co-administering Rifampicin 150 mg/Isoniazid 75 mg/Pyrazinamide 400 mg/Ethambutol Hydrochloride 275 mg Tablets USP with digoxin, the clinical efficacy and plasma concentration of digoxin should be monitored. A dose increase may be required.
Lidocaine + Rifampicin	Lidocaine intravenous CL ↑ 15%	No dose adjustment required
Amlodipine + Rifampicin	Amlodipine, like other calcium channel blockers, is metabolised by CYP3A; lower exposure is expected when co-treating with rifampicin	Monitor efficacy.
Enalapril + Rifampicin	No interaction expected	No dose adjustment required.
Simvastatin + Rifampicin	Simvastatin AUC ↓ 87% Simvastatin acid AUC ↓ 93%	Co-administration is not recommended.

GASTROINTESTINAL MEDICINES		
Ranitidine + Rifampicin	Ranitidine AUC ↓ 52%	Monitor for ranitidine efficacy, and increase dose if necessary.

Antacids + Ethambutol + Isoniazid + Rifampicin	Antacids may reduce the bioavailability of rifampicin by up to one third. Aluminium hydroxide impairs the absorption of ethambutol and isoniazid.	The clinical importance of this is unknown. Acid-suppressing drugs or antacids that do not contain aluminium hydroxide should be used if co-treatment with Rifampicin 150 mg/Isoniazid 75 mg/Pyrazinamide 400 mg/Ethambutol Hydrochloride 275 mg Tablets USP is necessary. Rifampicin 150 mg/Isoniazid 75 mg/Pyrazinamide 400 mg/Ethambutol Hydrochloride 275 mg Tablets USP should be taken at least 1 hour before antacids
PSYCHOTHERAPEUTIC MEDICINES		
Diazepam + Rifampicin	Diazepam AUC ↓ > 70%	Co-treatment is not recommended. If necessary, diazepam doses may need to be increased.
Chlorpromazine + Rifampicin + Isoniazid	Rifampicin may reduce chlorpromazine exposure. Also, chlorpromazine may impair the metabolism of isoniazid.	Co-administration should be avoided. If considered necessary, patients should be monitored carefully for isoniazid toxicity.
Haloperidol + Rifampicin	Haloperidol clearance is substantially increased by rifampicin.	If co-treatment with haloperidol is deemed necessary, monitor the clinical efficacy of haloperidol. A dose increase may be required.
Amitriptyline + Rifampicin	Case reports (supported by theoretical considerations) suggest that rifampicin considerably increases amitriptyline clearance.	Co-treatment should be avoided. If necessary, monitor efficacy and, if possible, plasma concentrations of amitriptyline.

HORMONES, OTHER ENDOCRINE MEDICINES AND CONTRACEPTIVES		
Prednisolone and other systemically administered corticosteroids + Rifampicin	Prednisolone AUC ↓ 66% Prednisolone exposure is likely to be substantially decreased when co-treating with rifampicin. This applies to other corticosteroids as well.	Co-administration of Rifampicin 150 mg/Isoniazid 75 mg/Pyrazinamide 400 mg/Ethambutol Hydrochloride 275 mg Tablets USP with corticosteroids should be avoided. If necessary, the clinical status of the patient should be carefully monitored, and corticosteroid doses adjusted as needed.
Glibenclamide + Rifampicin	Glibenclamide AUC ↓ 34%	Monitor blood glucose concentration closely. A dose increase of glibenclamide may be required.
Insulin		No interaction expected
Levothyroxine + Rifampicin	Case reports indicate that rifampicin may decrease the effect of levothyroxine.	Thyrotropin (thyroid stimulating hormone, TSH) levels should be

		monitored.
Ethinylestradiol + Rifampicin	Ethinylestradiol AUC ↓ 66%	Co-adminstration with Rifampicin 150 mg/Isoniazid 75 mg/Pyrazinamide 400 mg/Ethambutol Hydrochloride 275 mg Tablets USP may be associated with decreased contraceptive effect. Barrier or other non-hormonal methods of contraception should be used.
Norethisterone + Rifampicin	Norethisterone AUC ↓ 51%	Co-adminstration with Rifampicin 150 mg/Isoniazid 75 mg/Pyrazinamide 400 mg/Ethambutol Hydrochloride 275 mg Tablets USP may be associated with decreased contraceptive effect. Barrier or other non-hormonal methods of contraception should be used.

OTHERS		
Praziquantel + Rifampicin	Praziquantel AUC ↓ 80–99%	Co-treatment with Rifampicin 150 mg/Isoniazid 75 mg/Pyrazinamide 400 mg/Ethambutol Hydrochloride 275 mg Tablets USP should be avoided.
Disulfiram + Isoniazid + Ethambutol	Concurrent use of disulfiram and isoniazid may increase the incidence of effects on the central nervous system and concurrent use with ethambutol may increased risk for ocular toxicity.	Dose reduction or discontinuation of disulfiram may be necessary during therapy with Rifampicin 150 mg/Isoniazid 75 mg/Pyrazinamide 400 mg/Ethambutol Hydrochloride 275 mg Tablets USP.
Enflurane + Isoniazid	Isoniazid may increase the formation of the potentially nephrotoxic inorganic fluoride metabolite of enflurane	Avoid co-administration of Rifampicin 150 mg/Isoniazid 75 mg/Pyrazinamide 400 mg/Ethambutol Hydrochloride 275 mg Tablets USP with enflurane.
Probenecid + Pyrazinamide	There is a complex pharmacokinetic and pharmacodynamic two-way interaction between pyrazinamide and probenecid.	The appropriate dose of probenecid in co-treatment has not been established. Therefore, concomitant use with Rifampicin 150 mg/Isoniazid 75 mg/Pyrazinamide 400 mg/Ethambutol Hydrochloride 275 mg Tablets USP should be avoided.

Allopurinol + Pyrazinamide	Pyrazinamide major (active) metabolite pyrazoic acid AUC ↑ 70% Since pyrazinoic acid inhibits urate elimination, allopurinol is not effective in treating pyrazinamide-associated hyperuricaemia	Avoid co-administration of Rifampicin 150 mg/Isoniazid 75 mg/Pyrazinamide 400 mg/Ethambutol Hydrochloride 275 mg Tablets USP with allopurinol.

Interactions with food and drink
Alcohol: concurrent daily use of alcohol may increase the incidence of isoniazid-induced hepatotoxicity. Patients should be monitored closely for signs of hepatotoxicity and should be strongly advised to restrict intake of alcoholic beverages.

Cheese and fish (histamine- or tyramine-rich food): isoniazid may inhibit monoamine oxidase and diamine oxidase thus interfering with the metabolism of histamine and tyramine. This may result in redness or itching of the skin, feeling hot, rapid or pounding heartbeat, sweating, chills or clammy feeling, headache, and lightheadedness.

Interactions with laboratory tests
Isoniazid may cause a false positive response to copper sulfate glucose tests; enzymatic glucose tests are not affected.

Pyrazinamide may interfere with urinary ketone determination tests that use the sodium nitroprusside method.

Rifampicin may interfere with microbiological methods for measuring the concentration of folic acid and cyanocobalamin (vitamin B12) in plasma by competing with BSP and bilirubin. BSP test carried out the morning before taking rifampicin avoids false positive reaction.

4.6 Pregnancy and Lactation

Pregnancy
No adverse effects of isoniazid, ethambutol or pyrazinamide on the fetus have been reported. Use of rifampicin in the third trimester has been associated with postnatal haemorrhages in the mother and infant. Rifampicin 150 mg/Isoniazid 75 mg/Pyrazinamide 400 mg/Ethambutol Hydrochloride 275 mg Tablets USP should be used in pregnancy only if the benefits are considered to outweigh the risks. If Rifampicin 150 mg/Isoniazid 75 mg/Pyrazinamide 400 mg/Ethambutol Hydrochloride 275 mg Tablets USP is used in the last weeks of pregnancy, the mother and neonate should receive vitamin K.

Breastfeeding
Rifampicin, isoniazid, pyrazinamide and ethambutol pass into the breast milk. However, concentrations in breast milk are so low that breast-feeding cannot be relied upon for adequate tuberculosis prophylaxis or therapy for nursing

infants. No adverse effects in the baby have been reported.

4.7 Effects on Ability to Drive and Use Machines

Rifampicin 150 mg/Isoniazid 75 mg/Pyrazinamide 400 mg/Ethambutol Hydrochloride 275 mg Tablets USP 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

The most important adverse effects of rifampicin are hepatotoxicity, particularly cholestatic reactions, and skin reactions. Rifampicin may cause subclinical, unconjugated hyperbilirubinaemia or jaundice without hepatocellular damage, but occasionally causes hepatocellular injury. It can also potentiate the hepatotoxicity of the other anti-tuberculosis medicines.

The most important adverse effects of isoniazid are peripheral and central neurotoxic effects, and hepatotoxicity. Severe and sometimes fatal hepatitis associated with isoniazid therapy has been reported. The majority of cases have occurred within the first three months of therapy, but hepatotoxicity may also develop after a longer treatment.

The most important adverse effect of pyrazinamide is liver damage, ranging from asymptomatic increases of serum transaminases to symptomatic liver dysfunction, and in rare cases also fatal liver failure.

The most important adverse effect of ethambutol is retrobulbar neuritis with reduced visual acuity. The frequency depends on the dose and duration of therapy. It has been reported in up to 3% of patients receiving ethambutol 20 mg/kg daily. Typical initial signs include impairment of colour vision (red-green blindness) and constriction of visual field (central or peripheral scotoma). These changes are often reversible on discontinuing therapy. To avoid irreversible optic atrophy, visual acuity should be monitored regularly and ethambutol must be discontinued immediately if visual disturbances occur.

Adverse events considered at least possibly related to treatment are listed below by body system, organ class and frequency. They are not based on adequately sized randomised controlled trials, but on published data, generated mostly during post-approval use. Therefore, often frequency cannot be given. Frequencies are defined as very common (≥ 1 in 10), common (1 in 100 to 1 in 10), uncommon (1 in 1000 to 1 in 100), rare (1 in 10 000 to 1 in 1000), very rare (≤ 1 in 10 000), and ‘not known’ (frequency cannot be estimated from the available data).

Nervous system disorders	
Very common	peripheral neuropathy, usually preceded by paraesthesia of the feet and hands. The frequency depends on the dose and on predisposing conditions such as malnutrition, alcoholism or diabetes. It has been reported in 3.5 to 17% of patients treated with isoniazid. Concomitant pyridoxine administration largely reduces this risk.
Uncommon	headache, lethargy, ataxia, difficulty concentrating, dizziness, seizures, toxic encephalopathy
Not known	tremor, vertigo, hyperreflexia, insomnia

Psychiatric disorders	
Uncommon	memory impairment, toxic psychosis
Rare	hyperactivity, euphoria
Not known	confusion, disorientation, hallucination
Gastrointestinal disorders	
Common	diarrhoea, abdominal pain, nausea, anorexia, vomiting
Rare	erosive gastritis, pseudomembranous colitis
Very rare	pancreatitis
Not known	metallic taste, dry mouth, flatulence, constipation
Hepatobiliary disorders	
Very common	transient elevation of serum transaminases
Uncommon	elevated serum bilirubin and alkaline phosphatases, hepatitis
Renal and urinary disorders	
Rare	acute renal failure, interstitial nephritis
Not known	urinary retention
Metabolic and nutritional disorders	
Very common	hyperuricaemia, especially in patients with gout
Very rare	aggravated porphyria
Not known	hyperglycaemia, metabolic acidosis, pellagra
General disorders	
Very common	flushing
Common	reddish discolouration of body fluids and secretions, such as urine, sputum, tears, saliva and sweat
Not known	allergic reactions with skin manifestations, pruritus, fever, leucopenia, anaphylaxis, allergic pneumonitis, neutropenia, eosinophilia, vasculitis, lymphadenopathy, rheumatic syndrome, lupus-like syndrome, hypotension, shock
Blood and lymphatic system disorders	
Not known	anaemia (haemolytic, sideroblastic, or aplastic), thrombocytopenia, leucopenia, neutropenia with eosinophilia, agranulocytosis, blood clotting affected
Respiratory, thoracic and mediastial disorders	
Not known	pneumonitis, dyspnoea
Musculoskeletal disorders	
Very common	arthralgia
Not known	Gout
Skin and subcutaneous tissue disorders	

Common	erythema, exanthema, pruritus with or without rash, urticaria
Rare	photosensitivity, exfoliative dermatitis, pemphigoid reactions, purpura
Not known	Lyell's Syndrome, Stephens-Johnson Syndrome

Eye disorders	
Common	ocular redness, permanent discoloration of soft contact lenses, visual disturbances due to optic neuritis (retrobulbar neuritis)
Rare	exudative conjunctivitis
Reproductive system and breast disorders	
Common	disturbances of the menstrual cycle
Rare	gynaecomastia

Suspected adverse reactions should be reported to the relevant National Regulatory Authority.

4.9 Overdose

Symptoms

Anorexia, nausea, vomiting, gastrointestinal disturbances, fever, headache, dizziness, slurred speech, hallucinations and visual disturbances have occurred within 30 minutes to 3 hours after ingestion of isoniazid. With marked isoniazid overdoses (≥ 80 mg/kg body weight) respiratory distress and CNS depression, progressing rapidly from stupor to profound coma, along with severe intractable seizures are to be expected. Typical laboratory findings are severe metabolic acidosis, acetonuria, and hyperglycaemia.

When overdosed, rifampicin may cause a reddish-orange discoloration of the skin ('red man syndrome'). Further symptoms include facial oedema, pruritus, nausea, vomiting and abdominal tenderness. In adults, a total dose of 14 g has caused cardiopulmonary arrest.

Data on pyrazinamide overdosing are scarce. However, liver toxicity and hyperuricaemia may occur. Data on ethambutol overdose are scarce.

Treatment

Emesis, gastric lavage and activated charcoal may be of value if instituted within a few hours of ingestion. Subsequently, pyridoxine (intravenous bolus on a gram-per-gram basis, equal to the isoniazid dose, if latter dose is unknown an initial dose of 5 g in adults or 80 mg/kg in children should be considered), intravenous diazepam (in case of seizures not responding to pyridoxine) and haemodialysis may be of value. There is no specific antidote. Treatment is symptomatic and supportive with special attention to monitoring and support of ventilation and correction of metabolic acidosis.

5.Pharmacological Properties

5.1 Pharmacodynamic Properties

Pharmacotherapeutic group: Antimycobacterials, combinations of drugs for treatment of tuberculosis ATC Code J04AM06

Rifampicin is bactericidal in vitro against a wide range of organisms, including Mycobacterium tuberculosis. It inhibits bacterial DNA-dependent RNA

polymerase, inhibiting transcription. In tuberculosis rifampicin is bactericidal for both intracellular and extracellular microorganisms. Microbial resistance may occur, and is a result of alterations in the target enzyme (RNA polymerase).

Isoniazid is highly active against Mycobacterium tuberculosis. It is bactericidal in vitro and in vivo against actively dividing tubercle bacilli. Its primary action is to inhibit the synthesis of long-chain mycolic acids, which are unique constituents of mycobacterial cell wall. Resistance to isoniazid occurs rapidly if it is used alone in the treatment of clinical disease caused by mycobacteria.

Pyrazinamide is a prodrug that is converted into its active form, pyrazinoic acid, by a mycobacterial enzyme, pyrazinamidase, as well as through hepatic metabolism. Pyrazinoic acid is bactericidal to Mycobacterium tuberculosis at acid pH values but not at neutral pH. The precise mechanism of action is unknown. Pyrazinamide is inactive against atypical mycobacteria. Resistance develops rapidly if pyrazinamide is used as the sole antituberculosis agent.

Ethambutol at the recommended doses is a bacteriostatic that acts specifically against tubercle bacilli, also against those resistant to other antimycobacterial agents. It possesses very little sterilizing activity. One suggested mechanism of action is that ethambutol inhibits cell wall synthesis by preventing the incorporation of mycolic acids. When ethambutol has been used alone for treatment of tuberculosis, tubercle bacilli from these patients have developed resistance to ethambutol. No cross-resistance between ethambutol and other antituberculosis agents has been reported. Ethambutol reduced the incidence of the emergence of mycobacterial resistance to isoniazid when both drugs were used concurrently.

5.2 Pharmacokinetic Properties Ethambutol

Absorption

Approximately 80% of ethambutol is absorbed after oral administration.
Following single-dose administration of 1 tablet of Rifampicin 150 mg/Isoniazid 75 mg/Pyrazinamide 400 mg/Ethambutol Hydrochloride 275 mg Tablets USP in healthy volunteers, used to compare the bioavailability of this product with the individual reference formulations, the mean (± SD) ethambutol Cmax value was 1.29 µg/ml (± 0.24 µg/ml), and the corresponding value for AUC was 4.66 µg·hour/ml (± 1.17 µg·hour/ml). The median (± SD) ethambutol tmax value was 2.45 hours (± 0.50 hours).

Distribution

It is reported that, depending on the administered dose, about 10–40% of the drug is bound to plasma protein.

Metabolism

The main path of metabolism appears to be initial oxidation of the alcohol to an aldehyde intermediate, followed by conversion to a dicarboxylic acid

Elimination

The plasma concentration falls biphasically, the half-life being about 4 hours

initially and 10 hours subsequently; 50 to 70% of the dose is excreted unchanged in the urine and 7 to 15% as inactive aldehyde and carboxylic acid metabolites. Between 20 and 22% of the initial dose is excreted in the faeces as unchanged drug.

Renal impairment
The elimination of the drug is delayed in subjects with reduced renal function.

Isoniazid
Absorption
After oral administration, isoniazid is rapidly absorbed with a bioavailability of ≥ 80%, and peak serum concentration reached after 1–2 hours. The rate and extent of absorption are reduced when isoniazid is administered with food. Isoniazid undergoes significant pre-systemic (first-pass) metabolism in the gut wall and liver.

Following single dose administration of 1 tablet of Rifampicin 150 mg/Isoniazid 75 mg/Pyrazinamide 400 mg/Ethambutol Hydrochloride 275 mg Tablets USP in healthy volunteers, used to compare the bioavailability of this product with the individual reference formulations, the mean (± SD) isoniazid Cmax value was 1.59 µg/ml (± 0.52 µg/ml), and the corresponding value (± SD) for AUC was 5.33 µg·hour/ml (± 2.54 µg·hour/ml). The median (± SD) isoniazid tmax value was 1.08 hours (± 0.45 hours).

Distribution
Isoniazid is distributed in the body with an apparent volume of distribution volume of 0.57–
0.76 litre/kg; protein binding is very low (0–10%).
Metabolism
Isoniazid undergoes extensive metabolism in the mucosal cells of the small intestine and in the liver. Firstly, isoniazid is inactivated through acetylation. Subsequently, acetyl-isoniazid is hydrolysed. The capacity to acetylate isoniazid is genetically determined (due to genetic polymorphism in the enzyme N-acetyl transferase) and individuals are termed 'fast acetylators' or 'slow acetylators'. The proportion of acetylator phenotypes varies across different ethnic groups.

Acetylator status is the main determinant of isoniazid exposure at a given dose. At recommended doses, exposure in fast acetylators is about half that in slow acetylators.

Excretion
Up to 95% of the ingested isoniazid is excreted in the urine within 24 hours, primarily as inactive metabolites. Less than 10% of the dose is excreted in the faeces. The main excretion products in the urine are N-acetylisoniazid and isonicotinic acid.

Renal impairment
The documentation of the pharmacokinetics of isoniazid and its metabolites in

patients with renal impairment is incomplete. However, the half-life of isoniazid is prolonged and exposure is increased, in slow acetylators. Renal impairment is likely to increase exposure to the (inactive) metabolites of isoniazid in both fast and slow acetylators.

Pyrazinamide

Absorption

Pyrazinamide is almost completely absorbed from the gastrointestinal tract.
Following single-dose administration of 1 tablet of Rifampicin 150 mg/Isoniazid 75 mg/Pyrazinamide 400 mg/Ethambutol Hydrochloride 275 mg Tablets USP in healthy volunteers, used to compare the bioavailability of this product with the individual reference formulations, the mean (± SD) pyrazinamide Cmax value was 18.7 µg/ml (± 3.0 µg/ml), and the corresponding value (± SD) for AUC was 145 µg·hour/ml (± 25 µg·hour/ml). The median (± SD) pyrazinamide tmax value was 1.98 hours (± 0.63 hours).

Distribution

Pyrazinamide is widely distributed to most fluid compartments and tissues. The volume of distribution has been reported as 0.57–0.84 litre/kg. The plasma protein binding of pyrazinamide is low, approximately 10–20%.

Metabolism

Pyrazinamide is hydrolysed by a microsomal deaminase to the active metabolite, pyrazinoic acid, which is then hydroxylated by xanthine oxidase to 5-hydroxypyrazoinoic acid.

Elimination

Pyrazinamide is eliminated by the kidney, mostly in the form of various metabolites. Approximately 3% of a pyrazinamide dose is eliminated unchanged. The half-life of pyrazinamide is approximately 10 hours. The half-life for the active metabolite pyrazinoic acid after a single dose is approximately 10–20 hours.

Renal impairment

Pyrazinamide is excreted through renal elimination, mainly in the form of the active metabolite pyrazinoic acid. Hence, pyrazinamide doses should probably be reduced in patients with renal failure. A single-dose study in haemodialysis patients compared with healthy controls showed an approximately twofold increase in pyrazinamide AUC and a 5-fold increase in the AUC of pyrazinoic acid. The half-lives of pyrazinamide and pyrazinoic acid were estimated to 26 and 22 hours respectively.

Hepatic impairment

In a single dose, parallel-group study comparing the pharmacokinetics of pyrazinamide in patients with severe liver disease (hypoalbuminaemia, increased INR, ascites, in most cases hyperbilirubinaemia) and healthy volunteers demonstrated a 40% reduction in pyrazinamide clearance and a threefold increase in the exposure to pyrazinoic acid. The half-lives of pyrazinamide and pyrazinoic acid were increased by approximately 60% and 100%, respectively.

Rifampicin

Absorption

Rifampicin is rapidly absorbed from the gastrointestinal tract. Its bioavailability is 90–95% in adults, but may be lower in children. Concomitant intake of food delays absorption and reduces the peak concentration, but does not decrease bioavailability.

Following single dose administration of 1 tablet of Rifampicin 150 mg/Isoniazid 75 mg/Pyrazinamide 400 mg/Ethambutol Hydrochloride 275 mg Tablets USP in healthy volunteers, used to compare the bioavailability of this product with the individual reference formulations, the mean (± SD) rifampicin Cmax value was 2.21 µg/ml (± 1.34 µg/ml), and the corresponding value (± SD) for AUC was 8.90 µg·hour/ml (± 4.94 µg·hour/ml). The median (± SD) rifampicin tmax value was 1.83 (± 0.64) hours.

Distribution

Rifampicin is 60–90% bound to plasma proteins and has a volume of distribution of approximately 0.9 litre/kg. CSF concentrations are in the same order of magnitude as the unbound concentrations in plasma. Rifampicin readily crosses the placenta.

Metabolism

Rifampicin is metabolised by hydrolysis and desacetylation into several metabolites, including the active metabolite desacetylrifampicin. Rifampicin induces its own metabolism; after repeat doses bioavailability is reduced to approximately 70% and apparent clearance is increased.

Excretion

The half-life of rifampicin after a single dose is approximately three hours. After repeat doses this is reduced to approximately 1–2 hours. Rifampicin and its metabolites are mainly excreted in bile, and rifampicin undergoes enterohepatic recirculation. Approximately 25% of a dose is excreted in the urine.

Hepatic impairment

The half-life of rifampicin has been reported to be prolonged in patients with liver impairment or biliary obstruction.

5.3 Preclinical safety data

Rifampicin

After oral administration of 100 mg/kg bodyweight rifampicin for 6 months in rats no toxic effects were observed. After chronic administration of 200 mg/kg swelling and hydropic degeneration of the liver were observed.

In monkeys, vomiting, anorexia and weight loss were observed at chronic doses of 105 mg/kg daily.

Because only limited evidence is available on the carcinogenicity of rifampicin in mice and in the absence of epidemiological studies, the carcinogenicity potential of rifampicin in humans cannot be evaluated.

The available studies on mutagenicity indicate an absence of a mutagenic effect. Rifampicin concentrations in cord blood reach 12–33% of maternal blood concentrations.
Teratogenic effects were noted in rodents treated with high doses. Rifampicin 100 to 150 mg/kg daily in rodents have been reported to cause cleft palate and spina bifida.

In rats neither fertility nor perinatal and postnatal development was impaired.

Malformation and death in infants born to mothers exposed to rifampicin were reported at the same frequency as in the general population.

Isoniazid, ethambutol, pyrazinamide
Conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, and toxicity to reproduction reveal no special hazard for humans at recommended doses.

6.Pharmaceutical Particulars

6.1 List of Excipients

- Colloidal Silicon Dioxide
- Microcrystalline Cellulose
- Croscarmellose Sodium
- Maize Starch
- Sodium Starch Glycolate
- Purified Talc
- Magnesium Stearate
- Colour Iron Oxide Red
- Hydroxy Propyl Methyl Cellulose
- Titanium Dioxide
- Isopropyl Alcohol
- Methylene Chloride
- Polyethylene Glycol 6000

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

36 Months

6.4 Special Precautions for Storage

Store in cool and dry place below 25°C. Protect from Light
Keep out of reach of children

6.5 Nature and Contents of Container

Primary Packing : 28 tablets packed in an ALU PVC blister.
Secondary Packing : Such 24 blisters are packed in a printed carton alongwith

a insert..

6.6 Special Precautions for Disposal

No special requirements.

Any unused product or waste material should be disposed of in accordance with local requirements.

7. Marketing Authorization Holder SVIZERA LABS PRIVATE LIMITED

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8. Marketing Authorization Number: --

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